VOLUME 34 JUNE 1969 NUMBER 6

Coden: JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY

CONJUGATES OF STEROID HORMONES

by **HARRY EARLE HADD,** *Department of Obstetrics and Gynecology, Indiana Medical School, Indianapolis,* and **ROBERT T. BLICKENSTAFF,** *Medical Research Laboratory, Veterans Administration Hospital, Department of Biochemistry, Indiana University Medical School, Indianapolis, Indiana*

This book is written for the organic chemist and the biochemist who need an overall view of research activity on the synthesis, isolation, assay and metabolism of steroid conjugates. The emphasis is on those steroid hormone conjugates (and their analogs) which recently have been shown to reside in the mainstream of steroid metabolism. The authors have described how these conjugates of the steroid hormones are isolated from natural sources and synthesized enzymically and chemically. *Topics include:* Isolation of Steroid Conjugates, Sulfates of Steroid Hormones, Glucuronides of Steroid Hormones, Metabolism of Steroid Conjugates, Other Glycosides of Steroid Hormones; and Phosphates of Steroid Hormones.

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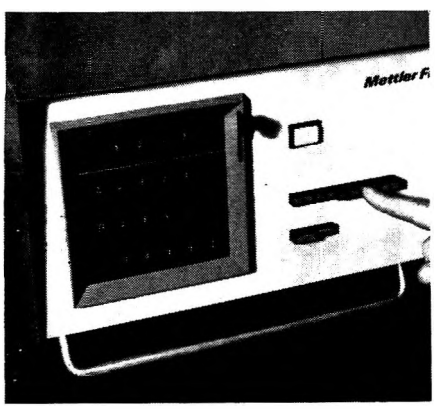

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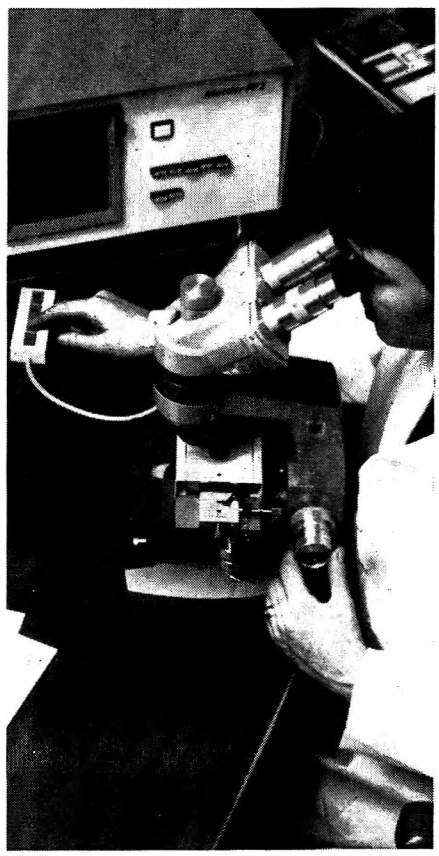

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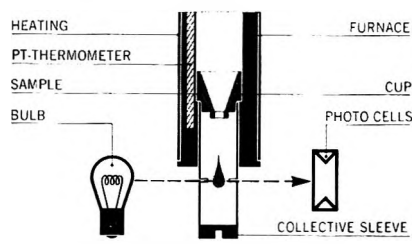

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THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 6

JUNE 1969

IUPAC–IUB Revised Tentative Rules for Nomenclature of Steroids*†

Contents

Introduction

The rules of steroid nomenclature originate from a discussion held at the Ciba Foundation in London, England, in 1950 between the representatives of many schools. These were published in *Chemistry & Industry*, Jan 23, pp SN 1–11 (1951), and also in French and German. They were subsequently taken over by the International Union of Pure and Applied Chemistry and published in an official form in the *Comptes rendus* of the Zurich meeting in 1952 (also IUPAC Nomenclature of Organic Chemistry, Sections A & B, 1957, Butterworths Scientific Publications, London, 1st ed, 1958; 2nd ed, 1966, pp 71–82; and numerous reprints and translations), including *J. Am. Chem. Soc. 82*, 5577–5581 (1960)).

In 1960 a group of specialists under the chairmanship of Professor T. Reichstein, including representatives of the IUPAC Commissions of the Nomenclature of Organic Chemistry and of Biochemical Nomenclature, met in Basle, Switzerland, for discussions of amendments and additions to the rules. Agreement was not reached on all the points discussed, and the results of this meeting were therefore published in discussion form in the IUPAC *Information Bulletin*, No. 11. They have generally been referred to as the "Basle Proposals."

Since then, many points in the Basle Proposals have become almost universally accepted in the literature. In 1965 the two International Commissions concerned, namely, the IUPAC Commission of the Nomenclature of Organic Chemistry and the Commission on Biochemical Nomenclature (now jointly responsible to IUPAC and IUB), decided that the time had come for as many as possible of the Basle Proposals to be formulated as rules.

The present rules include: all the original rules, mostly renumbered (with additions and amendments arising from the Basle proposals or from current practice in the literature); and most of the Basle Proposals, namely, those that have been generally accepted. Further, adoption of the sequence-rule procedure‡ for general stereochemical descriptions in much of the chemical literature has permitted its introduction now also for some sections of steroid nomenclature that were previously in dispute or intractable. Decisions on a few of the Basle Proposals have, however, been postponed; it is hoped that further experience will indicate the most appropriate ways of dealing with them.

General Application

Although these rules are called "Rules for Nomenclature of Steroids," many of the principles therein have become almost universally accepted also in diterpene and triterpene chemistry; also to some extent for sesquiterpenes and for several groups of alkaloids. It is suggested that the same principles may be applied to a number of other specialized groups of natural products, perhaps without the need for further official rules, so long as the basic ideas are followed. These principles include: (i) clear definition of stem names and the stereochemistry implied in them; (ii) systematic application of the rules of general organic chemical nomenclature, with modifications where special considerations make this necessary; (iii) application of the methods of skeletal modification given in these rules, *viz.*, the use of homo and nor for, respectively, stepwise expansion and contraction of ring systems, the use of seco for reductive fission of ring systems, and the use of *abeo* for formal bond migrations (this flexible concept was first proposed by D. H. R. Barton at an informal meeting of terpene chemists convened by the Chemical Society in London, England).

* These rules shall be known as the IUPAC–IUB 1967 Revised Tentative Rules for Steroid Nomenclature.

† These rules are issued by the IUPAC Commission on the Nomenclature of Organic Chemistry [P. E. Verkade (Chairman), L. C. Cross, G. M. Dyson, G. Kersaint, K. L. Loening, N. Lozac'h, H. S. Nutting, S. Veibel; associate members, R. S. Cahn, J. Rigaudy; observers, K. A. Jensen, W. Klyne], and by the IUPAC–IUB Commission on Biochemical Nomenclature [O. Hoffmann-Ostenhof (Chairman), A. E. Braunstein, W. E. Cohn, J. S. Fruton, P. Karlson, B. Keil, W. Klyne, C. Liébecq, E. C. Slater, E. C. Webb; corresponding member, N. Tamiya; observer, S. Veibel], and are published by permission of the IUPAC, the IUB, and the official publishers to IUPAC, Butterworths Scientific Publications. Reprints of these Revised Tentative Rules may be obtained from the NAS–NRC Office of Biochemical Nomenclature (Dr. Waldo E. Cohn, Director), Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn. 37830.

‡ Cahn, R. S., Ingold, C. K., and Prelog, V. (1966), *Angew. Chem. Intern. Ed. Engl. 5*, 385; *Angew. Chem. 78*, 413 (in German). For a partial simplified account see Cahn, R. S. (1964), *J. Chem. Educ., 41*, 116.

Comments

Comments on and suggestions for future revisions of these Tentative Rules should be sent to: Professor P. E. Verkade, 's-Gravenhage, Ary Schefferstraat, 217, The Netherlands, or Professor O. Hoffmann-Ostenhof, Biochemische Abteilung, Organisch-Chemisches Institut der Universität Wien, 1090 Vienna, Währinger Strasse 68, Austria, or to any member of the Commissions named in the footnote on p 2227.

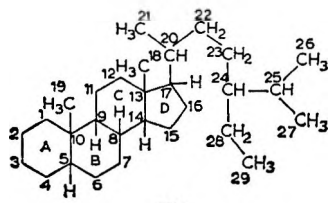
Rules

Rules are numbered 2S-1, 2S-2, 2S-3, etc., the first "2" denoting that this is the second or revised set of rules. The numbers of the corresponding previous rules (see Introduction), where they exist, are included for comparisons.

General

Rule 2S-1 (Expanded from Rules S-1 and S-2)

1.1. Steroids are numbered and rings are lettered as in formula 1 If one of the two methyl groups attached to C-25 is substituted,



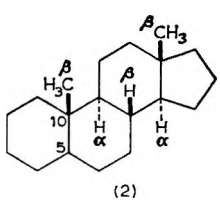
(1)

it is assigned the lower number (26); if both are substituted, that carrying the substituent cited first in the alphabetical order or order of complexity is assigned the lower number (*cf.* IUPAC 1965 Rule* C-15.11(e)). For trimethyl steroids see Rule 2S-2.3, Note 3.

1.2. If one or more of the carbon atoms shown in (1) is not present and a steroid name is used, the numbering of the remainder is undisturbed.

1.3. For a steroid, the name, including stereochemical affixes, and its structural formula (see Rule 2S-1.4) denote the absolute configuration at each asymmetric center (see also Rule 2S-1.5). When the configuration at one or more centers is not known, this is indicated by Greek letter(s) ξ (xi) prefixed by the appropriate numeral(s).

1.4. When the rings of a steroid are denoted as projections onto the plane of the paper, the formula is normally to be oriented as in (2). An atom or group attached to a ring depicted as in the orientation (2) is termed α (alpha) if it lies below the plane of the



(2)

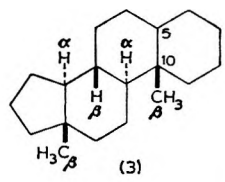
paper or β (beta) if it lies above the plane of the paper. In formulae, bonds to atoms or groups lying below the plane of the paper are shown as broken (- - -) lines, and bonds to atoms or groups lying above the plane of the paper are shown as solid lines (preferably thickened). Bonds to atoms or groups whose configuration is not known or is unspecified are denoted by wavy lines (∿∿).

Notes. (1) Projections of steroid formulae should not be oriented as in formulas 3, 4, or 5 unless circumstances make it obligatory.

(2) With the preferred orientation (2), and with (3), α bonds appear as broken lines and β bonds as solid (thickened) lines. The reverse is true for (4) and (5). Wavy lines denote ξ bonds for all orientations of the formula.

(3) A perspective representation of the stereochemistry of formula 2 as in (2a) or (2b) may also be used.

* IUPAC (1965), Nomenclature of Organic Chemistry, Section C, Butterworths Scientific Publications, London; also *Pure Appl. Chem. 11*, No. 1 and 2.



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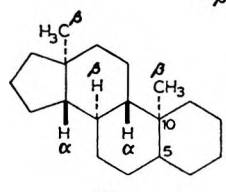

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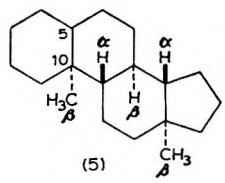

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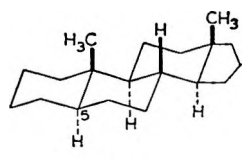
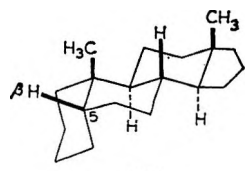


(2a)
A 5α-steroid



(2b)
A 5β-steroid

(For the significance of the prefixes 5α- and 5β- see Rule 2S-I.5.)

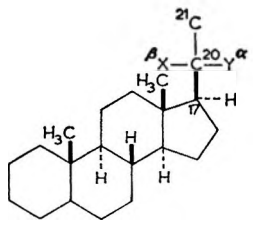
When steroid formulae are drawn in this way, bonds pointing upward are, by convention, drawn bold and bonds pointing downward are drawn broken; these representations correspond to the β and α bonds of projection formulae such as (2) and do not conform to the general practice that bold and broken lines denote bonds projecting respectively above and below the plane of the paper. Note, however, that the general practice is followed with chair and boat forms of spirostans (see Rule 2S-3.3).

(4) All hydrogen atoms and methyl groups attached at ring-junction positions must always be inserted as H and CH_3, respectively (Me may be used in place of CH_3 if editorial conventions require it). The practice, sometimes followed, of denoting methyl groups by bonds without lettering is liable to cause confusion and should be abandoned. This is essential in view of customs in other fields and applies also to other groups of compounds such as cyclic terpenes and alkaloids for which steroid conventions are commonly used.

1.5. Unless implied or stated to the contrary (see Rules 2S-3, 2S-4.3, 2S-5, and 2S-11), use of a steroid name implies that atoms or groups attached at the ring-junction positions 8, 9, 10, 13, and 14 are oriented as shown in formula 2 (*i.e.*, 8β, 9α, 10β, 13β, 14α), and a carbon chain attached at position 17 is assumed to be β oriented (see Notes below). The configuration of hydrogen (or a substituent) at the ring-junction position 5 is always to be designated by adding α, β, or ξ after the numeral 5, this numeral and letter being placed immediately before the stem name. The configuration of substituents attached at other centers of asymmetry in the tetracyclic system A–D is stated by adding α, β, or ξ after the respective numerals denoting their position.

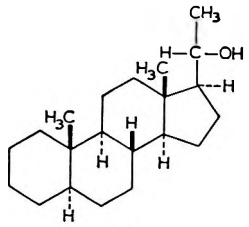
Notes. For the purpose of this rule a carboxyl group at position 17 is not considered to constitute a carbon "chain" (for the nomenclature used, see Rule 2S-4.3). For pent a-and hexacyclic derivatives, see Rule 2S-3, and for stereochemical modifications, see Rule 2S-5.

1.6. When the configuration at position 20 in the side chain of a pregnane derivative is as depicted in the projection formula 6 (*i.e.*, a Fischer projection but with the highest number at the top), substituents shown to the right of C-20 are termed α and those to the left are termed β.



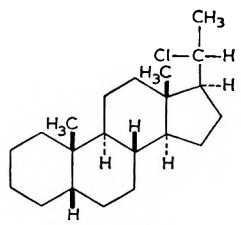
(6)

Examples



(7)

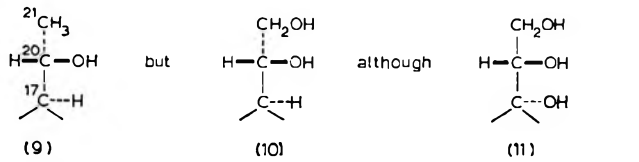
5α-Pregnan-20α-ol*



(8)

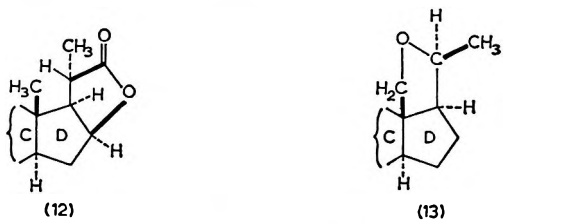
20β-Chloro-5β-pregnane*

Notes. (1) The 20α/20β nomenclature is continued because of long tradition. When a longer side chain is present at C-17, the sequence-rule procedure (see Cohn *et al.*, 1966) is more generally convenient (see Rule 2S-1.7), and it may also be used to designate stereochemistry at C-20 in pregnanes, being particularly useful for C-20 substituents that may cyclize with a substituent at another position [*e.g.*, carboxylic acids as in example 12]. For 20-hydroxy, 20-alkoxy, 20-acyloxy, 20-amino, and 20-halogeno derivatives of pregnane without a substituent on C-17 or C-21, 20α is equivalent to (20*S*), and 20β to (20*R*); however, these equivalences are sometimes reversed when additional substituents are present, *e.g.*, on C-17 or C-21, and in such cases ref 1 should be consulted.



(9) (10) (11)

20α-ol (20*S*) 20α,21-diol (20*R*) 17,20α,21-triol (20*S*)



(12) (13)

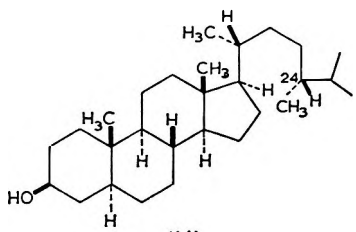
(20*S*)-16β-Hydroxypregnane-20-carboxylic acid lactone (≡ 20α)

(20*S*)-18,20-Epoxypregnane (≡ 20α)

(2) When stereochemistry at C-20 is denoted by a Fischer-type projection, as in (6)–(11) or for cardenolides as (37) or bufanolides as (43), the 17,20 bond is preferably denoted by an ordinary line; the stereochemistry at C-17 is then adequately denoted by a thick or a broken bond to the H or to the other substituent (*e.g.*, OH) at position 17. In such formulae, representing the 17,20 bond by a thick or a broken line cannot be correct for both C-17 and C-20; this has, however, frequently been done, then involving the additional convention that the way in which this bond is written is neglected when considering the stereochemistry at C-20.

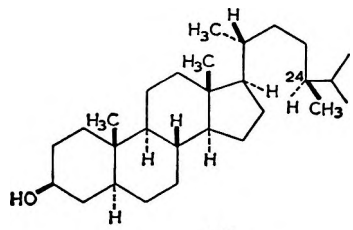
1.7. The stereochemistry at C-20 and other positions in steroid side chains longer than ethyl is described by the sequence-rule procedure.**

Examples



(14)

(24*R*)-24-Methyl-5α-cholestan-3β-ol*
(formerly 24α-methyl)
(trivial name: campestanol)



(15)

(24*S*)-24-Methyl-5α-cholestan-3β-ol*
(formerly 24β-methyl)
(trivial name: ergostanol)

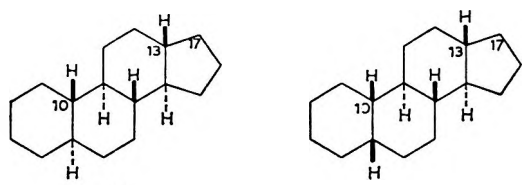
Notes. (1) The sequence-rule procedure is also used when the side chain is cyclized (see Rules 2S-3.3 and 2S-3.4).

(2) The backbone of a C-17 side chain is best denoted as in the plane of the paper (lines of ordinary thickness), the 17,20 bond being similarly denoted. Except for pregnane derivatives, stereochemistry due to substituents on the chain is then indicated by the customary thick or broken lines denoting bonds that project, respectively, above and below the plane of the paper.

Fundamental Carbocycles

Rule 2S-2 (Expanded from Rules S-3.1 to S-3.5)

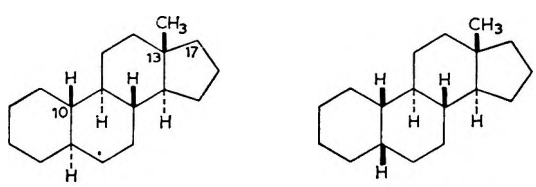
2.1. The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and without a side chain at C-17 is named "gonane."



(16) (17)

5α-Gonane 5β-Gonane

2.2. The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and without a side chain at C-17 is named "estrane."

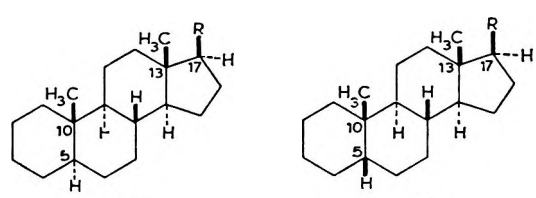


(18) (19)

5α-Estrane 5β-Estrane

Note. Names of compounds having a methyl group attached to C-10 and a hydrogen atom attached to C-13 are to be based on 18-norandrostane (see Rules 2S-2.3 and 2S-7.1) and not on 10-methylgonane.

2.3. The names given in Table I are used for the hydrocarbons 20 and 21 with methyl groups at both C-10 and C-13.

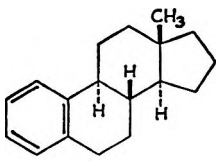


(20) (21)

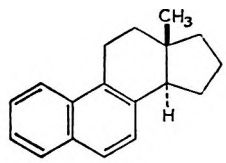
Notes. (1) Unsaturation and substituents are denoted in the names of steroids by the usual methods of organic chemistry (*cf.* Rule 2S-4). Examples (22)–(25) illustrate some simple cases.

* For the names "pregnane" and "cholestane," see Rule 2S-2.3.

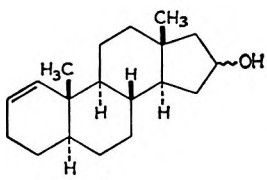
** See Cahn *et al.* (1966).



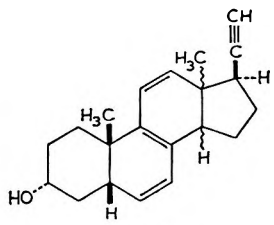
(22)
1,3,5(10)-Estratriene



(23)
1,3,5(10),6,8-Estrapentaene

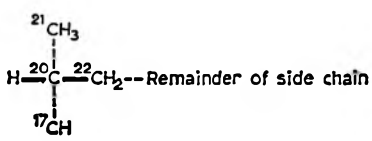


(24)
5α-Androst-1-en-16ξ-ol



(25)
5β,13ξ,14ξ-Pregna-6,8,11-trien-20-yn-3α-ol

(2) The names "cholane," "cholestane," "ergostane," and "stigmastane" imply the configuration at C-20 shown in partial formula 26; this is 20*R* except for some derivatives containing additional substituents (*cf.* Note to Rule 2S-1.6).

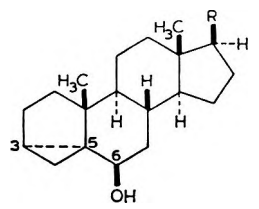


(26)

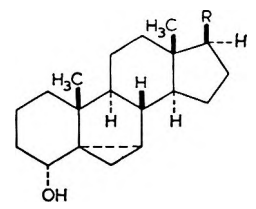
(3) Tetracyclic triterpenoids may be regarded as trimethyl steroids, the three additional methyl groups being numbered 30 (attached to C-4 with α configuration), 31 (attached to C-4 with β configuration), and 32 (attached to C-14); for example, 5α-lanostane (27) is 4,4,14α-trimethyl-5α-cholestane, the former name implying 14α,20*R* configuration. Trivial names are common in this series of compounds, and some are illustrated in examples (27)–(31).

2.4. When an additional ring is formed by means of a direct link between any two carbon atoms of the steroid ring system or the attached side chain, the name of the steroid is prefixed by "cyclo"; this prefix is preceded by the numbers of the positions joined by the new bond and the Greek letter (α, β, or ξ) denoting the configuration of the new bond, unless that designation is already implicit in the name.

Examples



(32)

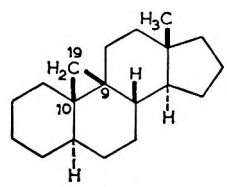


(33)

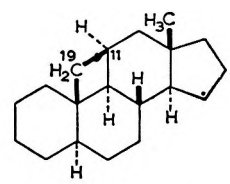
R = $CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$

3α,5-Cyclo-5α-cholestan-6β-ol

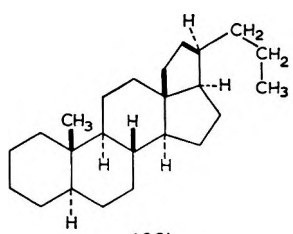
5,7α-Cyclo-5α-cholestan-4α-ol



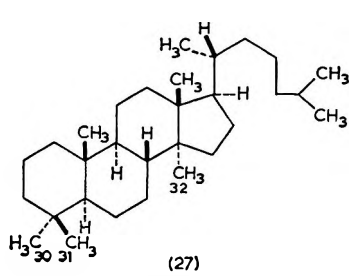
(34)
9,19-Cyclo-5α,9β-androstane



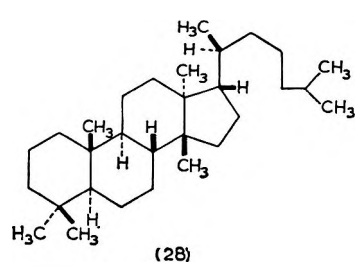
(35)
11β,19-Cyclo-5α-androstane



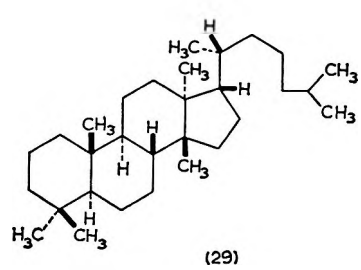
(36)
(20*R*)-18,21-Cyclo-5α-cholane



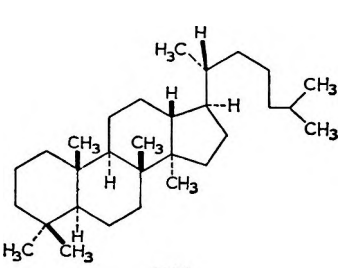
(27)
5α-Lanostane



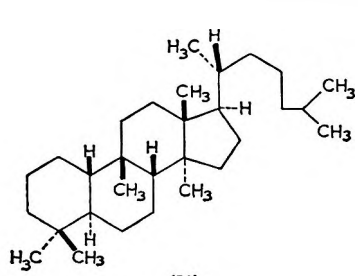
(28)
5α-Tirucallane
5α,13α,14β,17α,20*S*-Lanostane



(29)
5α-Euphane
5α,13α,14β,17α-Lanostane
(20*R* implied in the name)



(30)
5α-Dammarane
8-Methyl-18-nor-5α-lanostane (all configurations except 5α are implied in the name)

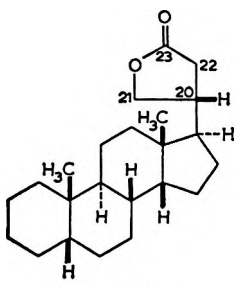


(31)
5α-Cucurbitane
19(10→9β)*abeo*-5α-Lanostane (for the *abeo* nomenclature see Rule 2S-9)

TABLE I

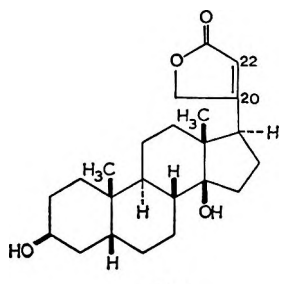
R	(20) 5α Series	(21) 5β Series
H	5α-Androstane	5β-Androstane (*not* testane)
C_2H_5	5α-Pregnane (*not* allopregnane)	5β-Pregnane
[a]$CH(CH_3)CH_2CH_2CH_3$	5α-Cholane (*not* allocholane)	5β-Cholane
[a]$CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$	5α-Cholestane	5β-Cholestane (*not* coprostane)
[a]$CH(CH_3)CH_2CH_2\overset{24b}{C}H(CH_3)CH(CH_3)_2$	5α-Ergostane	5β-Ergostane
[a]$CH(CH_3)CH_2CH_2\overset{24c}{C}H(C_2H_5)CH(CH_3)_2$	5α-Stigmastane	5β-Stigmastane

[a] 20*R* configuration. [b] 24*S* configuration. [c] 24*R* configuration.



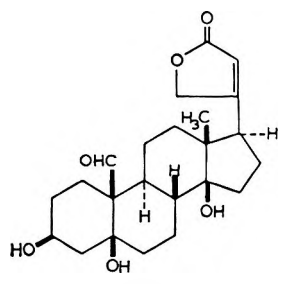
(37)

5β,14β-Cardanolide



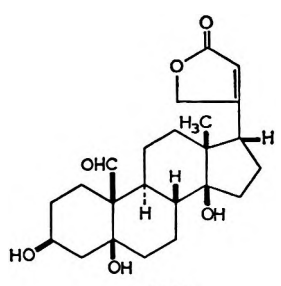
(38)

3β,14-Dihydroxy-5β,14β-card-20(22)-enolide (= digitoxigenin*)



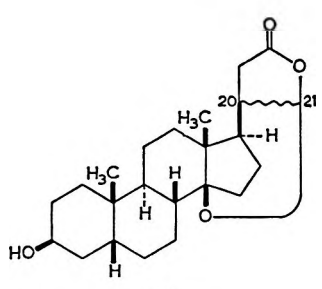
(39)

3β,5,14-Trihydroxy-19-oxo-5β,14β-card-20(22)-enolide (= strophanthidin*)



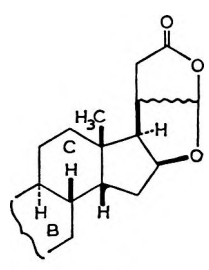
(40)

3β,5,14-Trihydroxy-19-oxo-5β,14β,17α-card-20(22)-enolide (= 17α-strophanthidin*) (also, allostrophanthidin**)



(41)

3β-Hydroxy-14,21ξ-epoxy-5β,14β,20ξ-cardanolide (= isodigitoxigenin**)



(42)

A 16β,21ξ-epoxy-14β,20ξ-cardanolide

Penta- and Hexacyclic Modifications

Rule 2S-3 (Amended Versions of Rules S-3.6 to S-3.9)

3.1. (a) The name "cardanolide" is used for the fully saturated system (37) of digitaloid lactones whose configuration is as illustrated (the configuration at position 20 is shown as a Fischer-type projection‡ and is the same as that in cholesterol, *i.e.*, 20*R*). Notwithstanding Rule 2S-1.5, the configuration at position 14 must always be stated as an affix to the names of these compounds.

(b) Names such as "20(22)-cardenolide" are used for the naturally occurring unsaturated lactones of this type.

(c) The names "14,21-" and "16,21-epoxycardanolide" are used for the compounds containing a 14,21 or a 16,21 oxygen bridge, respectively.

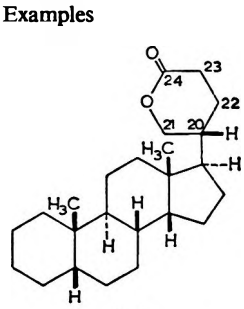
Note. Statement of the configuration at C-14 for all cardanolides is a change from the earlier steroid rules and is in line with current practice.

Examples are given in (37)–(42) above.

3.2. The name "bufanolide" is used for the fully saturated system (43) of the squill-toad poison group of lactones, with the configuration at position 20 shown (this configuration is drawn as a Fischer-type projection (see Note to Rule 2S-3.1(a)) and is the same as in cholesterol, *i.e.*, 20*R*. Notwithstanding Rule 2S-1.5, the configuration at position 14 must always be stated as an affix to the names of these compounds. Unsaturated derivatives are named by replacing the suffix -anolide by -enolide, -adienolide, etc.; thus, the name "20,22-bufadienolide" is used for the naturally occurring doubly unsaturated lactones.

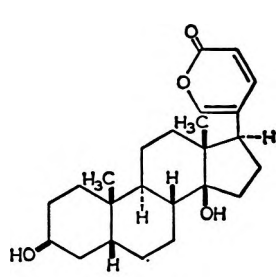
Note. Statement of the configuration at C-14 for all bufanolides is a change from the earlier steroid rules and is in line with current practice.

Examples



(43)

5β,14β-Bufanolide



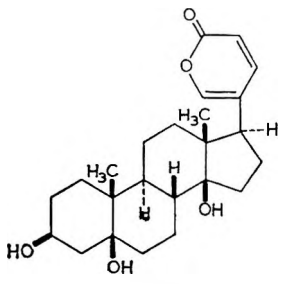
(44)

3β,14-Dihydroxy-5β,14β-bufa-20,22-dienolide (= bufalin*)

* Denotes a trivial name; the systematic name is preferred.

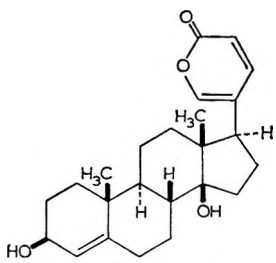
** Denotes a previous trivial name now considered unacceptable.

‡ This method of drawing is customary for the steroids. Since the highest numbered atom is at the top, the usual Fischer projection has been rotated in the plane of the paper through 180°.



(45)

3β,5,14-Trihydroxy-5β,14β-bufa-20,22-dienolide (= telecinobufagin*)

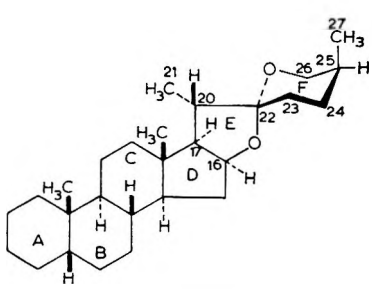


(46)

3β,14-Dihydroxy-14β-bufa-4,20,22-trienolide (= scillarenin*)

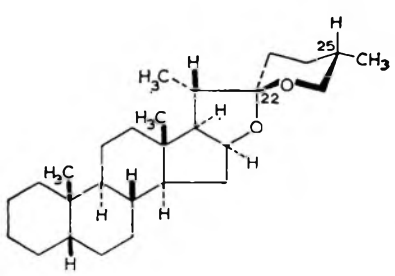
3.3. The name "spirostan" is used for the compound of structure 47;** this name specifies the configurations shown for all the asymmetric centers except positions 5 and 25. A prefix 5α or 5β is added in the usual way (see Rule 2S-1.5). Configurations at C-16 and C-17, if different from those shown in formula 47, are designated as 16β(H) and 17β(H). Configurations at C-20 and C-22, if different from those shown in formula 47, are designated by the sequence-rule procedure‡ or, if unknown, by ξ. Steric relations of substituents at C-23, C-24, C-25, or C-26 are in all cases designated by the sequence-rule procedure‡ or, if unknown, by ξ.

Examples



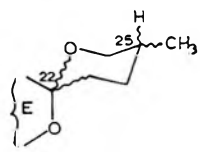
(47)

(25*S*)-5β-Spirostan



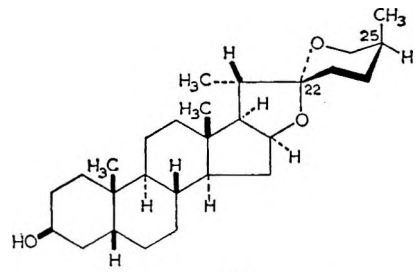
(48)

(22*S*,25*S*)-5β-Spirostan



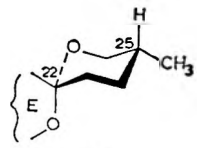
(49)

22ξ,25ξ-



(50)

(25*S*)-5β-Spirostan-3β-ol (= sarsasapogenin*)



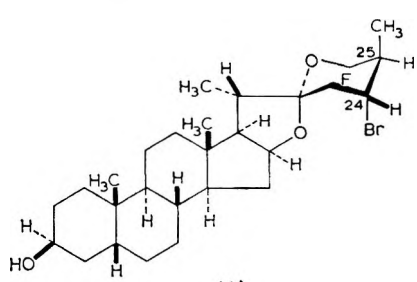
(51)

(25*R*)-

Notes. Several other methods have been used in the past for designating stereochemistry at C-22 and C-25 in the spirostans and related series; all involve serious difficulties (*cf.* the Basle Proposals, IUPAC *Information Bulletin*, No. 11; also L. F. Fieser and M. Fieser, "The Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 21). The sequence-rule procedure is adopted in these rules because it gives an unequivocal symbolism.

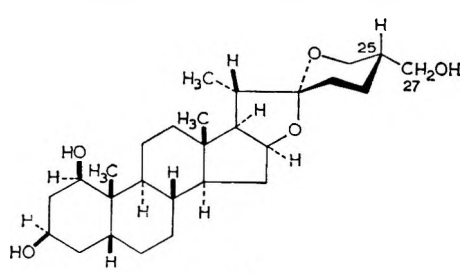
It is to be noted that, although ring E, like rings A, B, C, and D, can conveniently be shown by projection onto the plane of the paper, ring F cannot be adequately represented in this way since the oxygen atom, C-26, C-24, and C-23 lie in one plane that is perpendicular to the plane of the paper. Ring F is conveniently drawn as in formulae 47–51; in formula 47, for instance, the broken line from C-22 to oxygen denotes that the oxygen atom and C-26 of ring F lie behind the plane of the paper and that consequently C-23 and C-24 lie in front of the plane of the paper (configuration *R* at C-22). In formula 48, the configuration at C-22 is reversed and must be stated in the name (*S*). It is conventional to draw ring F as a chair, but this conformation is not implied in the name "spirostan"; whatever the conformation of ring F, C-27 and the 25-hydrogen atom both lie in the plane of the paper and so cannot be denoted by broken or thickened lines or designated α or β. In (47), the methyl group is axial (above the general plane of ring F), and in (48) it is equatorial (in the general plane of ring F); in both cases the configuration at C-25 is *S*, but this identity of *R*,*S* designation arises only because the configuration at C-22 has also been reversed between (47) and (48); a 25*R* configuration is shown in (51). The wavy lines in (49) denote unspecified or unknown configurations at both C-22 and C-25.

The *R*,*S* specification may also be affected by substitutents attached to ring F or C-27, as in compounds A and B.



(A)

(24*R*)-Bromo-(25*R*)-5β-spirostan-3β-ol



(B)

(25*S*)-5β-Spirostan-1β,3β,27-triol

3.4. The name "furostan" is used or the compound of structure 52 (16β,22-epoxycholestane); this name specifies the configurations at all the asymmetric centers except positions 5, 22, and (if position 26 is substituted) also 25. Configuration at C-5 is designated by use of α or β in the usual way (see Rule 2S-1.5), and configurations

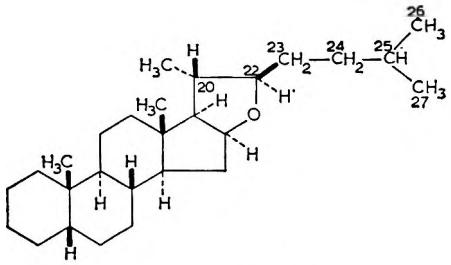
* Denotes a trivial name; the systematic name is preferred.

** This is a 16,22:22,26-diepoxycholestane.

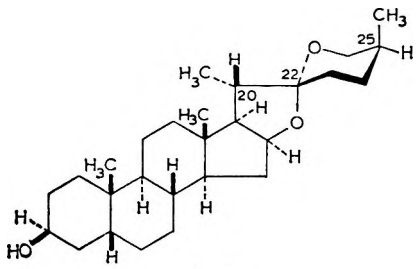
‡ See Cohn *et al.* (1966).

at C-22 and, if necessary, C-25 by the sequence-rule procedure, or in all these cases by ξ if unknown.

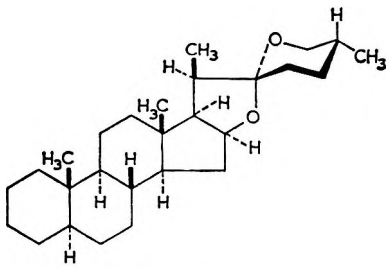
Example



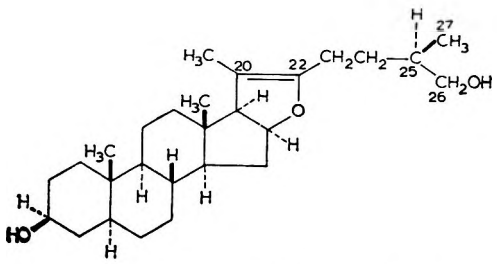
(52)
(22*R*)-5β-Furostan



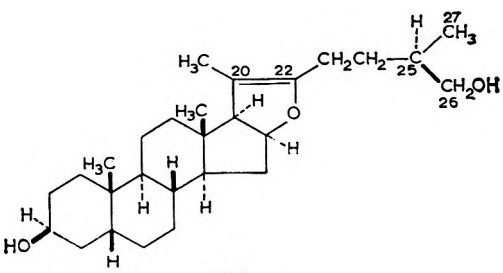
(53)
(25*S*)-5β-Spirostan-3β-ol
(Sarsasapogenin*)



(55)
(20*R*,22*R*,25*R*)-5α-Spirostan
(Cyclopseudoisogenin*)



(57)
(25*R*)-5α-Furost-20(22)-en-3β,26-diol
(Pseudotigogenin*)



(59)
(25*S*)-5β-Furost-20(22)-en-3β,26-diol
(Pseudosarsasapogenin*)

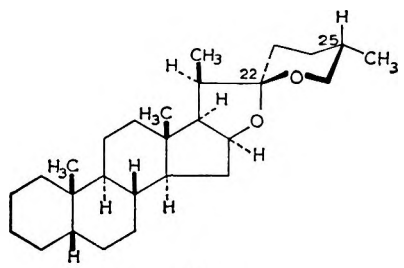
Note. Representative examples of the new standard names and old names** for some common types of spirostan, furostan, and derived structures are given in Table II and formulae 53–59.

Derivatives

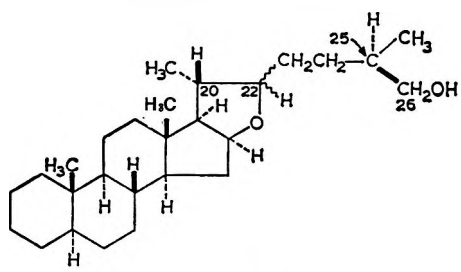
Rule 2S-4 (Extended Version of Rule S-4)

4.1. Steroid derivatives that can be considered to be formed by modification of, or introduction of substituents into, a parent compound are named by the usual methods of organic chemistry (see IUPAC Nomenclature of Organic Chemistry, Sections A & B (1957), *J. Am. Chem. Soc. 82*, 5545–5574 (1960), and Section C (1965), Butterworths Scientific Publications, London, *Pure Appl. Chem. 11*, No. 1 and 2 (1965)).

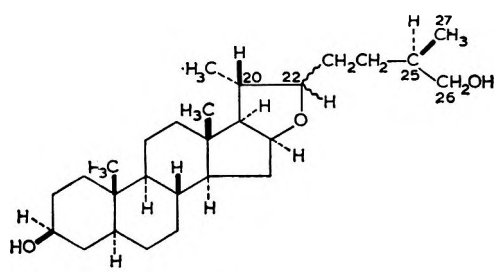
Notes. For the benefit of the specialist, those rules of general substitutive nomenclature that apply most often to steroids are outlined here. For full detail, the IUPAC rules cited above should be consulted.



(54)
(20*R*,22*S*,25*S*)-5β-Spirostan
(Cyclopseudoneogenin*)



(56)
(20*S*,22ξ,25*S*)-5α-Furostan-26-ol
(Dihydrogenin*)



(58)
(20*S*,22ξ,25*R*)-5α-Furostan-3β,26-diol
(Dihydropseudotigogenin*)

I. Unsaturation is indicated by changing terminal "-ane" to "-ene," "-adiene," "-yne," etc., or "-an" to "-en," "-adien," "-yn," etc.; *e.g.*, 5α-cholest-6-ene, 5β-cholesta-7,9(11)-diene, 5-spirosten; see also the names of examples (22)–(25).‡

* Denotes a trivial name; the standard name is preferred.

** Standard names are preferred.

‡ For uniformity with the IUPAC rules cited above, the conventions of *Chemical Abstracts* are used also in the present rules for the position of locants (positional numerals) and designation of unsaturation. In such matters, and in use of Δ (Greek capital delta) to designate unsaturation (which is not recommended by IUPAC), authors should

TABLE II: Spirostans and Furostans

Formula Type	Standard Name	Configurations Implied in Standard Name	Old Names (with trivial names for particular compounds in brackets)[a]
47	(25*S*)-Spirostan	20*S*,22*R*	Sapogenin (without prefix) Neogenin 25-L-Genin [Sarsasapogenin is (53)]
51	(25*R*)-Spirostan	20*S*,22*R*	Isogenin 25-D-Genin [Smilagenin is (25*R*)-5β-spirostan-3β-ol Tigogenin is (25*R*)-5α-spirostan-3β-ol]
54	(20*R*,22*S*,25*S*)-Spirostan		Cyclopseudoneogenin
55	(20*R*,22*R*,25*R*)-Spirostan		Cyclopseudoisogenin
56	(22*R*) (or *S* or ξ), (25*R*) (or *S* or ξ)-Furostan	20*S*	Dihydrogenin (26-ol) and dihydropseudogenin (26-ol) [Dihydrosarsasapogenin is 5β,22ξ,25*S*-furostan-3β,26-diol Dihydropseudotigogenin is (58); *cf.* (57)]
57	(25*R*) (or *S* or ξ)-Furost-20(22)-en		Pseudogenin [Pseudotigogenin is (57) Pseudosarsasapogenin is (59) Pseudosmilagenin is (25*R*)-5β-furost-20(22)-en-3β,26-diol]

[a] The standard name is preferred.

II. Most substituents can be designated either as suffixes or as prefixes; a few can be named only as prefixes, the commonest of these being halogens, alkyl, and nitro groups. When possible, one type of substituent must be designated as suffix. When more than one type is present that could be designated as suffix, one type only may be so expressed and the other types must be designated as prefixes. Choice for suffix is made according to an order of preference that is laid down in the rules cited above; the most important part of this order, for steroids, is as follows, in decreasing preference: 'onium salt, acid, lactone, ester, aldehyde, ketone, alcohol, amine, ether. Suffixes are added to the name of the saturated or unsaturated parent system, the terminal "e" of "-ane," "-ene," "-yne," "-adiene," etc., being elided before a vowel (presence or absence of numerals has no effect on such elisions). The following examples illustrate the use of these principles.

(a) Acids
Suffix for $-CH_3 \rightarrow -COOH$: -oic acid
Suffix for $CH \rightarrow C-COOH$: -carboxylic acid
Examples: 11-oxo-5α-cholan-24-oic acid
(20*S*)-3α-hydroxy-5-pregnene-20-carboxylic acid

(b) Lactones, other than cardanolides and bufanolides.
The ending "-ic acid" or "-carboxylic acid" of the name of the hydroxy acid is changed to "-lactone" or "-carbolactone," respectively, preceded by the locant of the acid group and then the locant of the hydroxyl group, and the prefix "hydroxy" is omitted for the lactonized hydroxyl group.
Examples: 3β-hydroxy-5α-cholano-24,17α-lactone
(20*R*)-3β-hydroxy-5-pregnene-20,18-carbolactone

(c) Cardanolides and bufanolides.
The -olide ending of these names denotes the lactone grouping, and substituents must be named as prefixes.

(d) Esters of steroid alcohols.
Special procedures are used.
For esters of monohydric steroid alcohols, the steroid hydrocarbon radical name is followed by that of the acyloxy group in its anionic form. The steroid radical name is formed by replacing the terminal "e" of the hydrocarbon name by "yl" and inserting before this the locant and Greek letter, with hyphens, to designate the position and configuration.
Example: 5α-cholestan-3β-yl acetate
For esters of polyols the name of the polyol (*cf.* g below) is followed by that of the acyloxy group(s) in its anionic form, with locants when necessary.
Examples: 5β-cholestane-3α,12α-diol diacetate
5β-cholestane-3α,12α-diol 3-acetate 12-benzoate
estradiol-17β 17-monoacetate
When an acid, lactone, or spirostan group is also present, the ester group is designated by an acyloxy prefix.
Example: (25*S*)-3β-acetoxy-5β-spirostan

(e) Aldehydes.
Suffixes: -al (denotes change of $-CH_3$ to $-CHO$, *i.e.*, without change in the number of carbon atoms)
-aldehyde (denotes change of $-COOH$ to $-CHO$, *i.e.*, without change in the number of carbon atoms; name derived from that of the acid)
Prefix: oxo- (denotes change of $>CH_2$ to $>CO$, thus also of $-CH_3$ to $-CHO$, with no change in the number of carbon atoms)
Examples: 5α-androstan-19-al
5α-cholan-24-aldehyde
19-oxo-5α,17(αH)-etianic acid
Other methods are used for introduction of additional carbon atoms as $-CHO$ groups.

(f) Ketones
Suffix: -one
Prefix: oxo-
Examples: 5β-androstan-3-one
5-pregnene-3,20-dione
11-oxo-5α-cholan-24-oic acid

(g) Alcohols
Suffix: -ol
Prefix: hydroxy-
Examples: 5β-cholestane-3α,11β-diol
3α-hydroxy-5α-androstan-17-one

Notes. (1) Composite suffixes -olone and -onol, to denote simultaneous presence of hydroxyl and ketonic groups, are not permitted by IUPAC rules and should not be used.
(2) A few trivial names exist for hydroxy ketones, such as testosterone for 17β-hydroxy-4-androsten-3-one (see Rule 2S-4.2).

(h) Amines
Suffix: -amine
Prefix: amino-
The suffix may be attached to the name of the parent compound or of its radical.
Examples: 5-androsten-3β-ylamine
or 5-androsten-3β-amine
3β-(dimethylamino)-5α-pregnan-20α-ol

(i) Ethers are named as alkoxy derivatives when another group is present that has priority for citation as suffix.
Examples: 3β-ethoxy-5α-cholan-24-oic acid
17β-methoxy-4-androsten-3-one

When no such other group is present, ethers of steroid monoalcohols may be named by stating the name of the steroid hydrocarbon radical, followed by the name of the alkyl (or aryl, etc.) radical, and lastly by "ether"; in English these three parts of the name are printed as separate words, for example, 5α-androstan-3β-yl methyl ether. For ethers of steroid polyols, the same system may be used but with the name of the steroid hydrocarbon radical replaced by the name of the polyol; for partially etherified polyols, locant(s) precede the names of the alkyl (or aryl, etc.) group(s); for example, 5α-pregnane-3β,17α,20α-triol trimethyl ether, 5α-pregnane-3β,17α,20α-triol 3,17-dimethyl ether, cortisol 21-methyl ether.

respect the house customs of the journals to which their papers are submitted.

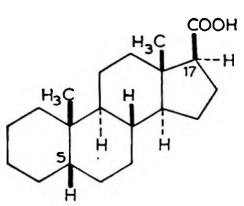
4.2. The following are examples of trivial names retained for important steroid derivatives, these being mostly natural compounds of significant biological activity.

Aldosterone	18,11-Hemiacetal of 11β,21-dihydroxy-3,-20-dioxo-4-pregnen-18-al
Androsterone	3α-Hydroxy-5α-androstan-17-one
Cholecalciferol*	9,10-Seco-5,7,10(19)-cholestatrien-3β-ol (for seco see Rule 2S-8)
Cholesterol	5-Cholesten-3β-ol
Cholic acid	3α,7α,12α-Trihydroxy-5β-cholan-24-oic acid
Corticosterone	11β,21-Dihydroxy-4-pregnene-3,20-dione
Cortisol	11β,17,21-Trihydroxy-4-pregnene-3,20-dione
Cortisol acetate	Cortisol 21-acetate
Cortisone	17,21-Dihydroxy-4-pregnene-3,11,20-trione
Cortisone acetate	Cortisone 21-acetate
Deoxycorticosterone	21-Hydroxy-4-pregnene-3,20-dione (*i.e.*, the 11-deoxy derivative of corticosterone)
Ergocalciferol*	9,10-Seco-5,7,10(19),22-ergostatetraen-3β-ol (for seco see Rule 2S-8)
Ergosterol	5,7,22-Ergostatrien-3β-ol
Estradiol-17α	1,3,5(10)-Estratriene-3,17α-diol
Estradiol-17β	1,3,5(10)-Estratriene-3,17β-diol
Estriol	1,3,5(10)-Estratriene-3,16α,17β-triol
Estrone	3-Hydroxy-1,3,5(10)-estratrien-17-one
Lanosterol	8,24-Lanostadien-3β-ol
Lithocholic acid	3α-Hydroxy-5β-cholan-24-oic acid
Progesterone	4-Pregnene-3,20-dione
Testosterone	17β-Hydroxy-4-androsten-3-one

Note. If these trivial names are used as a basis for naming derivatives or stereoisomers, the derived trivial name must make the nature of the modification completely clear and is preferably accompanied at first mention by the full systematic name. For example, in steroid papers "epi" is often used with trivial names to denote inversion at one center; the name "11-epicortisol" defines the compound fully since cortisol is already defined as the 11β alcohol; but the name "epicortisol" does not define the compound and is inadequate.

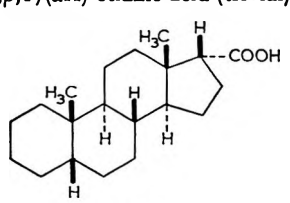
4.3. Androstane-17-carboxylic acids may be called "etianic acids," although the former (systematic) name is preferred. The orientation of the hydrogen atoms at positions 5 and 17 must in all cases be indicated as 5α or 5β, and 17(αH) or 17(βH), respectively.

Examples



(60)

5β-Androstane-17β-carboxylic acid (systematic) or 5β,17(αH)-etianic acid (trivial)



(62)

5β-Androstane-17α-carboxylic acid (systematic) or 5β,17(βH)-etianic acid (trivial)

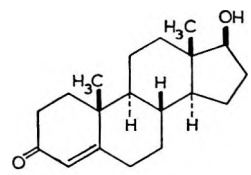
* Included in the List of Trivial Names for Miscellaneous Compounds of Biochemical Importance published by the IUPAC–IUB Commission of Biochemical Nomenclature; see, for example, IUPAC Information Bulletin No. 25, 19 (1966), or *J. Biol. Chem. 241*, 2987 (1966), or *Biochim. Biophys. Acta 107*, 1 (1965).

Stereochemical Modifications

Rule 2S-5 (Extended Version of Rule S-5)

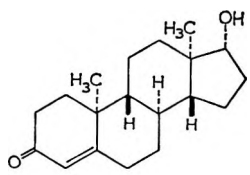
5.1. If, as for instance in a synthetic compound, there is stereochemical inversion at all the asymmetric centers whose configurations do not require to be specified in a name, the italicized prefix *ent-* (a contracted form of *enantio-*) is placed in front of the complete name of the compound. This prefix denotes inversion at all asymmetric centers (including those due to named substituents) whether these are cited separately or are implied in the name.

Examples



(64)

17β-Hydroxy-4-androsten-3-one (Testosterone)

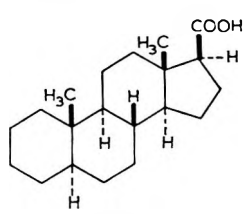


(65)

ent-17β-Hydroxy-4-androsten-3-one (*ent*-Testosterone)

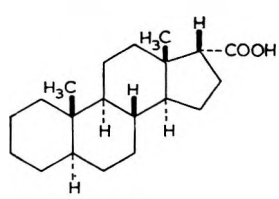
Note. When roman or arabic numerals are used to enumerate formulae, the prefix *ent-* may be used to indicate the enantiomer. Thus, *e.g.*, (65) above may be designated (*ent*-64).

5.2. If there is stereochemical inversion at a minority of the asymmetric centers whose configurations do not require to be specified in a name, the configuration of the hydrogen atoms or substituents at the affected bridgeheads, or the carbon chain (if any) at position 17, are stated by means of a prefix or prefixes α or β, each with its appropriate positional numeral, placed before the stem name laid down in the preceding rules



(61)

5α-Androstane-17β-carboxylic acid (systematic) or 5α,17(αH)-etianic acid (trivial)

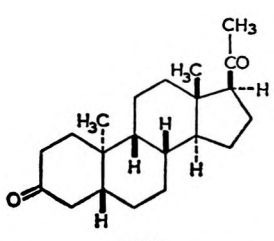


(63)

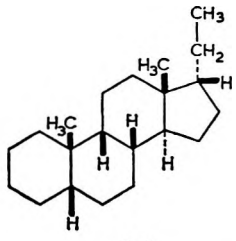
5α-Androstane-17α-carboxylic acid (systematic) or 5α,17(βH)-etianic acid (trivial)

Examples of Rule 5.2 are given in structures 66 and 67.

5.3. The enantiomer of a compound designated as in Rule 5.2 is given the same name preceded by *ent-*.



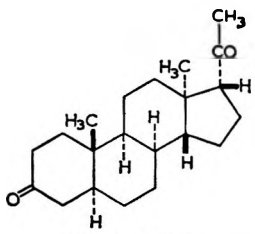
(66)
5β,9β,10α-Pregnane-3,20-dione



(67)
5β,9β,17α-Pregnane

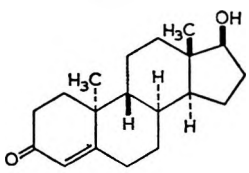
Note. This rule covers the compounds in which there is inversion at a majority, but not all, of the asymmetric centers that do not require to be specified in the name.

Examples



(68)=(*ent*-66)

***ent*-5β,9β,10α-Pregnane-3,20-dione**
(not 5α,8α,13α,14β,17α-pregnane-3,20-dione)



(69)

ent-17α-Hydroxy-13α,14β-androst-4-en-3-one
(not 17β-hydroxy-8α,9β,10α-androst-4-en-3-one)

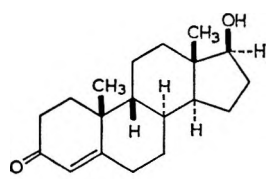
5.4. If there is stereochemical inversion at half of the asymmetric centers whose configurations are implied in the stem name of a "normal" steroid (*e.g.*, (70)), the prefixes to be specified in the name of the stereoisomer are that set that includes the number occurring first in the series 8,9,10,13,14,17 without or with the prefix *ent-* as appropriate.

5.5. Racemates, as for instance obtained by synthesis, are named by use of an italicized prefix *rac-* (an abbreviation of *racemo-*), placed before the complete name of the compound, the enantiomer chosen for naming being that required by Rules 2S-5.1 to 2S-5.4.

Example: A racemate composed of (64) and (65) (= *ent*-64) is named *rac*-17β-hydroxy-4-androsten-3-one or *rac*-testosterone.

5.6. (a) When the relative, but not the absolute, configuration of two or more asymmetric centers in a steroid derivative is known, as for instance for a compound obtained by synthesis, the 10β configuration is taken as basis for the name; or, if C-10 is not asymmetric or is absent, the lowest numbered asymmetric bridgehead is designated α (or *R*); the other asymmetric centers are then considered as α or β (or *R* or *S*) relative to that one; and the whole name is prefixed by *rel-* (italicized). Individual asymmetric centers may be referred to as α*, β*, *R**, or *S** (spoken as alpha star, R star, etc.), but these symbols are not used in the name of the compound.

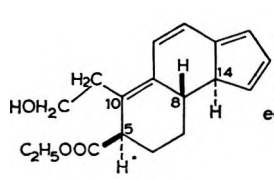
(b) When both enantiomers of known relative, but unknown absolute, configuration are prepared, they are distinguished by a prefix (+)-*rel-* or (−)-*rel-*, where the plus or minus sign refers to the direction of rotation of plane-polarized light (the wavelength, solvent, temperature, and/or concentration must be added when known to affect this sign).



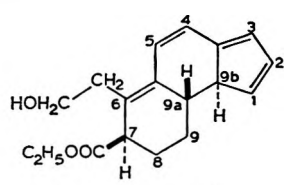
(73)

The dextrorotatory form having either this or the enantiomeric configuration would be named:

(+)-*rel*-17β-Hydroxy-8α,9β-androst-4-en-3-one

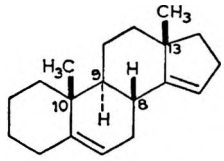
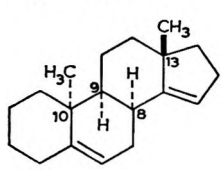
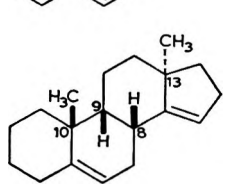


equal to



(74A) (74B)

(74A) *rel*-(Ethyl 2-hydroxy-2,3-seco-*A*-nor-5α-gona-9,11,13(17),15-tetraen-3-oate) (for seco see Rule 2S-8 and for nor see Rule 2S-7); or (74B) *rel*-[(7*R*,9a*S*,9b*S*)-Ethyl 8,9,9a,9b-tetrahydro-7*H*-cyclopenta[*a*]naphthalene-7-carboxylate]

		Configuration at asymmetric centres	Name
(70) "Normal" steroid		8β,9α,10β,13β	5,14-Androstadiene
(71) Steroid inverted at 8 and 10; "normal" at 9 and 13		8α,9α,10α,13β	8α,10α-Androsta-5,14-diene
(72) (*ent*-71) Steroid inverted at 9 and 13; "normal" at 8 and 10		8β,9β,10β,13α	*ent*-8α,10α-Androsta-5,14-diene

Note. (72) could also logically be named "9β,13α-androsta-5,14-diene"; this name might seem simpler, but it has the disadvantage that it does not indicate that (72) is the enantiomer of (71).

Note. At some stage in synthetic work on steroids, names of intermediates have to be changed from a system used in general organic chemistry to the steroid system. The names of (74A)

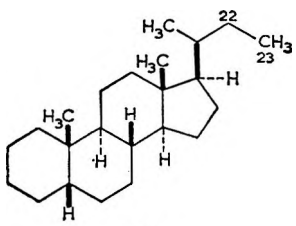
and (74B) illustrate such a change and it should be noted (i) that not merely the name but also the numbering are usually changed and (ii) that the steroid name usually avoids the need to specify the configuration at each asymmetric center. The latter factor will often indicate at what point in a synthesis the change of nomenclature is desirable.

Shortening of Side Chains and Elimination of Methyl Groups

Rule 2S-6 (Expanded from Rule S-6)

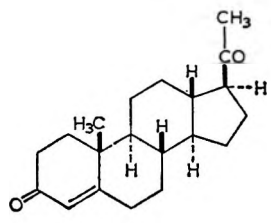
6.1. Elimination of a methylene group from a steroid side chain (including a methyl group) is indicated by the prefix "nor," which in all cases is preceded by the number of the carbon atom that disappears. When alternatives are possible, the number attached to nor is the highest permissible. Elimination of two methylene groups is indicated by the prefix "dinor."

Examples



(75)

24-Nor-5β-cholane



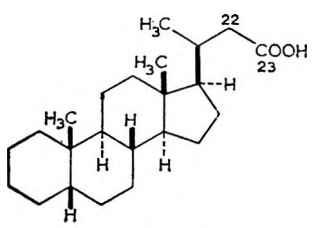
(76)

18-Nor-4-pregnene-3,20-dione

Exceptions. By Rules 2S-2.1 and 2S-2.2 the names gonane (for 18,19-dinorandrostane) and estrane (for 19-norandrostane) constitute exceptions to the above Rule 2S-6.1. The names gonane and estrane are used also as parent names for their derivatives.

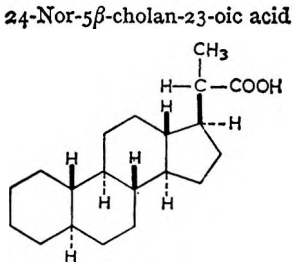
However, 18-nor- and 19-nor- are used with other trivial names, as in 19-norpregnane, 18,19-dinorspirostan, 18-norestrone.

The compound produced by shortening the C-17 side chain of pregnane is named 17-methylandrostane rather than 21-norpregnane. See also Note to Rule 2S-2.2.



(77)

24-Nor-5β-cholan-23-oic acid



(77a)

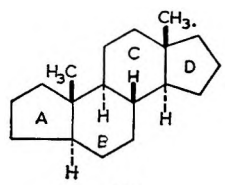
18,19-Dinor-5α-pregnane-20α-carboxylic acid

Ring Contraction or Expansion

Rule 2S-7 (Amended Version of Rule S-7)

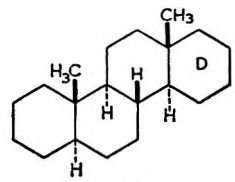
7.1. Ring contraction and ring expansion (other than insertion of atoms between directly linked bridgeheads or, when a steroid side chain is present, between C-13 and C-17) are indicated by prefixes "nor" and "homo," respectively, preceded by an italic letter indicating the ring affected. For loss or insertion of two methylene groups, "dinor" and "dihomo" are used. "Homo" and "nor," when occurring in the same name, are cited in alphabetical order.*

Examples



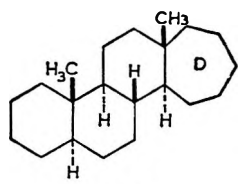
(78)

A-Nor-5α-androstane



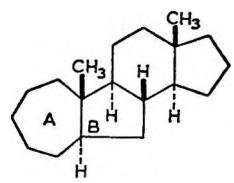
(79)

D-Homo-5α-androstane



(80)

D-Dihomo-5α-androstane



(81)

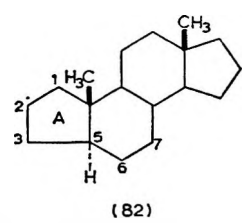
A-Homo-*B*-nor-5α-androstane

Notes. (a) By too extended use, this nomenclature can be applied to compounds whose steroid character is excessively modified. It is recommended that it be confined to steroids containing at least one angular methyl group, or a steroid C-17 side chain, or a steroidal group on ring D (*e.g.*, a spirostan); also that no more than two of the steroid rings may be altered by any combination of the operations denoted by "nor" and "homo." When these conditions are not met, general systematic nomenclature should be used.

(b) Names incorporating "homo" and "nor" are normally preferred to alternatives incorporating "cyclo" and "seco" [*cf.* example (86)].

7.2. On ring contraction, the original steroid numbering is retained, and only the highest number(s) of the contracted ring, exclusive of ring junctions, is deleted.

Example

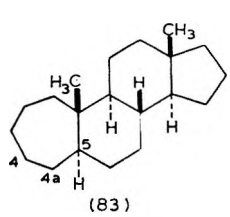


(82)

A-Nor-5α-androstane (Number 4 is omitted)

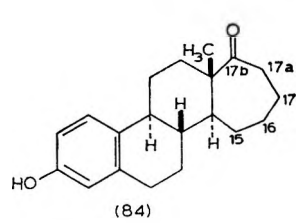
7.3. On ring expansion (other than insertion of atoms between directly linked bridgeheads or, when a C-17 side chain is present, between C-13 and C-17), the letter a (and b, etc., as necessary) is added to the highest number in the ring enlarged exclusive of ring junctions, and this letter and number are assigned to the last peripheral carbon atom in the order of numbering of the ring affected.

Examples



(83)

A-Homo-5α-androstane



(84)

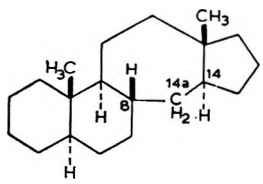
3-Hydroxy-*D*-dihomo-1,3,5(10)-estratrien-17b-one

* Alphabetical order is used for any combination of cyclo, homo, nor, and seco; they are placed immediately before the stem name and after any prefixes denoting substituents.

7.4. Ring expansion by formal insertion of a methylene group between directly linked bridgeheads is indicated as shown below. The italic capital letters denote the ring(s) affected; the locants in parentheses (which are included in the name) are those of the inserted methylene groups.

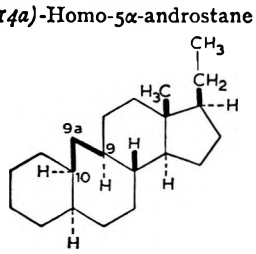
CH_2 added between	Prefix used
C-5 and C-10	*AB(10a)*-Homo
C-8 and C-9	*BC(8a)*-Homo
C-8 and C-14	*C(14a)*-Homo
C-9 and C-10	*B(9a)*-Homo
C-13 and C-14	*CD(13a)*-Homo

Examples



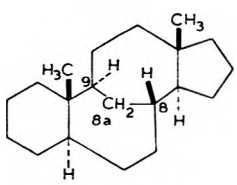
(85)

***C(14a)*-Homo-5α-androstane**



(86)

B(9a)*-Homo-19-nor-5α,10α(H)-pregnane

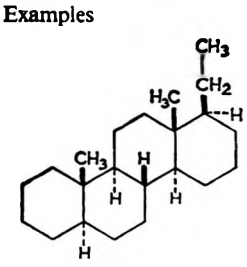


(87)

BC(8a)-Homo-5α-androstane

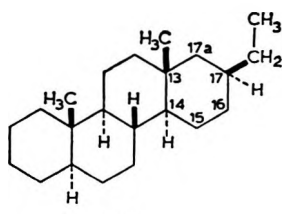
7.5. Expansion of ring D by insertion of atoms between C-13 and C-17: the names "*D*-homopregnane," "*D*-homocholane," etc., are used only for the isomer with the side chain at position 17a [*cf.* example (88)]. Isomers with the side chain at position 17 (formed by formal insertion of a methylene group between C-13 and C-17) are named as derivatives of androstane, estrane, or gonane [*cf.* example (89)]. As exceptions, furostans and spirostans into which a methylene group has been formally inserted between C-13 and C-17 are given these names with an added prefix "*D(17a)*-homo" [*cf.* example (90)].

Examples



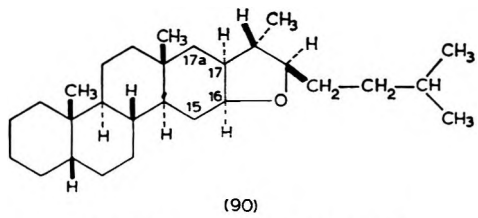
(88)

D-Homo-5α-pregnane



(89)

17β-Ethyl-*D*-homo-5α-androstane



(90)

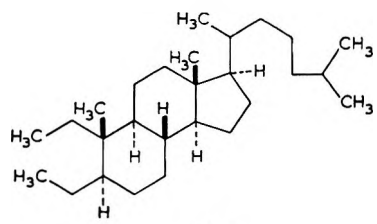
(22*R*)-*D(17a)*-Homo-5β-furostan

Ring Fission

Rule 2S-8 (Unchanged from Rule S-7.4)

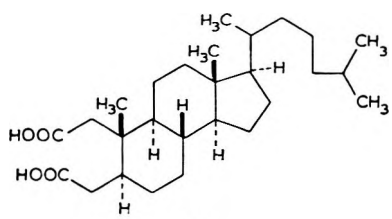
8.1. Fission of a ring, with addition of a hydrogen atom at each terminal group thus created, is indicated by the prefix "seco-," the original steroid numbering being retained.*

Examples



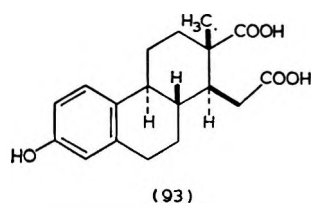
(91)

2,3-Seco-5α-cholestane



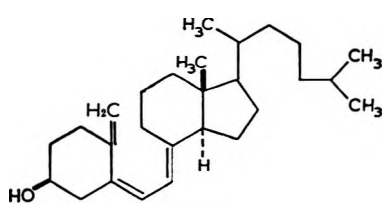
(92)

2,3-Seco-5α-cholestane-2,3-dioic acid



(93)

3-Hydroxy-16,17-seco-1,3,5(10)-estratriene-16,17-dioic acid



(94)

9,10-Seco-5,7,10(19)-cholestatrien-3β-ol (trivial name: cholecalciferol**)

* This name is preferred to 9β,19-cyclo-9,10-seco-5α,10(αH)-pregnane (see note b to Rule 2S-7.1). This skeleton is contained in some *Buxus* alkaloids.

* If more than one ring is opened, general systematic nomenclature may be preferable. The principles of note a to Rule 2S-7.1 apply also to seco steroids.

** This trivial name is retained (see Rule 2S-4.2).

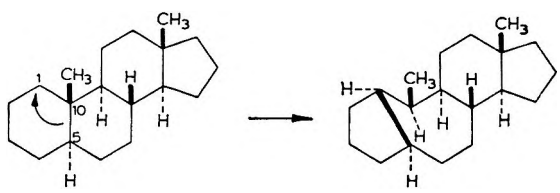
Modification by Bond Migration (*abeo* system)

Rule 2S-9 (New)

9.1. A compound that does not possess a steroid skeleton but may be considered formally to arise from a steroid by bond migration may be given the name laid down in the preceding rules for the steroid in question, to which is attached a prefix of the form *x*(*y*→*z*)-*abeo*-. This prefix is compiled as follows: A numeral denoting the stationary (unchanged) end of the migrating bond (*x*) is followed by parentheses enclosing (i) the number denoting the original position (*y*) from which the other end of this bond has migrated, (ii) an arrow, and (iii) the number (*z*) denoting the new position to which the bond has moved. The closing parenthesis is followed by *abeo*- (Latin, I go away) (italicized) to indicate bond migration. The original steroid numbering is retained for the new compound and is used for the numbers *x*, *y*, and *z*. Such of the customary letters as are necessary are added to specify the resulting stereochemistry.

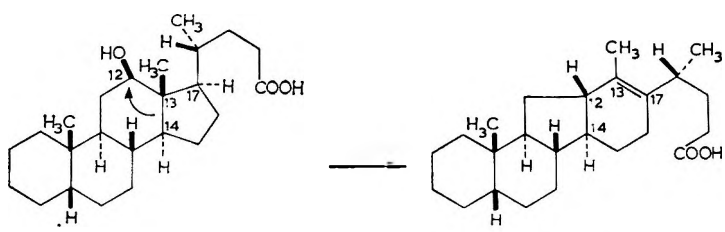
Note. The *abeo* nomenclature described in this rule is permissive, not compulsory. It is most suitable for use in discussions of reaction mechanism and biogenesis. For registration in a general (nonsteroid) compendium the general systematic names may be preferable, particularly when names of steroid type can be conveniently assigned by the homo–nor method. Differences in numbering between *abeo* names and other systematic names should be particularly noted [*cf.* example (96)].

Examples



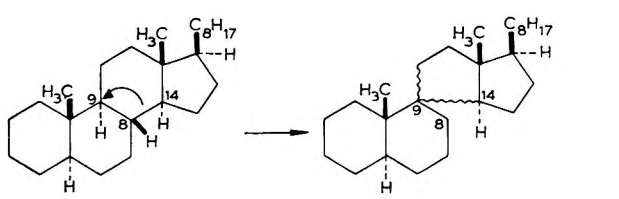
(95)

5α-Androstane — 5(10 → 1αH)*abeo*-5α-Androstane**



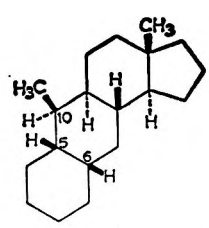
(96)

12β-Hydroxy-5β-cholan-24-oic acid — 14(13 → 12βH)*abeo*-5β-Chol-13(17)-en-24-oic acid*



(97)

5α-Cholestane — 14(8 → 9ξ)*abeo*-5α-Cholestane‡



(98)

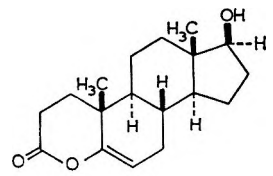
1(10 → 6βH)*abeo*-5β-Androstane (an anthrasteroid)

Hetero Modifications

Rule 2S-10 (Unchanged from Rule S-7.5)

10.1. If hetero atoms occur in the ring system of a steroid the replacement ("oxa-aza") system of nomenclature is used with steroid names and numbering (*cf.* IUPAC Rule B-4; also Introduction to IUPAC Rules C-0.6).

Example



(99)

17β-Hydroxy-4-oxa-5-androsten-3-one

Steroid Alkaloids

Rule 2S-11 (New)

11.1. When readily possible, systematic names for steroid alkaloids are derived from pregnane or some other steroid parent name. Trivial names for other steroid alkaloids are chosen so that the name for the saturated system ends in "-anine." In names for unsaturated compounds this ending is changed to "-enine," "-adienine," etc., as appropriate. When asymmetry exists at positions 8, 9, 10, 13, 14, 16, 17, 20, or 23, it is implied in the name, as set out in Table III and formulae, and divergences are designated as laid down in Rule 2S-5. Configurations at positions 5, 22, and 25 must be specified with the name. Sequence-rule symbols are used for positions numbered 20 or higher.

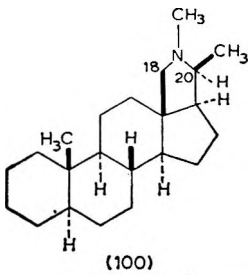
Examples

Typical examples of parent names for groups of alkaloids are given in Table II and the formulae therein. It must be noted that substitution or unsaturation may alter the *R*,*S* designations for derivatives.

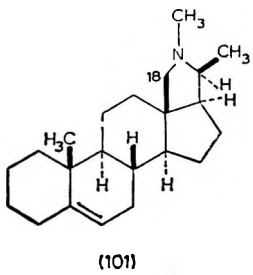
* Name according to Rules 2S-2.4 and 2S-8.1: 12α,14β-cyclo-13,14-seco-5β-chol-13(17)-en-24-oic acid.

** Name according to Rule 2S-7.4: 9αβ-methyl-*B*(9*a*)-homo-*A*-nor-5α,10α-estrane.

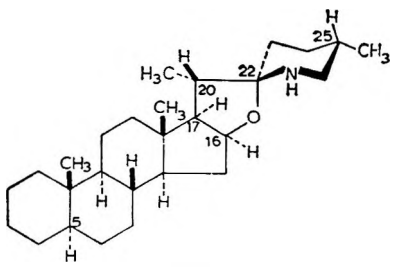
‡ The configuration at C-9, if known, is assigned by the sequence-rule procedure (Cahn *et al.*, 1966).



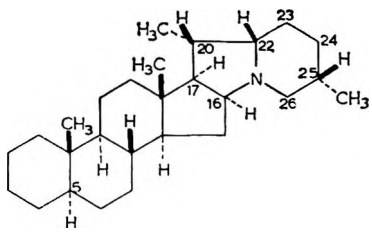
(100)
5α-Conanine*



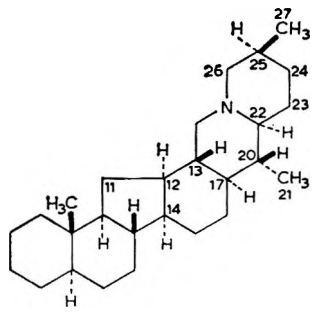
(101)
5-Conenine*



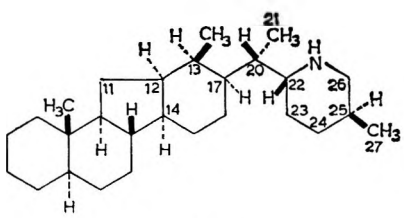
(102)
(22*S*,25*S*)-5α-Tomatanine



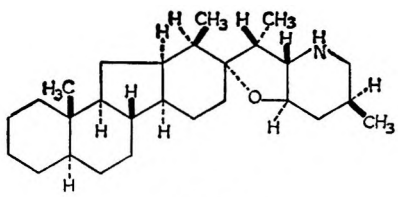
(103)
(22*S*,25*S*)-5α-Solanidanine



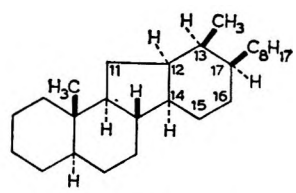
(104)
(22*S*,25*S*)-5α-Cevanine



(105)
(22*R*,25*S*)-5α-Veratranine



(106)
(22*S*,23*R*,25*S*)-5α-Jervanine



(107)
5α-Jervane**

TABLE III: Parent Names for Groups of Steroid Alkaloids[a]

Formula	Name of Parent	Stereochemistry[b] Implied in Name, as Shown in Formula	Stereochemistry to be Indicated by Sequence-Rule Prefixes (or ξ)
100	Conanine	17αH,20*S*	
102	Tomatanine[c]	16αH,17αH,20*S*	22, 25
103	Solanidanine[d]	16αH,17αH,20*S*	22, 25
104	Cevanine[e]	13βH,17αH,20*R*	22, 25
105	Veratranine[e,f]	17αH,20*S*	22, 25
106	Jervanine[e,f]	17αO, 20*R*	22, 23, 25

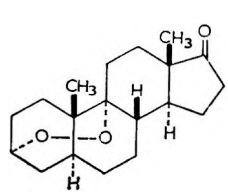
[a] Some of the names in this table were suggested in the Introduction to "Optical Rotatory Power, 1a, Steroids," Tables des Constantes, Pergamon Press, Oxford, 1965, pp 2a and 2f. [b] Additional to that at positions 8, 9, 10, 13, and 14. [c] The compounds are oxa-aza analogs of the spirostans (which are dioxa spiro compounds). Formulae are conveniently drawn analogously to those of the spirostans. [d] This group includes rubijervine and isorubijervine. [e] These structures contain a *D*-homo-*C*-nor skeleton, with the stereochemistry shown. However, they are commonly considered as 14(13→12)*abeo* structures and are numbered as such. [f] Jervanine, as defined here, is the same as veratranine except for addition of an epoxy bridge, but it is convenient to have two separate names: the veratranine skeleton [see (105)] is present in the alkaloid veratramine. It should be noted that the name 5α-jervane has been used for the rearranged hydrocarbon skeleton (107) [Fried, J., and Klingsberg, A. (1953), *J. Am. Chem. Soc. 75*, 4934], for which the *abeo*-type numbering given in (107) is here recommended.

* *Cf.* Haworth, R. D., and Michael, M. (1957), *J. Chem. Soc.*, 4973.
** See Table III, footnote *f*.

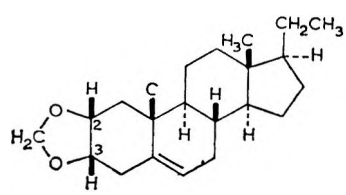
Appendix. Guide Lines for Steroids Containing Additional Rings

1. General. When additional rings are formed within, or on, a steroid nucleus, situations often arise where either the resemblance to a normal steroid is obscured or the steroid-type name becomes so complex that recourse to general systematic nomenclature is preferable. On the other hand, the general rules, with one exception, are based on that form of each component that contains the maximum number of conjugated double bonds, the whole fused system is then renumbered, and the stereochemistry must be defined separately for each chiral position; the final name resulting is then cumbrous and in a form that is often barely recognizable by a steroid specialist chemist and even less so by a biochemist or biologist. The paragraphs below give suggestions as to how general nomenclature may be modified to incorporate steroid names, but without an attempt to legislate rigidly or to cover every case. The decision whether any one compound shall receive such a modified steroid name or a general systematic name is left to authors and editors in the particular circumstances of each case. Nor are the requirements of journals and compendia or abstracts necessarily identical.

2. Rings Derived from Functional Groups. Bivalent functional groups such as –O– and –O–O– linked to two different positions, thus forming additional rings, are named by the ordinary methods of organic chemistry; for example, (108) is 3α,9-epidioxy-5α-androstan-17-one. Similarly, methylenedioxy derivatives are best named as such, *e.g.*, (109) 2α,3α-methylenedioxy-5-pregnene. In the same way, lactones and acetals formed by linkage between



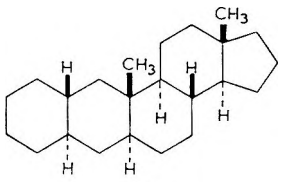
(108)



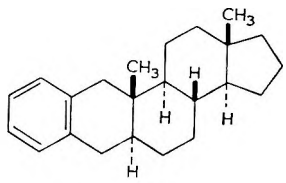
(109)

two different positions of a steroid skeleton are best named as such instead of by framing the name on the newly modified ring system.

3. Additional Carbocyclic or Heterocyclic Fused Rings. It is tempting to adapt the simple substitutive procedure for fusion of steroid nuclei with simple carbocyclic rings, particularly if the latter are saturated. Thus (110) might be named 2α,3β-tetramethylene-5α-androstane.* However, formation of additional rings by



(110)



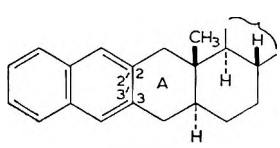
(111)

alkylene (-[CH_2]$_x$-) prefixes is not in accord with IUPAC nomenclature and is often difficult to apply when unsaturation is present. Alternatives are thus preferable.

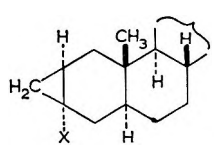
The exceptional case (Rule A-23.5) referred to above enables 2,3-benz-5α-androst-2-ene to be a name for (111), and a slight extension of the rule would allow (110) to be called 2α,3β-cyclohexano-5α-androstane. Such methods might be used in simple cases but these too become difficult when complex ring systems are fused and often when unsaturation is present in the additional component.

For a general procedure it is better to modify systematic IUPAC general practice to permit the steroid component to be cited in a reduced state, the reason why modification is necessary at all being of course the wish to keep the description of the stereochemistry as simple as possible. The suggestions below are closely similar to present practices of *Chemical Abstracts*.

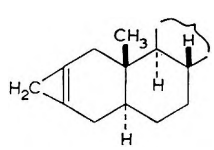
An additional carbocyclic component is cited in its most unsaturated form by its fusion name (usually ending in -o), placed in front of the name of the steroid component, and the position of fusion is indicated by numerals in brackets; for instance, benz[2,3]-5α-androst-2-ene for (111). Here note that the unsaturation of the benzo ring causes unsaturation also in the steroid component and this must be cited (-2-ene). Similarly, (112) is naphth[2′,3′:2,3]-5α-androst-2-ene; the steroid *A* ring is still considered unsaturated



(112)



(113)



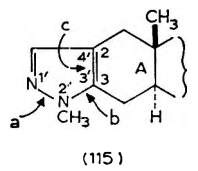
(114)

even though it may be preferred to write the naphthalene double bonds as in the formula shown; note also that the locants for the nonsteroid component receive primes, and that, when choice is possible, its locants for ring fusion are as low as possible and in the same direction as in the steroid component (*i.e.*, not 6′,7′:2,3 or 3′,2′:2,3).

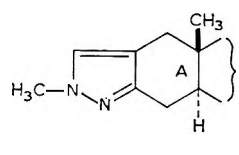
The reduced compound (110) is then 2β,3α,3′,4′,5′,6′-hexahydrobenz[2,3]-5α-androstane. Note the citation of the configuration at the new ring-junction positions and that the steroid component is now cited in its saturated state.

Two further points can be illustrated with (113). Consider first the hydrocarbon where X = H. The additional ring is cited as cyclopropa, denoting an unsaturated three-membered ring as in (114). In (114) the position of the "extra" (indicated) hydrogen must be cited as 3′*H*. Reduction of (114) to (113; X = H) adds 2α,3α-dihydro to the name, which thus becomes 2α,3α-dihydro-2′*H*-cycloprop[2,3]-5α-androstane. If X were not hydrogen but, say, OH, the hydro prefixes would still be needed to show the state of hydrogenation and the OH group would be named additionally; in such cases it is preferable to state the configuration for the OH group that is present rather than that of the H atom that has been replaced; the name then becomes 2α,3′-dihydro-2′*H*-cycloprop-[2,3]-5α-androstan-3α-ol.

The same fundamental principle can be used for heterocyclic components, but conveniently modified to accord with general nomenclature as follows: (a) the heterocyclic component is cited after the steroid component (to permit modification of the ending for salt formation, etc.), and (b) the position of fusion of the heterocyclic component is cited by letters as in the standard IUPAC and Ring Index method. Thus, (115) is 2′-methyl-2′*H*-5α-androst-2-eno[3,2-c]pyrazole; note the numbering of the pyrazole ring so that numbers for ring fusion are as low as possible; if the methyl group in (115) were replaced by hydrogen, the double bonds would



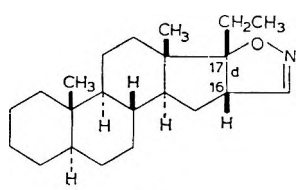
(115)



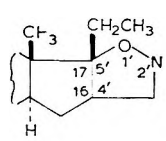
(116)

be placed in the mesomeric pyrazole ring just as in (115) so as to retain this low numbering for ring fusion. In the isomer (116) the steroid component is no longer unsaturated and is therefore cited as androstano-; the full name for (116) is 1′-methyl-1′*H*-5α-androstano[3,2-*c*]pyrazole.

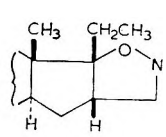
Further problems arise when ring fusion involves a quaternary carbon atom. The name for (117), for instance, could be built up as follows: to 5α-pregnane is fused an isoxazole skeleton, giving



(117)



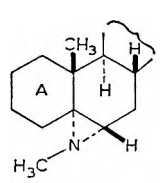
(118)



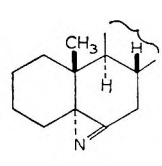
(119)

(118); into this, only one double bond can be introduced, so that one hydrogen atom must be added as indicated hydrogen, which gives a 4′β*H*- prefix and a skeleton (119). The last step, inserting the double bond, gives the full name 4′β*H*-5α-pregnano[16,17-*d*]-isoxazole, even though it appears in (117) as if the heterocyclic ring should be named as the partly hydrogenated system isoxazoline.

Not all such fusions cause all these complications. For instance,



(120)



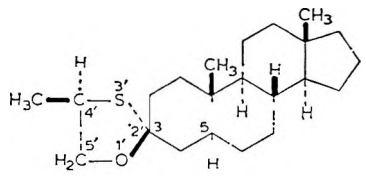
(121)

for (120) one fuses androstane to azirine, obtaining a skeleton into which one inserts a double bond as in the hypothetical compound 121; then, clearly, (120) is 1′,3′-dihydro-1′-methyl-5α-androstano[5,6-*b*]azirine.

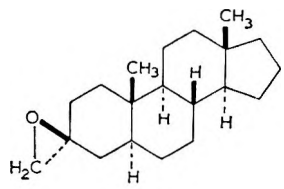
4. Stereochemistry. Stereochemistry in additional rings that lie in the approximate plane of rings A–D is cited as α or β, but in other cases by means of sequence-rule symbols.

* For simplicity, nomenclature in this Appendix is mostly described in terms of androstane, and partial formulae are to be understood accordingly. The principles, however, are general.

5. Spiro Derivatives. Spiro derivatives of steroids are named n accordance with the principles laid down in IUPAC Rules A-41, A-42, B-10, and B-11. Additional stereochemistry due to the spiro junction and substituents in the nonsteroid ring is designated by the sequence-rule procedure. Alternative names permitted by IUPAC rules are illustrated for (122) and (123).



(122)
4′*R*-Methyl-(*R*)-spiro[5α-androstane-3,2′-(1′,3′-oxathiolane)]
or 5α-androstane-3(*R*)-spiro-2′-(4′*R*-methyl-1′,3′-oxathiolane)



(123)
(3*S*)-Spiro[5α-androstane-3,2′-oxiran]
or (3*S*)-5α-androstane-3-spiro-2′-oxiran

Acknowledgment

We are indebted to the editors and publishers (Elsevier Publishing Company) of *Biochimica et Biophysica Acta* for permission to reproduce photographically the chemical structures that appeared in their publication of these tentative rules.

Phosphonic Acids and Esters. XX.[1] Preparation and Ring-Opening Reactions of α,β- and β,γ-Epoxyalkylphosphonates. The Proton Magnetic Resonance Spectra of Vicinally Substituted Ethyl- and Propylphosphonates

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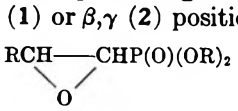
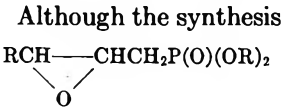
Received November 5, 1968

Diethyl (**3a**) and dimethyl (**3b**) α,β-epoxyethylphosphonates have been prepared by the epoxidation of the corresponding vinylphosphonates with *t*-butyl hydroperoxide in the presence of a basic catalyst. These epoxides fail to undergo thermal or acid-catalyzed rearrangements in contrast to the behavior of their β-substituted analogs. Both **3** and diethyl β,γ-epoxypropylphosphonate (**4**) undergo conventional hydrations, alcoholyses, and aminolyses to give α,β-disubstituted ethyl- and β,γ-disubstituted propylphosphonates, respectively. In every case, the products are formed by attack of nucleophile at the terminal carbon of the epoxide and isomerically pure products are formed. Attempted sodium borohydride reductions and Grignard reactions with **3** and **4** failed. The structures of **3** and **4** and their transformation products were established by proton magnetic resonance spectroscopy. Certain aspects of these spectra, namely, geminal β-proton nonequivalence in XCH_2–CHY–P systems and three- (P–C–O–H) and four- (P–O–C–C–H, P–C–C–C–H) bond spin–spin couplings, are discussed.

Despite their obvious potential as synthetic intermediates, relatively little attention has been directed to the preparation and reactions of dialkyl alkylphosphonates possessing an epoxide function in either the α,β (**1**) or β,γ (**2**) positions. Although the synthesis of

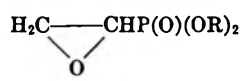


1

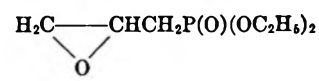


2

2 can be achieved by standard methods, *e.g.*, the Arbuzov reaction of epiiodohydrin with trialkyl phosphites,[2] the synthesis of **1** is more difficult. The formation of α-substituted **1** as by-products in the reactions of sodium dialkyl phosphonates with halomethyl ketones has been reported,[3,4] but the yields are low and a complex mixture of products (enol phosphate, β-ketoalkylphosphonate, and **1**) is formed. Similarly, α-substituted **1** may be prepared by alkaline treatment of the halohydrins formed by the addition of dialkyl phosphonates to halomethyl ketones,[4] but the slow rate of reaction and low yields limit the utilization of the reaction. To date, the most effective method for the preparation of **1** and its β,β-disubstituted analogs is the Darzens condensation of aromatic aldehydes and aryl and alkyl ketones with dialkyl chloromethylphosphonates.[5–7] The reaction is, however, ineffective for the preparation of β-alkyl and α-alkyl or aryl substituted **1**.[7] Because of our interest in the skeletal rearrangements of **1**[6,7] and the possible utilization of **1** and **2** as starting materials for the preparation of α,β- and β,γ-difunctionalized alkylphosphonates as substrates for neighboring-group participation studies,[8] we have examined alternative routes for the synthesis of **1** and certain ring-opening reactions of both **1** and **2**. The simplest examples of **1** and **2**, diethyl and dimethyl α,β-epoxyethylphosphonates (**3**), and diethyl β,γ-epoxypropylphosphonate (**4**),[2] respectively, were chosen as model compounds for these studies.



3a, R = C_2H_5
b, R = CH_3



4

(1) Part XIX: R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).

(2) B. A. Arbuzov and V. P. Lugovkin, *Zh. Obshch. Khim.*, **22**, 1193 (1952); *Chem. Abstr.*, **47**, 4872a (1953). However, the corresponding reaction with epichlorohydrin follows a different course, namely, formation of dialkyl methylphosphonate and dialkyl vinyl phosphate [V. S. Abramov and R. N. Savintseva, *J. Gen. Chem. USSR*, **37**, 2650 (1967)].

(3) G. Sturtz, *Bull. Soc. Chim. Fr.*, 2333 (1964); A. Meisters and J. M. Swan, *Aust. J. Chem.*, **18**, 159 (1956).

(4) B. A. Arbuzov, "Phosphoric Esters and Related Compounds," Chem. Soc. Special Publ. No. 8, The Chemical Society, London, 1957, pp 47–59.

(5) V. F. Martynov and V. E. Timofeev, *J. Gen. Chem. USSR*, **34**, 3383, 3950 (1964).

(6) R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.*, **88**, 1824 (1966).

(7) R. H. Churi, Ph.D. Thesis, University of Pittsburgh, 1966.

(8) R. B. Davison, Ph.D. Thesis, University of Pittsburgh, 1965; M. Gordon, V. A. Notaro, and C. E. Griffin, *J. Amer. Chem. Soc.*, **86**, 1898 (1964).

The most attractive and potentially most general route for the synthesis of **3** and its various α- and β-substituted analogs appeared to be the direct epoxidation[9] of the corresponding dialkyl vinylphosphonates, $R_2C{=}CRP(O)(OR')_2$ (**5**). The syntheses of **5** with essentially any desired combination of α and β substituents can be achieved readily by a number of procedures.[10] In view of the relative electrophilicity of the double bond of **5** and the tendencies of these compounds to undergo nucleophilic addition,[11a] *e.g.*, the Michael reaction, epoxidations with either strongly electrophilic peracids or nucleophilic oxidants (alkaline hydrogen peroxide and *t*-butyl hydroperoxide) were deemed most feasible. Attempted reaction of diethyl vinylphosphonate,[12] $H_2C{=}CHP(O)(OC_2H_5)_2$ (**6**), with buffered pertrifluoroacetic acid in methylene chloride[13] and with peracetic acid in ethyl acetate[14] under a variety of conditions failed to provide any evidence for oxidation of the double bond.[15] These reagents have been shown to be effective in the epoxidation of α,β-unsaturated carboxylic esters.[13,14]

However, reaction of **6** with the nucleophilic oxidants known[9] to be effective in the epoxidation of α,β-unsaturated ketones was successful. Treatment of **6** with methanolic hydrogen peroxide at pH 9.5–10.0[17] resulted in the formation of **3a** (10%). The structure of **3a** was established by elemental analysis and infrared (ir) and proton magnetic resonance (pmr) spectra. The ir spectrum of **3a** showed typical diethylphosphono group absorptions at 1256, 1162, and 1020 cm^{-1} and oxirane ring absorptions at 877 and 828 cm^{-1}.[18,19] The pmr spectrum of neat **3a** showed a triplet (6 H, CH_3CH_2O–, J_{HH} = 7.4 Hz) at τ 8.70, a doublet of quartets (4 H, CH_3CH_2O–, J_{PH} = 8.9 Hz[20]) at 5.90, a quartet (0.5 H, J = 3.2, 4.7 Hz) at 6.68, and a complex multiplet (2.5 H) centered at 7.08 ppm. The signals at τ 6.68 and 7.08 ppm are assigned to the oxirane ring protons; the chemical shifts of these protons are quite similar to those observed in substituted **1**[7] and simple substituted oxiranes, such as glycidonitrile.[21] It is probable that the downfield quartet represents the low field portion of the methine proton resonance; this resonance would consist of the A part of an ABCX spectrum and the observed multiplicity is correct. Additionally, the observed ^1H–^1H coupling constants (3.2, 4.7 Hz) are of the correct order for *trans*- and *cis*-vicinal coupling constants in substituted oxiranes.[7,21] However, the complexity of the 7.08-ppm multiplet precluded a trivial analysis of the spectrum.[22] The absence of vinylic groups in **3a** was established by both pmr and ir spectra.

Although repetitions of the hydrogen peroxide oxidation of **6** failed to improve the yields of **3a** to any significant extent, an acceptable yield (62%) of **3a** was obtained by the epoxidation of **6** with *t*-butyl hydroperoxide in benzene[23] using Triton B as a catalyst. In addition to **3a**, a significant amount of diethyl β-*t*-butoxyethylphosphonate (**7a**) was also formed in this

$$(CH_3)_3COCH_2CH_2P(O)(OR)_2$$

7a, R = C_2H_5
b, R = CH_3

reaction. Presumably, **7a** is formed by the Michael addition[11a] of *t*-butoxide ion, a by-product of the epoxidation reaction, to **6**, although attempts to prepare **7a** by the reactions of potassium *t*-butoxide with **6** or *t*-butyl alcohol with **6** in the presence of Triton B failed.[24] Dimethyl α,β-epoxyethylphosphonate (**3b**) was also successfully prepared from dimethyl vinylphosphonate (**8**)[26] by this route. The structure of **3b** was established by the similarity of its ir and pmr spectra to those of **3a**. As in the case of **3a**, the formation of **3b** was accompanied by the addition of *t*-butoxide ion to **8** to yield **7b**. In neither the hydrogen peroxide nor the *t*-butyl hydroperoxide preparations was any evidence obtained for the formation of products resulting from the attack of nucleophiles on the oxiranes **3a** and **3b**.

Diethyl β,γ-epoxypropylphosphonate (**4**)[2] was readily prepared by the Arbuzov reaction of epibromohydrin and triethyl phosphite. Although the reactions of trialkyl phosphites with oxiranes to yield β-alkoxyalkylphosphonates have been reported,[11b] no products from analogous reactions were observed in the formation of **4**.

Two types of reactions of these epoxyalkylphosphonates, namely, the rearrangement of **3** to oxoalkylphosphonates and the reactions of **3** and **4** with nucleophiles to produce α,β- and β,γ-difunctionalized alkylphosphonates, were of potential interest. It has been shown[6,7] that β-mono- and β,β-disubstituted α,β-epoxyethylphosphonates (**1**) undergo both thermal (170–300°) and acid- (boron trifluoride etherate in benzene) catalyzed rearrangements to yield, as a result of dialkoxyphosphono-group migration, substituted α-formylmethylphosphonates (**9**). The phosphono group migration is apparently specific in these

(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 109–123; M. S. Malinovskii, "Epoxides and Their Derivatives," D. Davey, New York, N. Y., 1965, pp 39–68.

(10) E. L. Gefter, "Organophosphorus Monomers and Polymers," Associated Technical Services, Inc., Glen Ridge, N. J., 1962, pp 3–21; W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961); T. Hullar, *Tetrahedron Lett.*, 4921 (1967); D. C. Wysocki, Ph.D. Thesis, University of Pittsburgh, 1967.

(11) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967: (a) pp 220–221; (b) p 190.

(12) (a) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947); (b) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **70**, 1971 (1948).

(13) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).

(14) D. L. MacPeek, P. S. Starcher and B. Phillips, *ibid.*, **81**, 680 (1959).

(15) However, since the completion of this work, Hunger[16] has reported the formation of **3a** and certain of its methyl substitution products in good yield by reaction of the vinylphosphonates with unbuffered pertrifluoroacetic acid. Hunger also achieved the formation of **3a** (10%) by epoxidation of **6** with permaleic acid, but found that reaction with buffered pertrifluoroacetic acid gave only trace amounts (0.8%) of **3a**.

(16) K. Hunger, *Chem. Ber.*, **101**, 3530 (1968).

(17) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., p 552.

(18) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963.

(19) Hunger[16] reports a strong oxirane absorption for **3a** at 860–870 cm^{-1}.

(20) For typical coupling constants and chemical shifts in diethyl alkylphosphonates, see M. P. Williamson and C. E. Griffin, *J. Phys. Chem.*, **72**, 4043 (1968).

(21) C. A. Reilly and J. Swalen, *ibid.*, **32**, 1378 (1960).

(22) On irradiation of the ^{31}P nucleus at 24.3 MHz, the pmr spectrum of **3a** collapsed, as expected, giving a tightly coupled ABC spectrum, typical of substituted oxiranes,[18] for the ring protons. A complete analysis of the spectrum of **3a** is in progress.

(23) N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

(24) In previous studies of epoxidations of α,β-unsaturated ketones with *t*-butyl hydroperoxide,[23] no products corresponding to the Michael addition of *t*-butoxide ion to the substrate have been reported, although the analogous addition of *t*-butyl peroxide ion to yield *t*-butyl alkyl peroxides has been observed.[23,25]

(25) D. Harman, U. S. Patent 2,508,256 (May 16, 1950); *Chem. Abstr.*, **44**, 7341i (1950).

(26) A. Ya. Yakubovich, L. Z. Soborovskii, L. I. Muler, and V. A. Faermark, *J. Gen. Chem. USSR*, **28**, 313 (1958).

reactions, since no evidence for the formation of the isomeric hydrogen migration products (**10**) was

$R_2CP(O)(OR)_2$ $R_2CHCOP(O)(OR)_2$
|
CHO

9 **10**

obtained.[6,7] Rearrangement of **3a** would correspondingly yield either diethyl formylmethylphosphonate, $OHCCH_2P(O)(OC_2H_5)_2$ (**11**), by phosphono-group migration or diethyl acetylphosphonate, $CH_3COP(O)(OC_2H_5)_2$ (**12**), by hydrogen migration. However, **3a** failed to undergo thermal rearrangement at either 210° (15 min) or 240–270° (45 min) under nitrogen.[27] In neither reaction was any evidence obtained for the formation of carbonyl compounds, although at the higher temperature some decomposition of **3a** to a polymeric material was observed. Similarly, treatment of **3a** with boron trifluoride etherate in benzene and other acidic catalysts failed to result in rearrangement; products of ring opening were isolated in all cases (*vida infra*).[28]

Evidence for a possible rearrangement of **3a** was obtained in only one instance. In the formation of **3a** by the hydrogen peroxide epoxidation of **6**, a small amount of a carbonyl-containing (ν_{CO} 1728 cm^{-1}) fraction was isolated. This material is apparently the formylmethylphosphonate **11** and not the acetylphosphonate **12** since the carbonyl frequency lies in the region typical of aldehydes;[18] ν_{CO} for **11** is reported[29] as 1726–1728 cm^{-1} and for **12**[30] as 1695 cm^{-1}. The pmr spectrum of this material was also in accord with structure **11**, showing typical $POCH_2CH_3$ resonances and a methylene doublet (J_{PH} = 21 Hz) at τ 7.03.[31,33] The formation of **11** in this reaction may be the result of rearrangement with phosphono migration of **3a** during isolation of the product or may be the result of some nonepoxidative reaction of hydrogen peroxide with **6**. The available evidence does not allow a choice between the two possibilities.

The formation of α,β- and β,γ-difunctionalized alkylphosphonates from **3** and **4**, respectively, was achieved readily by both acid-catalyzed and noncatalyzed openings of the oxirane rings. Treatment of **3a** with aqueous sulfuric acid led to the formation of the glycol **13**, while the glycol monoethers **14** and **15** were obtained by reaction of **3a** with methanolic and

$CH_2CHP(O)(OCH_2CH_3)_2$
| |
X OH

13, X = OH
14, X = OCH_3
15, X = OCH_2CH_3
16, X = NHC_6H_5
17, X = NH_2

ethanolic sulfuric acid. Similar acid-catalyzed ethanolysis of **3b** gave the glycol monoether **18**. Treatment

$CH_3CH_2OCH_2CHP(O)(OCH_3)_2$
|
OH

18

of **3a** and **3b** with boron trifluoride etherate in benzene also resulted in ethanolysis to yield **15** and **18**. Products **13–15** were formed in acceptable yields (50–62%) and in no case was any evidence obtained for the formation of the rearrangement products **11** or **12**.[35] Treatment of **3a** with aniline at 120° also resulted in ring opening with the formation of the amino alcohol **16** (90%). Attempted reaction of **3a** with aqueous ammonia under identical conditions resulted in the formation of black oils and the expected product (**17**) could not be isolated. However, **17** was obtained by reaction of **3a** with an excess of aqueous ammonia at room temperature; **17** decomposed on attempted distillation, but was successfully acetylated to give **19**.

$CH_3CONHCH_2CHP(O)(OCH_2CH_3)_2$
|
$OCOCH_3$

19

The openings of the oxirane rings of **3a** and **3b** to give **13–18** were apparently directionally specific; in no instance was evidence obtained for the formation of the isomeric products resulting from attack of nucleophile at the α carbon.[36]

Diethyl β,γ-epoxypropylphosphonate (**4**) underwent a similar series of ring-opening reactions. Acid-catalyzed hydration gave the glycol **20**,[37] while the glycol

$CH_2CHCH_2P(O)(OC_2H_5)_2$
| |
X OH

20, X = OH
21, X = OCH_3
22, X = OCH_2CH_3
23, X = NHC_6H_5
24, X = NH_2

monoethers **21** and **22** were formed by acid-catalyzed alcoholyses. The ethoxy compound **22** was also produced by the action of boron trifluoride etherate in benzene. The amino alcohol **23** was formed by reaction of **4** with aniline at 120°, while **24** was produced by reaction with aqueous ammonia at room temperature.

(27) Similarly, Hunger[16] obtained no evidence for thermal rearrangements of **3a** and its α-methyl and α,β-dimethyl analogs. However, the α,β,β-trimethyl analog readily underwent rearrangement during distillation to yield diethyl α,α-dimethylacetonylphosphonate.

(28) The failure to detect the formation of **11** in these acid-catalyzed reactions may not bar the possibility of its formation since it has been shown[25] that **11** readily undergoes an aldol trimerization followed by dehydration to yield 1,3,5-trisdiethoxyphosphonobenzene.

(29) A. I. Razumov and V. V. Moskva, *J. Gen. Chem. USSR.*, **34**, 2612 (1964).

(30) K. D. Berlin, D. M. Hellwege, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1265 (1965).

(31) The methylene resonance of a suitable model compound, $CH_3COCH_2P(O)(OC_2H_5)_2$, is observed at τ 7.03 ppm (J_{PH} = 23.0 Hz).[32] Berlin and coworkers have reported τ 7.57 ppm (J_{PH} = 5 Hz) for the methyl resonance of **12**.[30]

(32) M. Gordon, Ph.D. Thesis, University of Pittsburgh, 1965.

(33) Infrared[34] and nmr[7] studies indicate that the α-phenyl analog of **11** is totally enolic in character. However, neither the ir nor nmr spectrum of **11** provided evidence for any detectable enol content. Apparently, the stabilizing effect of the phenyl substituent is a requisite for enolization.

(34) L. E. Tammelin and L. Fagerlind, *Acta Chem. Scand.*, **14**, 1353 (1960).

(35) Churi[7] also found acid-catalyzed methanolysis of β-substituted α,β-epoxyethylphosphonates to be unaccompanied by rearrangement, but attempted acid-catalyzed hydrations resulted only in rearrangement with phosphono-group migration.

(36) The reaction products from the alcoholyses of **3a**, **3b**, and **4** were subjected to careful chromatographic separations which failed to show evidence for the presence of the isomeric glycol monoethers.

(37) Arbuzov and Lugovkin[2] have reported the isolation of the barium salt of β,γ-dihydroxypropylphosphonic acid from the hydrolysis of **4** with aqueous sodium hydroxide. To the best of our knowledge, this reaction represents the only reported transformation of the oxirane ring of either **3** or **4**.

As in the case of **17**, attempted distillation of **24** resulted in decomposition, but the compound was characterized by acetylation to give **25**. Compounds

$$CH_3CONHCH_2\underset{\displaystyle OCOCH_3}{\underset{|}{C}}HCH_2P(O)(OC_2H_5)_2$$

25

20–25 were formed in 42–88% yield. As in the reactions with **3a** and **3b**, the opening of the oxirane ring of **4** is apparently directionally specific; no evidence was obtained for the formation of the isomeric products resulting from attack of nucleophiles at the β position.

Two types of attempted reactions of **3a** and **4** failed to give the expected products. Treatment of **3a** with ethylmagnesium bromide and **4** with both methyl- and ethylmagnesium bromides resulted in the formation of the glycols **13** (50%) and **20** (42–55%), respectively No evidence for the formation of the expected monohydroxy alkylphosphonates was obtained. Apparently, the oxirane rings of **3a** and **4** are opened by reaction with magnesium bromide to yield the halohydrins,[38] which undergo hydrolysis to the glycols during product isolation. Attempted reactions of **3a** and **4** with sodium borohydride led to recovery of the starting materials.

The structures of the ring-opening products **13–25** were established by studies of their ir and prm spectra. The hydroxyl (3170–3300) and phosphoryl (1220–1230 cm^{-1}) stretching frequencies of those compounds possessing free hydroxyl groups in either the α or β positions were in the normal ranges for intra- or intermolecularly hydrogen-bonded hydroxyalkylphosphonates.[18] For example, the ranges ν_{OH} 3180–3285 cm^{-1} and ν_{PO} 1230–1232 cm^{-1} have been cited for α-hydroxyalkylphosphonates.[39] Normal[18] $POCH_2CH_3$ signals were observed at 1150–1170 and 1020–1022 cm^{-1}. The acetylated derivatives **19** and **25** showed typical[18] ester (1735–1745) and amide (1660–1682 cm^{-1}) carbonyl absorptions; the low ν_{PO} (1217–1220 cm^{-1}) values observed for these compounds indicate a probable hydrogen bonding with the amide proton.

The pmr spectra of **13–25** were in full accord with the postulated structures; parameters for selected compounds and certain of their derivatives are listed in Tables I and II. In all cases, the observed chemical shifts, peak multiplicities, coupling constants, and integrated intensities were consistent with the postulated structures. However, the extensive occurrence of overlap between the α and β proton resonances of **13–18** and the β and γ proton resonances of **20–24** with the ester (OCH_2) resonances did not allow a consistent and unequivocal confirmation of the secondary nature of the hydroxyl groups in these compounds. Confirmation was obtained by the use of either DMSO-d_6 [40] as solvent or by conversion of the alcohols into urethan derivatives (**26–30**) by reaction with trichloroacetyl isocyanate (TAI).[41] The hydroxyl resonances of all the alcohols examined were either sharp or broadened singlets in $CDCl_3$. However, in DMSO-d_6, the hydroxyl resonances of **21** and **22** were observed as doublets (J_{HCOH} = 5.4–5.5 Hz), confirming the secondary nature of the hydroxyl group.[40] A similar confirmation was obtained for **18** (*vida infra*). Corresponding hydroxyl–carbinol ^1H–^1H couplings were not observed in the spectra of the other hydroxylic compounds in DMSO-d_6; in all cases, the hydroxyl resonances were broadened, but no resolution of the multiplets was achieved.[42] The secondary nature of the alcoholic function in the latter compounds, as well as **21** and **22**, was established by examination of the spectra of their TAI derivatives.[41] For example, conversion of **14** into its TAI derivative **27** resulted in a 1.30-ppm downfield shift of the methine multiplet; the remaining resonances of **27** were shifted only slightly from the corresponding resonances of **14**. It has been shown that conversion of secondary alcohols into their urethan derivatives results in a deshielding of the carbinol proton by 1.0–1.5 ppm; a smaller deshielding (0.5–0.9 ppm) is observed for primary alcohols.[41,43] Except for the glycols **13** and **20**, no evidence for the presence of primary alcoholic functions was obtained.

Two additional aspects of the pmr spectra of these compounds merit comment. The α-proton resonances of the urethans **27** and **28** and the acetyl derivative **19** are sufficiently well resolved to permit analysis. The multiplets comprise the M parts of ABMX (X = phosphorus) spectra, indicating the geminal β protons to be nonequivalent. In similar fashion, the β protons of **18** (in DMSO-d_6) were also found to be nonequivalent. Presumably, the β protons are also nonequivalent in the remaining α,β-disubstituted ethylphosphonate derivatives (**13–17** and **26**), but the α-proton resonances of these compounds were not sufficiently well resolved to allow analysis. The geminal proton nonequivalence observed in **18**, **19**, **27**, and **28** may be the result of either restricted rotation about the C_α–C_β bond or the presence of an asymmetric center in the molecule.[44] The latter origin appears to be more likely since it was found that the spectra of both **18** and **28** were temperature independent over the range 35–145°. The appearance of the spectrum of dimethyl β-*t*-butoxyethylphosphonate (**7b**) was also indicative of geminal (in this case, α) proton nonequivalence. The α-proton multiplet of **7b** consisted of a doublet of triplets arising from coupling with the phosphorus nucleus and the two equivalent β protons; further additional small and incompletely resolved splittings consistent with different chemical shifts for the two α protons were present.[45] No comparable nonequivalence was observed in the spectrum of the corresponding

(38) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(39) C. D. Miller, R. C. Miller, and W. Rogers, Jr., *J. Amer. Chem. Soc.*, **80**, 1562 (1958).

(40) (a) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964); (b) J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).

(41) V. Goodlett, *Anal. Chem.*, **37**, 431 (1965); I. R. Trehan, C. Monder, and A. K. Bose, *Tetrahedron Lett.*, 67 (1968).

(42) Traynham and Knesel[40b] have previously noted the lack of such couplings in the spectra of alcohols possessing adjacent strong electron acceptors.

(43) Both primary (0.32 ppm) and secondary (1.67 ppm) deshieldings were observed in the spectrum of the TAI derivative (**26**) of glycol **13**.

(44) The same structural features are present in the β,γ-disubstituted propyl compounds **20–25**, **29**, and **30** and, consequently, both α- and γ-proton nonequivalence might be expected. However, no evidence for nonequivalence was obtained from the spectra of these compounds. In general, neither the β- nor γ-proton resonances were sufficiently well resolved to permit analysis. In two instances (**20** and **29**), the γ-proton resonance was resolved, consisting of a doublet of doublets, indicative of either geminal proton equivalence or a neglible chemical-shift difference between the two protons. The α-proton resonances in all cases indicated geminal proton equivalence.

(45) Double-irradiation experiments (β-proton and phosphorus irradiation) showed these small splittings to originate with the α protons.

TABLE I

PMR PARAMETERS (τ, PARTS PER MILLION) FOR DIETHYL α,β-DISUBSTITUTED ETHYLPHOSPHONATES[a]

$$\begin{matrix} CH_2CHP(O)(OCH_2CH_3)_2 \\ \quad | \quad | \\ \quad X \quad OY \end{matrix}$$

Compound X = Y =	13 OH H	26 OCONHCOCCl$_3$ CONHCOCCl$_3$	14 OCH$_3$ H	27 OCH$_3$ CONHCOCCl$_3$	15 OCH$_2$CH$_3$ H	28 OCH$_2$CH$_3$ CONHCOCCl$_3$	19[b] NHCOCH$_3$ COCH$_3$	18[c] OCH$_2$CH$_3$ H	
CH_3COP	8.67	8.62	8.68 (7.5)	8.63[d] (7.4) [1.2]	8.68	8.67[d] (7.4) [1.4]	8.63		t[e]
XCH_2–	6.05	5.73	6.32	6.40	6.37	6.17	6.33	6.48	m
–OCHP–	6.05	4.38	5.82	4.52[f] (5.0, 5.9) [11.0]	5.80	4.53[f] (6.2, 6.1) [11.5]	4.63[f] (4.8, 7.5) [10.3]	5.83	m
–$POCH_2$–	5.72	5.73	5.82	5.77	5.80	5.77	5.80 (7.6) [7.6]		dq
HO–	5.02		4.82		4.92			5.17	s
–NH–		0.12, −0.42		−0.53		−0.60	3.00		s
CH_3O–			6.60	6.62				6.39[g]	s
CH_3COC					8.78	8.85		8.80	t
CCH_2OC					6.37	6.17[h]		6.48	m

[a] All spectra were recorded in $CDCl_3$ solution. For procedural details, see Experimental Section. ^1H–^1H coupling constants are given in parentheses and ^{31}P–^1H coupling constants are given in brackets (both in hertz). [b] τ_{COCH_3} 7.87 (s), 8.03 (s) ppm. [c] Dimethyl ester. [d] Doublet of triplets. [e] Multiplicities, unless otherwise noted: s, singlet, t, triplet; dq, doublet of quartets, m, unresolved multiplet. [f] M portion of ABMX spectrum. [g] $POCH_3$ doublet. [h] Quartet.

TABLE II

PMR PARAMETERS (τ, PARTS PER MILLION) FOR DIETHYL β,γ-DISUBSTITUTED PROPYLPHOSPHONATES[a]

$$\begin{matrix} CH_2CHCH_2P(O)(OCH_2CH_3)_2 \\ \quad | \quad | \\ \quad X \quad OY \end{matrix}$$

Compound X = Y =	20 OH H	21[b] OCH$_3$ H	29[c] OCH$_3$ CONHCOCCl$_3$	22[d] OCH$_2$CH$_3$ H	30[e] OCH$_2$CH$_3$ CONHCOCCl$_3$	23[f] NHC$_6$H$_5$ H	24 NH$_2$ H	25[g] NHCOCH$_3$ COCH$_3$	
CH_3COP	8.75	8.68	8.68	8.68	8.68	8.80	8.72	8.67	t[h]
–CH_2P–	8.05 (6.4) [18.7]	8.00 (6.7) [18.3]	7.75 (6.2) [19.6]	7.97 (6.3) [18.2]	7.77 (6.8) [18.7]	7.98[i] [~16]	8.03 (6.9) [18.2]	7.95[i]	dd
XCH_2–	6.64[k] (5.2) [1.2]	6.57	6.40[k] (3.6) [1.1]	6.57[i] (5.5)	6.35	6.58	7.28	5.95	m
–CCHC–	5.98	6.25	4.65[l]	5.87	4.63[m]	6.58	5.65	4.75	m
–$POCH_2$–	5.98	5.88	5.87	5.87	5.87	6.03	5.95	5.95	dq
HO–	5.32	5.55[n]		5.67[n]		3.22	5.65[i]		s
–NH–			−0.40		−0.25	2.70[i]	5.65[i]	2.53	s
Solvent	DMSO-d_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	DMSO-d_6	DMSO-d_6	$CDCl_3$	

[a] For procedural details, see Experimental Section. ^1H–^1H coupling constants are given in parentheses and ^{31}P–^1H coupling constants are given in brackets (both in hertz). [b] τ_{OCH_3} 6.63 (s) ppm. [c] τ_{OCH_3} 6.62 (s) ppm. [d] τ_{CH_3COC} 8.82 (t), τ_{CCH_2OC} 6.46 (q) ppm. [e] τ_{CH_3COC} 8.82 (t) ppm (7.0), τ_{CCH_2OC} 6.40 (q) ppm. [f] $\tau_{C_6H_5}$ 2.70 (m) ppm. [g] τ_{COCH_3} 7.62 (s), 7.98 (s) ppm. [h] Multiplicities, unless otherwise noted: s, singlet; dd, doublet of doublets; t, triplet; q quartet; dq doublet of quartets; m, unresolved multiplet. [i] Broad doublet. [j] Multiplet. [k] Doublet of doublets. [l] Poorly resolved six-line multiplet. [m] Poorly resolved eight-line multiplet. [n] In DMSO-d_6, τ_{OH} 5.11–5.12 (d) ppm (5.4–5.5).

TABLE III
ELEMENTAL ANALYSES

Compound	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
3a	$C_6H_{13}O_4P$	40.00	7.22	17.22	39.78	7.44	17.46
3b	$C_4H_9O_4P$	31.58	5.92	20.52	31.39	6.09	20.51
7a	$C_{10}H_{23}O_4P$	50.42	9.66	13.02	50.60	9.51	12.91
7b	$C_8H_{19}O_4P$	45.71	9.05	14.76	45.88	8.89	15.01
13	$C_6H_{15}O_5P$	36.41	7.58	15.65	36.20	7.50	15.44
14	$C_7H_{17}O_5P$	39.70	8.02	14.63	39.83	7.94	14.78
15	$C_8H_{19}O_5P$	42.47	8.40	13.71	42.64	8.31	13.79
16	$C_{12}H_{20}NO_4P$	53.28	7.66	11.31	53.40	7.90	11.49
18	$C_6H_{15}O_5P$	36.41	7.58	15.65	36.49	7.73	15.80
19	$C_{10}H_{20}NO_6P$	42.70	7.12	11.03	42.94	7.31	10.87
20	$C_7H_{15}O_5P$	39.70	8.02	14.63	39.81	7.80	14.53
21	$C_8H_{19}O_5P$	42.50	8.40	13.71	42.54	8.34	13.90
22	$C_9H_{21}O_5P$	44.99	8.75	12.92	44.85	9.01	13.08
23	$C_{13}H_{22}NO_4P$	54.20	7.98	10.78	53.95	7.69	10.48
25	$C_{11}H_{22}NO_6P$	46.31	7.72	10.88	46.16	7.77	11.15

ethyl ester **7a**. Since **7b** possesses no formally asymmetric center, the α-proton nonequivalence must be the result of either restricted rotation about the C_α–C_β bond or the intrinsic asymmetry of the α carbon.[20] The former explanation is apparently correct, since in the temperature range 60–85° the additional splittings in the α-proton resonance of **7b** disappeared and at temperatures above 90° this resonance consisted of a simple doublet of triplets.

Two types of long-range ^{31}P–^1H spin–spin couplings were observed in the spectra of these compounds. The $POCH_2CH_3$ resonances of **27** and **28** consisted of triplets of doublets. The triplet splitting arises from coupling with the methylene protons, while the smaller splitting (1.2–1.4 Hz) is the result of a long-range ($^4J_{PH}$) interaction with the phosphorus nucleus. Somewhat smaller (0.3–1.2 Hz) couplings of this type have been observed previously in the spectra of ethyl esters of phosphorus acids.[20] In the spectra of **20** and **29**, the γ protons were observed to be coupled ($^4J_{PH}$ = 1.1–1.2 Hz) to the phosphorus nucleus. Although long-range ^{31}P–^1H couplings have been observed commonly in systems containing π bonds,[46] *e.g.*, HCC=CP, and hetero atoms,[20] *e.g.*, HCCOP, couplings through three sp^3-hybrid carbons (HCCCP) are rare. To the best of our knowledge, the only previous example of such a coupling was reported by Ross and Martz,[47] who observed coupling ($^4J_{PH} \leq 0.8$ Hz) between C_{19} protons and phosphorus in some 5α-phosphonocholestane derivatives.

Certain aspects of the spectrum of **18** in DMSO-d_6 were also of interest. The hydroxyl resonance appeared as a doublet of doublets as a result of coupling with the carbinol proton (J_{HCOH} = 6.9 Hz) and the phosphorus nucleus (J_{PCOH} = 10.0 Hz). Although the latter coupling is only through three bonds, to the best of our knowledge, such couplings have not been observed previously. The phenomenon is not general, since no comparable couplings were observed in the other α-hydroxy compounds examined in this study.[48] Both the nonequivalence of the β protons and J_{HCOH} were obvious in the α-proton multiplet, which comprised the M portion of an ABMXY (X = phosphorus; Y = OH) system. The resolution of this multiplet only allowed an approximate analysis, but double-resonance (X and Y decoupling) experiments permitted analysis; the couplings J_{MX}, J_{AX}, and J_{BX} were of the same order as those observed in **19**, **27**, and **28**.

The results of this study indicate that the epoxyalkylphosphonates **3** and **4** possess essentially normal oxirane reactivity and that they may be employed as synthetic intermediates for the preparation of more complex organophosphorus compounds.

Experimental Section

Pmr spectra were determined at ambient probe temperature (37°) with a Varian Associates A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Coupling constants were taken from 50-Hz sweep width spectra and are accurate to ±0.2 Hz. Unless otherwise noted, satisfactory integrated intensities were obtained for all compounds. Variable-temperature 60-MHz studies employed a V6040 variable-temperature controller. Heteronuclear decoupling experiments were performed with an NMR Specialties SD-60B heteronuclear spin decoupler with an irradiation frequency of 24.3 MHz. Homonuclear decoupling experiments were performed on a Varian Associates HA-100 spectrometer which was frequency swept in the HA mode, the field frequency being locked to the internal TMS; the irradiating frequency was provided by a Hewlett-Packard 201CR audiooscillator. Ir spectra were recorded as films or Nujol mulls on a Beckman IR-8 spectrophotometer using polystyrene calibration. Melting and boiling points are uncorrected. Results of elemental analyses are given in Table III.

Diethyl vinylphosphonate (**6**) was prepared in 67% over-all yield by reaction of ethylene bromide with triethyl phosphite,[12] followed by dehydrobromination with triethylamine in benzene.[12b] Dimethyl vinylphosphonate (**8**) [bp 45° (0.65 mm), lit.[26] bp 82–84° (3.5 mm)] was prepared in 40% over-all yield by the same sequence using trimethyl phosphite.[49,50] Triton B and *t*-butyl hydroperoxide were obtained from K and K Laboratories.

Hydrogen Peroxide Epoxidation of Diethyl Vinylphosphonate (6).—A solution of 24.6 g (0.15 mol) of **6** in 150 ml of methanol was treated with 60 ml of 30% hydrogen peroxide at room temperature. The solution was cooled in an ice bath and 75 ml

(46) For a summary of long-range ^{31}P–^1H coupling phenomena in systems of this type, see C. E. Griffin and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4427 (1967).

(47) J. A. Ross and M. D. Martz, *J. Org. Chem.*, **34**, 399 (1969).

(48) The spectra of three simple hydroxymethylphosphorus compounds [$HOCH_2P(O)RR'$, R = R' = CH_2Cl; R = CH_3, R' = CH_2Cl; R = CH_2OH, R' = OH] in DMSO-d_6 were also examined, but no evidence for the existence of J_{PCOH} was obtained. The hydroxyl resonances were broadened singlets in all cases.

(49) The previously reported[26] preparation of **8** utilized the dehydrochlorination of dimethyl β-chloroethylphosphonate.

(50) The structure of **8** was established by its pmr spectrum: τ 6.34 (d, J_{PH} = 11.1 Hz, $POCH_3$), 3.2–4.3 ppm (m, $-CH{=}CH_2$). The appearance of the vinylic multiplet is identical with that reported for **6**.[51]

(51) M. P. Williamson, S. Castellano, and C. E. Griffin, *J. Phys. Chem.*, **72**, 175 (1968).

of 1 *N* sodium hydroxide was added dropwise at a rate sufficient to maintain the pH at 9.5–10.0. After the addition was completed, the reaction mixture was stirred at room temperature for 3 hr to give a solution of pH 8.0. An additional 50 ml of 30% hydrogen peroxide was added and the pH was readjusted to 9.5 by the addition of 1 *N* sodium hydroxide. The reaction mixture was then stirred for an additional 20 hr at room temperature to give a solution of pH 7.0. This solution was poured into 100 ml of water, then saturated with sodium chloride, and extracted thoroughly with chloroform. The combined chloroform extracts were dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a 14-g residue which was fractionally distilled through a 5-in. Vigreux column to give 8 g of **6**, 1.89 g (10.4%) of **diethyl α,β-epoxyethylphosphonate (3a)** [bp 66–68° (0.2 mm), lit.[16] bp 124° (5 mm)], and 1.4 g (7.7%) of **diethyl formylmethylphosphonate (11)** [bp 89–90° (0.35 mm), lit.[52] bp 104–105° (3 mm); ir (film) 1728 (C=O), 1250 (P=O), 1162 (POC_2H_5), 1030 cm^{-1} (P–O-alkyl); pmr ($CDCl_3$) τ 8.65 (t, CH_3), 7.03 (d, J_{PH} = 21 Hz, PCH_2–), 5.87 ppm (dq, OCH_2–)].[53]

***t*-Butyl Hydroperoxide Epoxidation of Diethyl (6) and Dimethyl (8) Vinylphosphonates.**—A solution of 40% Triton B in methanol (0.84 g, 1 mmol) was added over a period of 2 hr to a mixture of 65.6 g (0.4 mol) of **6** and 20 ml (0.18 mol) of 90% *t*-butyl hydroperoxide in 200 ml of benzene at ice-bath temperatures. The reaction mixture was then allowed to warm to room temperature and stirred continuously overnight. The benzene solution was washed twice with 50-ml portions of water; the aqueous layer was saturated with sodium chloride and extracted thoroughly with chloroform. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure to give a 70-g residue which was fractionally distilled to yield 35 g of a mixture of **6** and *t*-butyl alcohol, 20 g (61.7%) of **3a**, and 10 g (23.4%) of **diethyl β-*t*-butoxyethylphosphonate (7a)** [bp 82° (0.2 mm); ir (film) 1250 (P=O), 1165 (POC_2H_5), 1020 (PO–alkyl), 880 cm^{-1} (*t*-C_4H_9O); pmr (neat) τ 8.78 [s, $(CH_3)_3CO$–], 8.72 (t, J_{HH} = 7.4 Hz, CH_3COP), 7.95 (dt, J_{HH} = 7.0, J_{PH} = 19.5 Hz, PCH_2–), 5.95 (m, CH_2OC), 5.95 ppm (dq, J_{PH} = 8.8 Hz, $POCH_2$–)].

The epoxidation of **8** was carried out by the same procedure using the same molar quantities of reactants. Distillation of the crude reaction product (58 g) gave 30 g of a mixture of **8** and *t*-butyl alcohol, 5 g (18%) of **dimethyl α,β-epoxyethylphosphonate (3b)** [bp 58° (0.4 mm); ir (film) 1250 (P=O), 1180 ($POCH_3$), 1020 (PO–alkyl), 872 and 830 cm^{-1} (oxirane); pmr ($CDCl_3$) τ 7.03 (m, 2.5, oxirane), 6.65 (m, 0.5, oxirane), 6.33 ppm (d, J_{PH} = 11 Hz, $POCH_3$)], and 20 g (53%) of **dimethyl β-*t*-butoxyethylphosphonate (7b)** [bp 85° (0.5 mm); ir (film) 1250 (P=O), 1185 ($POCH_3$), 1030 (PO–alkyl), 875 cm^{-1} (*t*-C_4H_9O); pmr (neat) τ 8.80 [s, $(CH_3)_3CO$–], 7.87 (dt, J_{HH} = 6.9, J_{PH} = 19.4 Hz, PCH_2–), 6.32 (d, J_{PH} = 11.2 Hz, $POCH_3$), 5.95 ppm (m, CH_2OC)].

Preparation of Diethyl β,γ-Epoxypropylphosphonate (4).—A mixture of 137 g (1 mol) of epibromohydrin and 166 g (1 mol) of triethyl phosphite was heated under a nitrogen atmosphere. Ethyl bromide distilled from the reaction mixture when the temperature reached 120°. The reaction mixture was held at 130° for 4 hr and then at 155° until the evolution of ethyl bromide ceased. Distillation of the reaction mixture through a 14-in. Vigreux column gave 120 g (61.9%) of **4**: bp 98° (0.6 mm) [lit.[2] bp 130–132° (11 mm)]; ir (film) 1250 (P=O), 1158 (POC_2H_5), 1020 (PO–alkyl), 868 and 838 cm^{-1} (oxirane); pmr (neat) τ 8.72 (t, CH_3COP), 7.7–8.3 (m, PCH_2–), 6.7–7.6 (m, oxirane), 6.10 ppm (dq, $POCH_2$–).

Hydration of Epoxides 3a and 4.—A solution of 3 g of the epoxide in 25 ml of water containing 6 drops of concentrated sulfuric acid was refluxed for 2.5 hr, allowed to cool to room temperature, and adjusted to pH 7.0 by the addition of aqueous sodium bicarbonate. The solution was concentrated under reduced pressure to yield a thick liquid which was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and concentrated to give a residue which was distilled to yield the product. **Diethyl α,β-dihydroxyethylphosphonate (13)** [bp 140° (0.3 mm)] was obtained in 55% yield from **3a**. **Diethyl β,γ-dihydroxypropylphosphonate (20)** [bp 142° (0.25 mm)] was obtained in 52% yield from **4**.

Alcoholysis of Epoxides 3a, 3b, and 4.—A solution of 3 g of the epoxide in 45 ml of ethanol or methanol containing 6 drops of concentrated sulfuric acid was refluxed for 1.5 hr, allowed to cool to room temperature, and adjusted to pH 7.0 by the addition of aqueous sodium bicarbonate. The mixture was then concentrated under reduced pressure to yield a thick oil (*ca.* 3.4 g) which was chromatographed on a 2 × 60 cm column of silicic acid (50 g, J. T. Baker) using *ca.* 250 ml of benzene followed by 400–500 ml of chloroform as eluents. The chloroform eluents were concentrated and distilled to yield the glycol monoethers. **Diethyl α-hydroxy-β-methoxyethylphosphonate (14)** [bp 108° (0.25 mm)] and **diethyl α-hydroxy-β-ethoxyethylphosphonate (15)** [bp 110° (0.25 mm)] were obtained from **3a**. **Dimethyl α-hydroxy-β-ethoxyethylphosphonate (18)**[54] [bp 105° (0.30 mm)] was obtained from **3b**. **Diethyl β-hydroxy-γ-methoxypropylphosphonate (21)** [bp 105° (0.16 mm)] and **diethyl β-hydroxy-γ-ethoxypropylphosphonate (22)** [bp 105° (0.2 mm)] were obtained from **4**. Compounds **14, 15, 18, 21,** and **22** were produced in 55–62% yield.

The glycol monoethyl ethers **15, 18,** and **22** were also obtained in 46–55% yield by refluxing a solution of 0.1 mol of the epoxide in 100 ml of benzene containing 0.2 mol of boron trifluoride etherate for 20 min. The reaction was washed with two 50-ml portions of water; the aqueous washings were saturated with sodium chloride and extracted with ether. The combined organic solutions were dried ($MgSO_4$) and reduced in volume to give a viscous liquid. Products were isolated by chromatography and distillation as in the preceeding experiment.

Reaction of Epoxides 3a and 4 with Aniline.—A mixture of 0.1 mol of the epoxide and 0.1 mol of freshly distilled aniline was heated in a sealed tube at 125° for 24 hr. The tube was cooled to −78° and opened, and the highly viscous reaction mixture was extracted repeatedly with hot absolute alcohol. The alcoholic extracts were then concentrated under reduced pressure to yield a pasty solid which was crystallized and recrystallized from a mixture of chloroform and ether. The products were dried under vacuum and the crystallization operations were carried out under an atmosphere of dry nitrogen because of the hygroscopic nature of the products. **Diethyl α-hydroxy-β-phenylaminoethylphosphonate (16)** [mp 95–97°; ir (Nujol) 3340–3160 (NH, OH), 1220 (P=O), 1170 (POC_2H_5), 1020 (PO–alkyl), 1600, 752, 695 cm^{-1} (C_6H_5); pmr (DMSO-d_6), τ 8.67 (t, CH_3COP), 5.4–7.1 (m, $-CH_2CH-$, $POCH_2$–, OH), 2.1–4.0 ppm (m, C_6H_5NH–)] was prepared from **3a** in 90% yield. **Diethyl β-hydroxy-γ-phenylaminopropylphosphonate (23)** [mp 91–92°; ir (Nujol) 3370–3150 (NH, OH), 1220 (P=O), 1150 (POC_2H_5), 1020 (PO–alkyl), 1598, 742, 690 cm^{-1} (C_6H_5)] was obtained from **4** in 88% yield.

Reaction of Epoxides 3a and 4 with Ammonia.—A mixture of 0.04 mol of the epoxide and 100 ml of aqueous ammonia (specific gravity 0.90) was allowed to stand at room temperature for 60 hr. The reaction mixture was concentrated under reduced pressure using a rotary evaporator to give a viscous residue. This residue was extracted with chloroform and the chloroform extracts were dried over magnesium sulfate. The products, **diethyl α-hydroxy-β-aminoethylphosphonate (17)** from **3a** and **diethyl β-hydroxy-γ-aminopropylphosphonate (24)** from **4**, were isolated as thick colorless to yellow oils by concentration of the chloroform solutions: ir (**17** and **24**, films) 3480–3160 (NH, OH), 1200 (P=O), 1158 (POC_2H_5), 1025 cm^{-1} (PO–alkyl). Both **17** and **24** decomposed on attempted vacuum distillation.

The amino alcohols were characterized by conversion into their acetyl derivatives. A solution of 1.5 g of **17** or **24** in 30 ml of acetic anhydride was refluxed for 2.5 hr. Excess acetic anhydride was removed under vacuum using a rotary evaporator to give a thick residue which was allowed to stand with 10 ml of water for 2 hr and then adjusted to pH 8.0 by the addition of saturated aqueous sodium carbonate. Water was removed under reduced pressure and the residue was extracted with chloroform.

(52) I. F. Lutsenko, M. Kirilov, and G. B. Postnikova, *J. Gen. Chem. USSR*, **32**, 257 (1962).

(53) The relative integrated intensities of the $POCH_2CH_3$ and PCH_2– resonances indicated **11** to be slightly contaminated by a $POCH_2CH_3$ system, although the structure of the contaminant could not be determined from the spectrum.

(54) Pmr (DMSO-d_6) τ 8.98 (t, CH_3COC–), 6.58 (m, $-CH_2OCH_2$–), 6.32 (d, $POCH_3$), 5.95 (m, $-CHP$–), 4.37 ppm (dd, J_{HH} = 6.9, J_{PH} = 10.0 Hz, OH). Both homo- (irradiation of 4.37 multiplet) and hetero– (24.3 MHz) nuclear decouplings resulted in the resolution of the 5.95-ppm multiplet into an analyzable eight-line pattern: J_{HOCH} = 5.1, 6.3, J_{HCOH} = 6.9, J_{PCH} = 11.1 Hz.

After drying ($MgSO_4$), the chloroform solution was concentrated and the residue distilled to yield the products. **Diethyl α-acetoxy-β-acetamidoethylphosphonate** (**19**) [bp 160° (0.25 mm); ir (film) 3300, 3080 (NH), 1745 (ester C=O), 1660 (amide C=O), 1220 (P=O), 1158 (POC_2H_5), 1018 cm^{-1} (PO-alkyl)] was obtained from **17** (30% yield from **3a**) and **diethyl β-acetoxy-γ-acetamidopropylphosphonate** (**25**) [bp 162° (0.25 mm); ir (film) 3300, 3075 (NH), 1735 (ester C=O), 1682 (amide C=O), 1217 (P=O), 1170 (POC_2H_5), 1020 cm^{-1} (PO-alkyl)] was obtained from **24** (75% yield from **4**).

Registry No.—**3b**, 19462-37-4; **7a**, 19462-38-5; **7b**, 19462-39-6; **13**, 19462-40-9; **14**, 19462-41-0; **15**, 19462-42-1; **16**, 19462-43-2; **18**, 19462-44-3; **19**, 19462-45-4; **20**, 1866-28-0; **21**, 19462-47-6; **22**, 19462-48-7; **23**, 19462-49-8; **24**, 19462-50-1; **25**, 19462-51-2; **26**, 19462-52-3; **27**, 19462-53-4; **28**, 19462-54-5; **29**, 19462-45-4; **30**, 19462-56-7.

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The Action of Hydrogen Fluoride on Nucleotides and Other Esters of Phosphorus(V) Acids[1,2]

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The action of hydrogen fluoride, both liquid and aqueous, on a number of mono- and diesters of orthophosphoric acid, two cyclic phosphates, mono and diesters of polyphosphates, phosphorofluoridate esters, and inorganic phosphates was investigated. The particular reactions which take place are found to be a function of temperature (−50 to +25°), time (0.04–28 hr), and acid concentration. A comparison of the acid-catalyzed reactions of phosphate esters in aqueous solution with the behavior of such compounds toward 60% hydrofluoric acid brings out several interesting contrasts. First, the reactions in 60% hydrofluoric acid which are described here are fast compared with reactions observed with ordinary aqueous acids. Second, in the reactions with 60% hydrofluoric acid all of the evidence points toward the conclusion that phosphorus–oxygen, rather than carbon–oxygen, bond cleavage takes place exclusively. Third, this acid is a highly specific dephosphorylating agent compared with ordinary aqueous acids. These three features of the chemical properties of hydrogen fluoride in relation to phosphorus(V) esters are correlated with information concerning the characteristics of hydrogen fluoride both as an anhydrous liquid and in concentrated aqueous solution. Since extended exposure to 60% hydrofluoric acid causes no deamination of adenine, guanine, or cytosine, a method was devised for the base analysis of ribonucleic acid (RNA) by degradation with this reagent.

Hydrogen fluoride, either as anhydrous liquid or aqueous solution (hydrofluoric acid), has been used relatively little in nucleotide chemistry in comparison with other areas of organic chemistry.[3] The structure proofs of A-3′:5′-P[4,5] and of the diastereoisomeric 2′:3′-benzylidene ribonucleosides[6] were dependent, in part, on degradations carried out with liquid hydrogen fluoride and hydrofluoric acid, respectively. Furthermore, 5-iodouridine 5′-triphosphate has been degraded with 60% hydrofluoric acid to 5-iodouridine 5′-phosphate and then to 5-iodouridine.[7]

The principal objective of this study was to investigate, in detail, the action of hydrogen fluoride on ordinary mononucleotides. The study includes, however, a broader spectrum of phosphorus compounds. It covers a number of mono- and diesters of orthophosphoric acid, two cyclic phosphates, mono- and diesters of polyphosphates, phosphorofluoridate esters, and inorganic phosphates. That the present results are of rather general interest is attested to by the fact that they already have been utilized to obtain structural information concerning the teichoic acids.[8]

Results and Discussion

Various acid-catalyzed reactions have been observed for nucleoside monophosphates in aqueous solution.

(1) (a) This investigation was supported, in part, by Public Health Service Research Grant No. CA-03870 from the National Cancer Institute and, in part, by Grant No. GB-2980 from the National Science Foundation. (b) The major portion of this paper is based on the Ph.D. dissertation of J. W. Ahrell, Washington University, St. Louis, Mo., 1965.

(2) For a brief summary of the results of this investigation, see D. Lipkin, J. W. Abrell, and B. E. Phillips, Abstracts, Seventh International Congress of Biochemistry, Tokyo, Aug 1967, No. B-57, p 631.

(3) K. Wiechert in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, pp 315–368.

(4) The abbreviations used follow: A-2′ (3′)-P, adenosine 2′(3′)-phosphate; A-5′-P, adenosine 5′-phosphate; A-2′:3′-P, adenosine 2′:3′- (cyclic) phosphate; A-3′:5′-P, adenosine 3′:5′- (cyclic) phosphate; A-5′-PF, adenosine 5′-phosphorofluoridate; ADP, adenosine 5′-diphosphate; APPA, P^1,P^2-diadenosine 5′-pyrophosphate; ATP, adenosine 5′-triphosphate; C-2′(3′)-P, cytidine 2′(3′)-phosphate; dA-5′-P, 2′-deoxyadenosine 5′-phosphate; DCC, dicyclohexylcarbodiimide; DNA, deoxyribonucleic acid; DPN, diphosphopyridine nucleotide; 2-dR-5-P, 2-deoxyribose 5-phosphate; G-2′(3′)-P, guanosine 2′(3′)-phosphate; Me A-5′-P, methyl ester of adenosine 5′-phosphate; Nam, nicotinamide; NR, nicotinamide riboside; NR-5′-P, nicotinamide riboside 5′-phosphate; NR-5′-PF, nicotinamide riboside 5′-phosphorofluoridate; RNA, ribonucleic acid; T-3′-P, thymidine 3′-phosphate; T-5′-P, thymidine 5′-phosphate; Tris, tris(hydroxymethyl)aminomethane; U-2′(3′)-P, uridine 2′(3′)-phosphate.

(5) (a) D. Lipkin, R. Markham, and W. H. Cook, *J. Amer. Chem. Soc.*, **81**, 6075 (1959); (b) D. Lipkin, W. H. Cook, and R. Markham, *ibid.*, **81**, 6198 (1959).

(6) (a) D. Lipkin, B. Phillips, and W. H. Hunter, *Tetrahedron Lett.*, No. 21, 18 (1959); (b) B. E. Phillips, Ph.D. Thesis, Washington University, St. Louis, Mo., 1961.

(7) D. Lipkin, F. B. Howard, D. Nowotny, and M. Sano, *J. Biol. Chem.*, **238**, PC2249 (1963).

(8) L. Glaser and M. M. Burger, *ibid.*, **239**, 3187 (1964).

TABLE I

DEGRADATION OF NUCLEOSIDE MONOPHOSPHATES[a]

Substrate	Reaction conditions: Time, hr	Reaction conditions: Temp, °C	Separation method[b]	Reaction products: Nucleotide, %	Reaction products: Nucleoside, %	Reaction products: Base, %	Loss, %
A-3′-P[c]	1	−23	D	42[d]	58		
A-2′(3′)-P	0.5	0	A	4	84	10	2
	28[e]	25	A			94[f]	6
A-5′-P	1	−23	A	53	43		4
	0.5	0	A	13	73	7	7
	14[e]	25	A			102[f]	
A-5′-PF	0.25	0	B	70[g]	30	Trace	
Me A-5′-P	1	0	A	63[h]	26	4	7
C-2′(3′)-P	1	0	A		96		4
	17[i]	25	Borate			86	14
G-2′(3′)-P	0.5	0	Water[j]	Trace	76	13	<11
	14[e]	25	Water[j]			96	5
U-2′(3′)-P	0.25	25	A		97		3
	2.5[i]	25	A			96	4
NR-5′-P[k]	0.5	0	Phosphate	22	52	17	9
T-3′-P	0.5	0	A	15	86		
T-5′-P	0.5	0	Carbonate	14	78		8
	1	0	Carbonate	Trace	95		<5
	4	25	Carbonate			87	13
dA-5′-P[l]	0.25	−25	C	15		85	

[a] All degradations were performed with 60% hydrofluoric acid unless otherwise noted. [b] Solvent or buffer used for separation of the components of the reaction mixtures. [c] Pure A-3′-P isomer was used. [d] 38% was pure A-3′-P, while 4% was A-2′:3′-P. [e] Actually these degradations of purine ribonucleotides to free bases are essentially complete in 1 hr at 25°. [f] Electrophoresis in borate buffer showed no trace of hypoxanthine. [g] This was unreacted A-5′-PF; no A-5′-P was present. [h] Only unchanged Me A-5′-P. [i] Sample treated with 100% liquid hydrogen fluoride. [j] Descending paper chromatography in water adjusted to pH 10.0–10.8 with ammonium hydroxide. [k] In some of the NR-5′-P degradations, an unidentified product was detected in trace amounts. [l] 2-dR-5-P was recovered from this reaction in good yield.

One of these is hydrolysis of the N-glycosidic bond;[9–11] another is deamination of heterocyclic bases;[12,13] and a third is phosphate migration from one hydroxyl to another of the sugar.[14] Table I is a summary of the results obtained in a study of the action of hydrogen fluoride on nucleoside monophosphates. It is obvious that the most striking feature of 60% hydrofluoric acid as a reagent is its remarkable specificity, even though it it is a very acidic medium with a Hammett acidity function, H_0, of −6 (25°).[15] Except with a purine deoxyribonucleotide (dA-5′-P), reaction conditions can be controlled (0°, 0.5 hr) so that N-glycosidic bond cleavage is negligible and dephosphorylation of a nucleotide to a nucleoside is essentially the only reaction observed. Its specificity is further emphasized by the finding that pure A-3′-P, for example, is *ca.* half-dephosphorylated in 1 hr at −23° with no isomerization to the 2′phosphate, even though a small amount of A-2′:3′-P is formed. Furthermore, deamination of adenine, guanine or cytosine does not take place when nucleosides derived from these bases are exposed to 60% hydrofluoric acid for periods of up to 50 hr at room temperature.

The behavior of dA-5′-P toward 60% hydrofluoric acid is an interesting contrast. Even at −25° for only 15 min, essentially compete conversion takes place into adenine and 2-dR-5-P; only a trace amount of an isomeric deoxyribose phosphate is formed. In this particular case, therefore, the rate of cleavage of the very labile N-glycosidic bond is rapid compared with the rate of dephosphorylation and the rate of phosphate migration. It is possible, nevertheless, to cleave essentially quantitatively the N-glycosidic bond in other purine and pyrimidine nucleotides (preceded by dephosphorylation) by changing reaction conditions (Table I). One such change is the use of liquid hydrogen fluoride with pyrimidine ribonucleotides. The free bases can be isolated and, in the case of the ribosides or ribotides, the free sugar can be recovered as well. Using 60% hydrofluoric acid the yield of ribose is as high as 85–90%, but with liquid hydrogen fluoride the yields are somewhat lower owing to the formation of polyriboses. Free 2-deoxyribose, on the contrary, is rapidly decomposed by 60% hydrofluoric acid even at −50° (2 hr) and it is found among the degradation products from deoxyribosides or deoxyribotides in but very small amounts at most.

The highly specific behavior of 60% hydrofluoric acid was emphasized by a study of the same acid at concentrations less than 24%. As the concentration is decreased, the degradation of nucleotides take place in a manner similar to that observed with other dilute mineral acids,[16] *i.e.*, a slow disappearance of substrate at room temperature by nonselective hydrolysis of the phosphate ester and N-glycosidic bonds in purine nucleotides. Further contrast with the selective and rapid dephosphorylating action of 60% hydrofluoric acid toward nucleotides was provided by a study of the behavior of A-5′-P in trifluoroacetic acid solutions at room temperature. The slow rate of disappearance of

(9) C. A. Dekker, *Ann. Rev. Biochem.*, **29**, 453 (1960).
(10) E. R. Garrett, *J. Amer. Chem. Soc.*, **82**, 827 (1960).
(11) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, New York, N. Y., 1963, pp 26, 141.
(12) A. Bendich in "The Nucleic Acids," E. Chargaff and J. N. Davidson, Ed., Academic Press, New York, N. Y., 1955, Vol I, p 117.
(13) H. S. Loring in ref 12, pp 191–199.
(14) (a) W. E. Cohn, *J. Amer. Chem. Soc.*, **72**, 2811 (1950); (b) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 44 (1952).
(15) H. H. Hyman and J. J. Katz in "Non-Aqueous Solvent Systems," T. C. Waddington, Ed., Academic Press, London and New York, 1965, Chapter 2.
(16) Reference 11, p 142.

TABLE II
DEGRADATION OF MISCELLANEOUS PHOSPHATES[a]

Substrate	Registry no.	Reaction conditions: Time, min	Reaction conditions: Temp, °C	Phosphorus-containing reaction products[b]
$NH_4PO_2F_2$	15252-72-9	30	0	PO_3F^{2-}, $PO_2F_2^-$ [c]
$(NH_4)_2PO_3F$	14312-45-9	30	0	Only PO_3F^{2-}
K_2HPO_4	7758-11-4	10	−50	Only PO_4^{3-}
		30	−25	PO_4^{3-}, PO_3F^{2-} [d]
		30	0	PO_3F^{2-}, trace PO_4^{3-}
$CH_3PO_4Li_2$	19375-46-3	30	0	Only PO_3F^{2-}
$(CH_3)_2PO_4Li$	2870-40-8	30	0	Only $(CH_3)_2PO_4^-$
CH_3PO_3FLi	19375-30-5	30	0	$CH_3PO_3F^-$, PO_3F^{2-}, $PO_2F_2^-$ [e]
		60	0	Only PO_3F^-

[a] The reagent was 60% hydrofluoric acid. [b] The products were separated by electrophoresis and chromatography. Detection was by the use of Hanes and Isherwood spray (see ref 45). [c] PO_3F^{2-} and $PO_2F_2^-$ were present in *ca.* a 3:1 ratio. [d] PO_4^{3-} and PO_3F^{2-} were present in *ca.* equal amounts. [e] $CH_3PO_3F^-$, PO_3F^{2-}, and $PO_2F_2^-$ were present in a ratio of *ca.* 3:2:1.

A-5′-P is indicated by the following sets of data, in which the first percentage represents the acid concentration, the second number the reaction time in hours, and the third number represents the amount of A-5′-P which disappeared: 100%, 6 hr, 45%; 90%, 7.5 hr, 37%; 80%, 7.5 hr, 21%; and 60%, 7.5 hr, 13%.[17] The only reaction products found were adenine and ribose phosphate; the absence of ribose or adenosine clearly indicated that no dephosphorylation took place. One other observation of interest was made in trifluoroactic acid as the medium. A pure sample of A-2′-P dissolved in 80% trifluoroacetic acid was allowed to stand at room temperature for 1 hr. The 2′ and 3′ isomers in approximately equal amounts were the only ultraviolet-absorbing materials recovered (90% yield) from the solution.

The inorganic phosphorus recovered from the adenylic acid degradations was identified as phosphorofluoridate. Unfortunately this observation does not contribute evidence toward any particular mechanism for the hydrogen fluoride degradation of phosphate esters, since it was observed that inorganic orthophosphate is converted rapidly into phosphorofluoridate by means of 60% hydrofluoric acid (Table II). This latter observation is particularly interesting in view of the fact that nucleotide recovered from reactions of 60% hydrofluoric acid with the adenylic and the thymidylic acids, which were interrupted short of completion, do not contain nucleoside phosphorofluoridates. Related to this latter set of observations is the behavior of A-5′-PF when treated with 60% hydrofluoric acid. A 30% yield of adenosine is obtained in 15 min at 0°, while the remainder of the substrate is recovered unchanged. It is important to note that no A-5′-P, which would result from acid-catalyzed hydrolysis of A-5′-PF, was found in the reaction mixture.

Me A-5′-P[18] is more resistant to 60% hydrofluoric acid than the corresponding monester, A-5′-P. The reaction products do not contain any A-5′-PF, methyl phosphorofluoridate, or A-5′-P; the only phosphorus-containing product which was recovered was inorganic phosphorofluoridate. Even if formed initially, they undoubtedly would have been further degraded in 1 hr at 0° (Tables I and II). The comparative stability of Me A-5′-P toward hydrofluoric acid parallels the relative kinetic stabilities of the conjugate acids of dialkyl and monoalkyl phosphates, $R_2H_2PO_4^+$ and $RH_3PO_4^+$, toward nucleophilic attack by water, even though these latter reactions involve mostly carbon–oxygen bond cleavage.[19]

Monomethyl phosphate, dimethyl phosphate, and methyl phosphorofluoridate were treated with 60% hydrofluoric acid (Table II). The qualitative results of these reactions are in agreement with the results obtained with the corresponding nucleoside derivatives. Obviously the substitution of a nucleoside residue for a methyl group does not appreciably affect the behavior of the phosphorus moieties toward 60% hydrofluoric acid.

The behavior of the two cyclic phosphates, A-3′:5′-P and A-2′:3′-P, on treatment with 60% hydrofluoric acid, is summarized in Table III. The behavior of the 3′:5′- (cyclic) phosphate was most surprising in view of the finding that the cyclic phosphate isolated from the reaction run at −23 or 0° was entirely the 2′:3′ isomer. This isomerization takes place, in all likelihood, through the conversion of A-3′:5′-P into A-3′-PF and this to A-2′:3′-P. It is obvious from the data in Table III that the C_5'-O-P structure is more rapidly attacked than the C_3'-O-P moiety, analogous to the results which were obtained in the acid-catalyzed hydrolysis of A-3′:5′-P.[5b] Also unexpected was the behavior of A-2′:3′-P. In view of the marked instability of A-2′:3′-P toward acid-catalyzed hydrolysis,[20] it was surprising to find *ca.* 50% of it still present in the reaction mixture after 1 hr. This may be due to the low concentration of the nucleophile H_2O in 60% hydrofluoric acid (see below) and to the fact that the equilibrium between A-2′:3′-P and A-2′- (and 3′-) PF, which would be formed by ring opening of A-2′:3′-P by HF, is far toward this cyclic phosphate. This latter statement is supported by three observations. First, condensation of adenosine and inorganic phosphorofluoridate by means of DCC leads to a considerable yield of A-2′:3′-P instead of A-2′- (and 3′-) PF. Second, attempted preparation of A-3′-PF by the reaction of 2,4-dinitrofluorobenzene with A-3′-P resulted in the formation of A-2′:3′-P.[21] Third, the aforementioned isomerization of A-3′:5′-P to A-2′:3′-P.

(17) The Hammett acidity function, H_0, for aqueous solutions of trifluoroacetic acid have been determined by J. E. B. Randles and J. M. Tedder [*J. Chem. Soc.*, 1218 (1955)]. They reported the following values (the first figure is the per cent concentration of acid; the second is the corresponding H_0 value): 90%, −2.3; 80%, −1.2; and 60%, −0.6.

(18) Me A-5′-P was prepared by the method described by M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 6204 (1958).

(19) J. R. Cox, Jr., and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

(20) F. H. Westheimer, *Accounts Chem. Research*, **1**, 70 (1968).

(21) R. Wittmann, *Chem. Ber.*, **96**, 771 (1963).

TABLE III

DEGRADATION OF ADENOSINE CYCLIC PHOSPHATES[a]

Substrate	Reaction conditions: Time, min	Reaction conditions: Temp, °C	Reaction products[b]: Cyclic phosphate, %	A-2′-P + A-3′-P, %	A-5′-PF, %	Adenosine, %	Loss, %
A-2′:3′-P	60	−23	57[c]	8		35	
A-3′:5′-P	60	−50	91[d]				9
	60	−23	48[c]	9	22	26	
	15	0	25[c]	8	14	50	3

[a] The degradations were carried out with 60% hydrofluoric acid. [b] All reaction mixtures were subjected to chromatography in solvent C for separation of the products. [c] A-2′:3′-P was the only cyclic phosphate present. This was demonstrated by hydroxide ion hydrolysis at room temperature. [d] 15% was A-2′:3′-P and 76% was A-3′:5′-P.

TABLE IV

DEGRADATION OF ADP AND ATP[a]

Substrate	Reaction time, min	Reaction products: ATP, %	ADP, %	A-5′-P, %	Adenosine, %	Loss, %
ADP	30			81	2	17
ATP	2[b]	50	31	22		
ATP	10[b,c]		47	36		15
ATP	60			84	4	9

[a] All reactions were carried out at −50° using 60% hydrofluoric acid. Reaction mixtures were separated by electrophoresis in citrate buffer. [b] Sodium hydroxide (1 *N*) was used for quenching the reaction mixture. [c] A trace component was present in this reaction mixture which behaved like A-5′-PF upon electrophoresis in borate buffer and chromatography in solvents B and C.

TABLE V

DEGRADATION OF APPA AND DPN[a]

Substrate	APPA	DPN	DPN
Reaction time, hr	0.5	0.5	0.5
Reaction temp, °C	−23	−25	0
Separation method	Solvent A	Citrate–borate, solvent B[c]	Phosphate, solvent B[c]
Recovery of reaction products, %[b]			
Substrate	13	18	
A-5′-P	37	30	12
NR-5′-P		35	15
A-5′-PF	39	38	29
NR-5′-PF		29	26
Adenosine	12	8	64
NR			34
Nam			13
Loss, %			
Adenine moiety		6	
Nicotinamide moiety		18	12

[a] The reagent was 60% hydrofluoric acid. [b] Recoveries for the DPN degradations were calculated separately for the adenine and nicotinamide moieties. [c] Some of the bands obtained in the electrophoretic separations were mixtures of reaction products. These were separated into pure components by subsequent chromatography of each such band in solvent B.

The behavior of polyphosphate esters on treatment with 60% hydrofluoric acid is summarized in Tables IV and V. If ADP were degraded by random nucleophilic attack of fluoride ion on either phosphorus atom, then adenosine and/or A-5′-PF would be major reaction products. Neither of these, both of which are stable under the conditions of the ADP degradation, was found in significant amount. Another possibility worth considering, however, is that the reaction may occur by elimination.[22] In this case, monomeric inorganic metaphosphate rather than "metapyrophosphate" must be the leaving group. Elimination of the latter from ADP would give adenosine and, as already indicated, this was found in only small amount.

The data for the ATP degradations are insufficient to determine whether phosphate is lost sequentially from the triphosphate chain or whether there is random attack at the central and unesterified terminal phosphorus atoms. It is certain, however, that the esterified phosphorus is not involved in the initial reaction, since little adenosine or A-5′-PF is found in the reactions run for 2, or even 10 min. Hood and Lange[23] suggested that liquid hydrogen fluoride removed phosphoryl groups sequentially from complex ethyl polyphosphates.

The reactions of APPA and DPN with 60% hydrofluoric acid (Table V) each lead to 1 mol of 5′-phosphate and 1 mol of 5′-phosphorofluoridate. This behavior is analogous to that observed when P^1,P^2-diethyl pyrophosphate was treated with liquid hydrogen fluoride.[23] These reactions are presumed to involve direct hydrofluorinolysis of the pyrophosphate bond.

No reaction takes place when A-5′-P is treated with 4 *M* potassium bifluoride solution at 0° for 0.5 hr, nor does ADP react with the saturated bifluoride in 0.5 hr at either 0° or room temperature. The highly nucleophilic character of fluoride ion[24] toward phosphorus-

(22) M. Tetas and J. M. Lowenstein, *Biochemistry*, **2**, 350 (1963).

(23) A. Hood and W. Lange, *J. Amer. Chem. Soc.*, **72**, 4956 (1950).

(24) Potassium bifluoride solution (4 *M*) contains a high concentration of fluoride ion since the equilibrium constant for the reaction, $HF_2^- \rightleftarrows HF + F^-$, is of the order of 10^{-1} (see ref 15, p 63).

TABLE VI
BASE COMPOSITION OF RNA[a]

	Yeast RNA		Calf liver RNA	
	HF degradation[b]	Methanolysis[c]	HF degradation[b]	Methanolysis[c]
Adenine	26 ± 2[d]	24.2	17 ± 1[e]	16.6
Guanine	32 ± 2	30.8	38 ± 1	36.7
Cytidine	20 ± 1	20.4	32 ± 1	31.7
Uridine	21 ± 1	22.8	13 ± 1	14.2
Unidentified		2.1		0.9

[a] Compositions are given as mole per cent of total amount of ultraviolet-absorbing material recovered. [b] These were carried out at 25° using 60% hydrofluoric acid. [c] Reference 28. [d] Average of three determinations. [e] Average of three determinations.

(V)[25-27] and these bifluoride experiments, as well as others already mentioned with hydrofluoric acid of relatively low concentrations, emphasize the point that the rapid degradation of ADP by 60% hydrofluoric acid at −50° (Table IV) is due to the highly acidic nature of the reaction medium.

A simple and rapid method was developed for determining the base composition of a polyribonucleotide by degradation of the polymer with hydrofluoric acid to purine bases and pyrimidine nucleosides. The results of these RNA degradations compare favorably with the base compositions obtained by Lipkin, *et al.*, on the same two RNA samples (Table VI) using methoxide ion catalyzed methanolysis.[28] It should be emphasized that the present analytical method has a decided advantage over others because of the fact that the hydrofluoric acid degradation is rapid and it does not bring about any detectable deamination of the heterocyclic bases over extended periods of time at room temperature. The common methods of degrading ribonucleic acids by hydrolysis with the usual acids or bases cause appreciable deamination of both aminopurines and -pyrimidines.[12,13]

DNA is degraded by 60% hydrofluoric acid in *ca.* 20 hr at room temperature to the four heterocyclic bases. In 0.5 hr, the ultraviolet-absorbing products are the two purine bases and the two pyrimidine nucleosides.

Wittmann[21] has indicated that nucleoside 5′-phosphorofluoridates are substrates for snake venom diesterase. The diesterase from *Crotalus adamanteus* effectively catalyzes the hydrolysis of A-5′-PF and NR-5′-PF to the corresponding 5′-phosphates.[29] Toward this enzyme then, which does not attack inorganic phosphorofluoridates, A-5′-PF and NR-5′-PF behave like typical phospho diesters. On the other hand, A-5′-PF does not act like a mixed acid anhydride in an appropriate system containing polynucleotide phosphorylase.[30] A-5′-PF is inactive as a substrate for this enzyme.

Mechanistic Considerations.[31]—A comparison of the acid-catalyzed reactions in aqueous solution of phosphate esters in general, and of nucleotides in particular, with the behavior of such compounds toward 60% hydrofluoric acid brings out several interesting contrasts. First, the reactions in hydrofluoric acid which are described here are fast compared with reactions observed with ordinary aqueous acids. Second, in the reactions with 60% hydrofluoric acid all of the available evidence points toward the conclusion that phosphorus–oxygen, rather than carbon–oxygen, bond cleavage takes place exclusively,[32] in contrast to the results obtained with the common aqueous acids.[19] Third, as indicated previously, 60% hydrofluoric acid is a highly specific reagent compared with ordinary aqueous acids.

Bunton, *et al.*,[33] have pointed out that methyl phosphate is hydrolyzed by halogen acids much more rapidly than by equivalent concentrations of perchloric or sulfuric acid and that this is due to the incursion of bimolecular reactions at carbon involving halide ions and the neutral or conjugate acid species. It should not have been too surprising to find, therefore, that phosphate esters are rapidly degraded by hydrogen fluoride. Although fluoride is a poor nucleophile toward saturated carbon, it is an unusally powerful nucleophile toward phosphorus(V) as already mentioned. Furthermore, because 60% hydrofluoric acid is a very strongly acidic medium,[15] it is an effective catalyst for the degradation. Regardless of the particular entity, or entities, responsible for the acidity, it is likely that in solutions of phosphate esters in 60% hydrofluoric acid there are present a variety of multiply protonated species or species hydrogen bonded to two or more HF molecules.

It is interesting to make a more quantitative comparison of the rates of degradation of phosphate esters by 60% hydrofluoric and 10 *M* perchloric acids, since both have approximately the same H_0.[34] The half-life of methyl phosphate in 10 *M* perchloric acid at 100° is *ca.* 9×10^3 sec.[33] By contrast, the half-life of A-5′-P in 60% hydrofluoric acid is *ca.* 4×10^3 sec at −23° (Table I). At 0°, furthermore, the half-life of A-5′-P, T-3′-P, or T-5′-P is calculated to be *ca.* 6×10^2 sec, assuming disappearance of phosphate ester by a first-order reaction. These data serve to emphasize the rapidity of the dephosphorylating action of 60% hydrofluoric acid on phosphate monoesters.

The fact that only phsophorus–oxygen bond cleavage

(25) I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 508 (1953).

(26) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4393 (1961).

(27) (a) W. Feldman, *Z. Anorg. Allg. Chem.*, **338**, 235 (1965); (b) R. E. Mesmer, *J. Inorg. Nucl. Chem.*, **28**, 691 (1966).

(28) D. Lipkin, J. S. Dixon, and P. T. Talbert, *J. Amer. Chem. Soc.*, **83**, 4772 (1961).

(29) A diesterase from Russell Viper venom (CalBiochem, Los Angeles) also catalyzes the hydrolysis of A-5′-PF to A-5′-P.

(30) We are indebted to Dr. Audrey Stevens, University of Maryland Medical School, Baltimore, Md., for a sample of this enzyme.

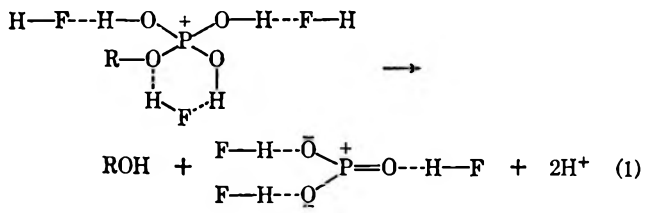
(31) Mechanistic interpretations are based on rate comparisons which are usually only single points on rate curves. The limitations inherent in this approach are realized, but it is believed that the conclusions reached are of significance.

(32) A compound such as a 5′-fluoro-5′-deoxynucleoside, which would be produced if there were carbon–oxygen bond cleavage, was not found in any of the reaction mixtures resulting from the action of 60% hydrofluoric acid on nucleotides. Furthermore, it has been demonstrated[5b] that dephosphorylation of A-2′(3′)-P by means of liquid hydrogen fluoride does not cause a change in the configuration of $C_{2'}$ (or $C_{3'}$) in the ribose moiety of the nucleotide.

(33) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

(34) H_0 for 10 *M* perchloric acid is *ca.* −6.2 [K. Yates and H. Wai, *J. Amer. Chem. Soc.*, **86**, 5408 (1964)]. Sulfuric acid has an H_0 (−6) equivalent to that of 60% hydrofluoric acid at a concentration of 72% [H. H. Hyman, M. Kilpatrick, and J. J. Katz, *ibid.*, **79**, 3668 (1957)].

is observed in the hydrofluoric acid reactions also may be explained by the highly nucleophilic character of fluoride toward phosphorus(V) compared with carbon. In 5 *M* perchloric acid solutions, the rate constant for the hydrolysis of methyl phosphate by phosphorus–oxygen cleavage is about one-half the constant for the carbon–oxygen cleavage reaction.[33] It is reasonable to assume that in the presence of fluoride the rate of the carbon–oxygen cleavage reaction becomes relatively negligible. However, another possible explanation of the observations that phosphate esters in 60% hydrofluoric acid solution always react by phosphorus–oxygen cleavage and that the reactions are rapid is that unimolecular deomposition of the highly protonated and hydrogen-bonded phosphate takes place to give monomeric inorganic metaphosphate (eq 1). The



solvated metaphosphate is then rapidly converted by fluoride into phosphorofluoridate. Monomeric inorganic metaphosphate has been suggested as an intermediate in reactions of monoesters of phosphoric acid,[19,22,33,35-37] but not in reactions under highly acidic conditions. The HF-solvated monoester on the left-hand side of the above equation is analogous to the water-solvated structure proposed by Westheimer, *et al.*,[35] as an intermediate species in the rapid hydrolysis of the monoanion, $RHPO_4^-$, *via* a metaphosphate intermediate.

In contrast, it is presumed that reactions which would lead to the formation of a monomeric metaphosphate *ester*, $ROPO_2$, as an intermediate are not favored and are slow compared with direct nucleophilic attack on phosphorus by fluoride. This statement is supported by facts such as the following: (1) A-5′-P is converted by 60% hydrofluoric acid into adenosine and inorganic phosphorofluoridate, but not to A-5′-PF; (2) diesters of phosphoric acid such as Me A-5′-P or dimethyl phosphate are degraded slowly by 60% hydrofluoric acid compared with the corresponding monoesters A-5′-P and methyl phosphate; and (3) ADP and ATP are degraded more rapidly than APPA or DPN by 60% hydrofluoric acid.

There remains unexplained the unusual specificity of the interaction of nucleotides with 60% hydrofluoric acid. As pointed out previously, dephosphyorylation in this highly acidic medium obviously has become a rapid reaction compared with such reactions as hydrolysis of N-glycosidic bonds (except in the purine deoxyribosides); deamination of heterocyclic bases; and phosphate migration. It is worth noting that 60% hydrofluoric acid is 37 *M* in HF and only 27 *M* in H_2O, in contrast to 10 *M* perchloric acid which is 32 *M* in H_2O. Furthermore, HF exerts a powerful effect in reducing the thermodynamic activity of H_2O in HF–H_2O mixtures.[38,39] Some of this specificity, therefore, could be explained on the basis of equilibria. On the other hand, the explanation may lie, in large part, in the fact that, since the concentration of the nucleophile H_2O is very small in the strongly acidic medium, 60% hydrofluoric acid, hydrolytic reactions consequently are relatively slow.

(35) (a) W. W. Butcher and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2420 (1955); (b) J. Kumamoto and F. H. Westheimer, *ibid.*, **77**, 2515 (1955).

(36) D. M. Brown and N. K. Hamer, *J. Chem. Soc.*, 1155 (1960).

(37) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4400 (1961).

Experimental Section

Whatman No. 1 or No. 3MM filter paper was used in descending paper chromatography. The solvent systems used for developing chromatograms, prepared on a volume basis, follow: 1-butanol–acetic acid–water, 4:1:1 (solvent A);[40] isopropyl alcohol–water, 80:20 (solvent B); isopropyl alcohol–water, 70:30, with an ammonia atmosphere (solvent C);[41] *t*-butyl alcohol–water, 80:20 (solvent D); water saturated with ammonium sulfate–1 *M* sodium acetate–isopropyl alcohol, 80:20:2 (solvent E).[42]

Paper electrophoreses were performed using apparatus and techniques that already have been adequately described.[43] The following buffers were used: 0.1 *M* ammonium formate–formic acid, pH 3.5; 0.1 *M* sodium acetate–acetic acid, pH 5.1; 0.05 *M* citric acid plus 0.01 *M* sodium borate, adjusted to pH 5.1 with 5 *M* sodium hydroxide; 0.05 *M* sodium citrate–citric acid, pH 5.2; 0.1 *M* sodium metabisulfite, adjusted to pH 5.5 with 5 *M* sodium hydroxide;[44] 0.05 *M* sodium phosphate, pH 7.2; 0.05 *M* sodium borate, pH 9.2; 0.05 *M* potassium bicarbonate, adjusted to pH 9.2 with 5 *M* potassium hydroxide; 0.05 *M* sodium carbonate–sodium bicarbonate, pH 10.2; and 0.1 *M* ethylenediamine plus 0.005 *M* sodium borate, adjusted to pH 11 with 5 *M* sodium hydroxide.

Ultraviolet-absorbing materials on paper chromatograms and electrophoretograms were detected visually and photographically by a method which already has been described.[5a] Three sprays also were used as needed: the Hanes and Isherwood reagent for phosphates;[45] periodate and benzidine sprays for vicinal glycol groups;[46] and a cysteine–sulfuric acid solution to detect the deoxyribose moiety.[47]

The components of reaction mixtures generally were identified by appropriate combinations of paper chromatography, paper electrophoresis, and ultraviolet (uv) spectroscopy.[48] R_f and M_R values not readily available in the literature are summarized in Table VII. Special chemical methods which were needed to complete identification of some products are indicated where necessary.

Charcoal, acid washed as previously described,[49] was partially deactivated with 2-octanol.[50] This charcoal will be referred to as charcoal A. For some experiments charcoal A was further deactivated by neutralization with 6 *N* ammonium hydroxide. The neutralized charcoal was then washed five times with water

(38) (a) J. H. Simons in "Fluorine Chemistry," J. H. Simons, Ed., Academic Press, New York, N. Y., 1950, p 249; (b) P. A. H. Wyatt *Discussions Faraday Soc.*, **24**, 167 (1957).

(39) Chemical evidence in support of the view that the thermodynamic activity of H_2O in 60% hydrofluoric acid is very low is provided by the fact that H_2PO_2F, A-5′-PF, and methyl phosphorofluoridate are not hydrolyzed to H_3PO_4, A-5′-P, and methyl phosphate, respectively, in 60% hydrofluoric acid (see Tables I and II). The half-life of PO_2F^{2-} in 0.4 *M* HCl at 39° is 18 min.[36] Nevertheless, the thermodynamic activity of H_2O cannot be negligible, since $PO_2F_2^-$ is converted rather rapidly into PO_4F^{2-} in 60% hydrofluoric acid at 0° (Table II).

(40) G. D. Dorough and D. L. Seaton, *J. Amer. Chem. Soc.*, **76**, 2873 (1954).

(41) R. Markham and J. D. Smith, *Biochem. J.*, **52**, 552 (1952).

(42) R. Markham and J. D. Smith, *Nature*, **168**, 406 (1951).

(43) R. Markham in "Modern Methods of Plant Analysis," K. Paech and M. V. Tracey, Ed., Springer-Verlag, Berlin, 1955, Vol. IV, pp 278–288.

(44) Addition of a small amount (0.01–0.1%) of sodium (ethylenedinitrilo)-tetraacetate to this buffer increases considerably its stability toward air oxidation.

(45) C. S. Hanes and F. A. Isherwood, *Nature*, **164**, 1107 (1949).

(46) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(47) J. G. Buchanan, *Nature*, **168**, 1091 (1951).

(48) Details of the methods used for the separation and unambigous identification of specific components of reaction mixtures are discussed by J. W. Abrell.[1b] They are too extensive to be repeated here.

(49) D. Lipkin, P. T. Talbert, and M. Cohn, *J. Amer. Chem. Soc.*, **76**, 2871 (1954).

(50) C. J. Threlfall, *Biochem. J.*, **65**, 694 (1957).

TABLE VII
CHROMATOGRAPHIC AND ELECTROPHORETIC MOBILITIES[a]

Compound	Chromatography				Electrophoresis				
	Solvent A	Solvent B	Solvent C	Solvent D	Solvent E	Formate, pH 3.5	Acetate, pH 5.1	Phosphate, pH 7.2	Bicarbonate, pH 9.2	Borate, pH 9.2
A-5′-PF	0.22	0.96	0.69	0.43	2.20	1.00	0.69	0.86	0.66	0.84
NR-5′-PF			0.39				0.21			0.53
H_2PO_3F	1.15	1.39	0.98	1.09		1.24	1.38		1.11	1.18
HPO_2F_2	4.02	1.43	0.97	5.60		1.46	1.38		1.00	1.20
$(CH_3)H_2PO_4$	1.84	1.81	0.98	1.79		1.06	1.01		0.97	
$(CH_3)HPO_3F$	2.87	3.08	2.35	4.95		1.24	1.01		0.87	
$(CH_3)_2HPO_4$		2.79	1.80			1.12	1.01		0.79	

[a] Chromatographic mobilities for A-5′-PF and NR-5′-PF are given relative to adenosine. The electrophoretic mobilities for these compounds are given relative to A-5′-P. All other mobilities are given relative to inorganic orthophosphate.

and dried in air at 80° (16 hr). This charcoal will be referred to as charcoal N.

The 60% aqueous hydrofluoric acid was a technical grade obtained from Baker and Adamson. Its freezing point was *ca.* −55 to −60°. Whenever liquid hydrogen fluoride was used as a reagent, it was drawn directly from a tank as a liquid into a polyethylene centrifuge tube chilled in an ice bath. No particular precautions were taken to keep the liquid anhydrous.

Hydrofluoric Acid Degradations. A. General Procedures.—A general procedure was developed for the degradation of various substrates by 60% hydrofluoric acid. The weighed substrate was transferred to a polyethylene centrifuge tube of appropriate size (2 ml for 2–15-mg samples). Hydrofluoric acid, cooled to the temperature[51] at which the reaction was to be run, was added to the sample by means of a polyethylene capillary pipet. All substrates dissolved immediately on addition of the acid (150–300 μl). The reaction was quenched by addition of sufficient saturated lithium hydroxide solution (*ca.* 5 *M*) to neutralize 75–80% of the hydrofluoric acid. Care was taken to avoid an appreciable rise in the temperature of the reaction mixture during this neutralization step. The reaction mixture then was brought to pH ~7 with solid lithium carbonate. After removal of the supernatant, the lithium fluoride precipitate was washed four times with small volumes of water. The supernatant and washings were combined and concentrated to *ca.* 0.5 ml. This solution was subjected to either paper chromatography or paper electrophoresis. The uv-absorbing bands which developed were eluted. In some experiments non-uv-absorbing areas were eluted for the inorganic phosphate or sugar. After spectroscopic properties of the eluents were determined, the samples were concentrated to *ca.* 0.5 ml for further examination.

Modifications of the above general procedure which were used are as follows. First, the guanylic acid degradations were quenched and neutralized with calcium hydroxide and calcium carbonate, respectively. The calcium fluoride precipitate then was washed with 0.1 *N* sodium hydroxide. Second, with the thymidylic acids, 1 *N* ammonium hydroxide washes were substituted for the water washes. Third, in all degradations involving the NR moiety, special care was taken during the neutralization to ensure that the pH did not exceed 6.5. Fourth, the neutralization procedure for some of the ATP degradations was changed to avoid coprecipitation of lithium fluoride and the substrate or ADP. The cold reaction mixture was partially neutralized with 850 μl of cold 5 *M* sodium hydroxide. After 50 mg of charcoal A was added, the mixture was brought to pH 7 with solid sodium carbonate. The charcoal then was washed four times with 0.5-ml portions of water. The combined supernatant and washings accounted for less than 5% of the original uv absorbance of the substrate. The charcoal was eluted with ten 1-ml portions of 50% ethanol. This eluate was concentrated to 0.5 ml prior to separation of the reaction products.

A general procedure for the degradation of nucleotides by liquid hydrogen fluoride already has been reported.[5b]

B. Ribonucleic Acids.—A 9–11-mg sample was treated with 200 μl of hydrofluoric acid for 3 hr at room temperature, cooled in an ice bath, quenched with 2 ml of saturated lithium hydroxide solution, and neutralized to pH 7.5 with lithium carbonate. After the supernatant was decanted, the lithium fluoride precipitate was washed four times with 0.5–0.75-ml portions of water. The residual solid is solid I. Washings and supernatant were combined and evaporated to dryness. The resulting residue (solid II) was washed five times with 0.25–0.5-ml portions of water. The washings were transferred to a 2-ml volumetric flask and diluted to the mark with water.

The following operations were done without interruption. A 500-μl portion of the above solution of reaction products was subjected to electrophoresis (ethylenediamine buffer, 2.25 hr at a gradient of *ca.* 40 V/cm) on a 20 × 60 cm doubly acid-washed paper (S. and S. Green Ribbon, Grade 589). Relative to adenine, the other three products have the following mobilities: guanine, 1.25; cytidine, 1.55; and uridine, 2.29. After electrophoresis the paper was dried in an oven at 80°. It was removed from the oven as soon as it was dry because continuing exposure to heat causes the paper to turn yellow. The four products, as well as two blanks, were eluted into 10-ml volumetric flasks—guanine and one blank with 0.1 *N* hydrochloric acid, the other three components and the second blank with water.

(51) Temperatures below 0° were maintained (±1°) by addition of Dry Ice to an acetone or propanol-2 bath.

Guanine was recovered quantitatively from solid I and the residue remaining after the washing of solid II by solution and reprecipitation of the lithium fluoride. The residues, in a polyethylene test tube, were dissolved in 6 *N* hydrochloric acid and precipitated by neutralization with 5 *N* ammonium hydroxide. Solution of the lithium fluoride and its reprecipitation were repeated four times. All supernatants were placed in a 25-ml flask and diluted to the mark with water. Spectrophotometric measurements were made on all solutions.

The average recovery of optical density units from the hydrofluoric acid degradations was 80%. In order to calculate this value, the optical density units per milligram of RNA sample were determined by subjecting a sample to complete hydrolysis with 1 *N* potassium hydroxide and then measuring the optical density of the neutralized hydrolysate at 260 mμ.

C. 2-Deoxyribose 5-Phosphate from Deoxyadenosine 5′-Phosphate.—A sample of dA-5′-P (162 mg, 465 μmol) was degraded with 2 ml of hydrofluoric acid (−25°, 15 min). The reaction tube was cooled in a Dry Ice bath before neutralization to pH 8 with 20 ml of a saturated lithium hydroxide solution. After centrifugation, the supernatant was decanted and the lithium fluoride precipitate was washed five times with 5-ml portions of water. The supernatant and washings were combined and concentrated to approximately 10 ml. To the concentrate 4.5 g of charcoal N was added to adsorb adenine and unchanged dA-5′-P. This mixture was centrifuged and, after removal of the supernatant, the charcoal was washed three times with 2-ml portions of water. The supernatant and washings were combined and concentrated. A sample of this solution, when subjected to electrophoresis in formate buffer, was shown to contain one major and three minor components which did not absorb in the uv. The major component was identified as 2-dR-5-P, while two of the three minor components were identified as 2-deoxyribose and inorganic phosphorofluoridate. The other component, which was present in trace amounts moved 1.17 times as fast as 2-dR-5-P in the formate buffer and was developed by both the deoxyribose and phosphate sprays.

To the concentrated solution containing 2-dR-5-P, 2-deoxyribose, inorganic phosphorofluoridate, and the trace amount of an isomerized deoxyribose phosphate, 1 ml of a saturated barium acetate solution was added. The precipitate which formed immediately was discarded after it was washed twice with cold water. The supernatant and washings were combined and mixed with an equal volume of methanol. The resulting precipitate was collected, washed three times with methanol, and dried in a vacuum desiccator. This solid contained 2-dR-5-P and the other deoxyribose phosphate. A portion of this solid (7 mg) in 1 ml of water was mixed with 3 mg of sodium sulfate. The resulting supernatant was combined with 400 μl of 0.1 *M* sodium metaperiodate. The mixture was allowed to react for 1.5 hr in the dark and then sodium borohydride (114 mg, 300 μmol) was added to the oxidized solution. After 16 hr at room temperature, the reaction mixture was brought to pH 6 by the addition of 3 *N* sulfuric acid. The residue obtained after evaporation of this mixture to dryness was washed three times with 0.5-ml portions of cold water. A saturated solution of barium acetate was added dropwise to the combined washings until precipitation ceased. The supernatant obtained by centrifugation was passed through a column containing 4 ml of Dowex 50 (H^+). The effluent from the column was concentrated and subjected to chromatography, together with an authentic sample of β-hydroxyethyl phosphate,[62] in solvents A and C and to electrophoresis in bicarbonate, formate, and acetate buffers. The behavior of the major reaction product was identical with that of known β-hydroxyethyl phosphate in all of the systems.

D. Nicotinamide Riboside 5′-Phosphorofluoridate from Diphosphopyridine Nucleotide.—A sample of DPN (351 mg, 502 μmol) was treated with 3 ml of hydrofluoric acid at −20° for 0.5 hr. The mixture was partially neutralized with 16 ml of saturated lithium hydroxide solution and then neutralized to pH 6 with lithium carbonate. The supernatant was decanted from the lithium fluoride precipitate, which in turn was washed four times with 3-ml portions of cold water. The combined supernatant and washings were added to 3–4 g of cellulose powder. This mixture was evaporated to dryness and then the residue was suspended in 10–20 ml of 2-propanol–water, 9:1 (v/v). This slurry was loaded onto a cellulose powder column (Whatman, ashless, standard grade) 8.1 cm^2 cross section and 60 cm long. Elution was first carried out using 3 l. of 2-propanol–water, 9:1; this was followed by 2.5 l. of 2-propanol–water, 85:15. Fractions of 20–24 ml were collected at a flow rate of 3 ml/min. The elution was followed by optical density determinations at 260, 266, and 280 mμ.

Nam, adenosine, and A-5′-PF were collected in that order in fractions 1–150, inclusive. The fractions (170–220) corresponding to the elution peak containing both A-5′-P and NR-5′-PF were pooled and evaporated to dryness. The resulting solid was dissolved in 10 ml of water and poured through a column containing 3 ml of Dowex-2 (formate). The effluent contains only NR-5′-PF, which is not adsorbed by the resin since it is a zwitterion. The phosphorofluoridate was adsorbed from the effluent by adding charcoal N. The charcoal was separated by centrifugation and it was washed three times with 5-ml portions of water. Elution from the charcoal was achieved with five 20-ml washings with a 50% ethanol solution. The eluate was evaporated to dryness. The resulting residue was dissolved in 5 ml of water and filtered to remove traces of charcoal. The filtrate contained 100 μmol of NR-5′-PF.

This NR-5′-PF has the same uv-absorption spectrum as NR-5′-P. The presence of vicinal hydroxyl groups in the compound was demonstrated by oxidation with 0.1% sodium metaperiodate followed by electrophoresis in bisulfite buffer. Its electrophoretic mobility was compared with that of an unoxidized sample. NR-5′-PF, when incubated with whole *Crotalus adamanteus* venom in 0.1 *M* Tris buffer, pH 8.5, was hydrolyzed to NR.

The fluoride in NR-5′-PF was determined by the same procedure as that described below for A-5′-PF. Triplicate fluoride determinations, using the venom diesterase, gave values of 65, 55, and 55% of theoretical based on the optical density of the NR-5′-PF solution used for the determinations. Electrophoresis in borate buffer of a small aliquot of each enzyme digest showed that complete hydrolysis of NR-5′-PF to NR-5′-P had occurred.

Adenosine 5′-Phosphorofluoridate.—This compound was isolated in low yield from a reaction mixture containing adenosine, tri-*n*-butylammonium phosphorofluoridate, DCC, and tri-*n*-butylamine in a dioxane–dimethylformamide solvent. The sample was purified by paper chromatography in solvent D. Recently a number of good general methods have become available for the preparation of ribo- and deoxyribonucleoside 5′-phosphorofluoridates.[53]

The uv-absorption spectrum of the compound is identical with that of A-5′-P. Vicinal hydroxyls were demonstrated by the same procedure as that used above for NR-5′-PF. The compound yields A-5′-P as the only uv-absorbing product when treated with 1 *N* potassium hydroxide (16 hr, room temperature) or saturated barium hydroxide solution (8 hr, room temperature).

The diesterase from *Crotalus adamanteus* venom (activity, 750 μmol of nucleotide released/hr by 1 ml of solution at 37°),[54] which catalyzes the hydrolysis of A-5′-PF to A-5′-P,[21] was adapted for a quantitative determination of fluoride in A-5′-PF. The reaction mixtures contained 1 ml of 0.1 *M* Tris buffer, pH 8.5, 10 μl of the diesterase solution, and the substrate. Substrates for five assays were A-5′-P (5.7 μmol), Me A-5′-P (6.9 μmol), and A-5′-PF (triplicate determinations with 6.9 μmol each). A-5′-PF is completely stable in 0.1 *M* Tris buffer, pH 8.5, at 37° for 22 hr. After incubation at 37° for 16 hr, 0.3 g of charcoal N was added to each assay. The supernatants and charcoal washings (five each with 2.5 ml of water) from each assay were passed through Dowex 50 (H^+) columns containing *ca.* 1 ml of resin. The eluents, collected in 100-ml volumetric flasks, were then subjected to a quantitative fluoride analysis using thorium chloranilate as the colorimetric reagent.[55] The A-5′-P and Me A-5′-P samples gave readings identical with those of the fluoride blank. The average value for the three A-5′-PF samples was 78% of the theoretical fluoride, based on the optical density of the A-5′-PF solution used for the determinations.

Methyl Phosphorofluoridate.—This compound was made by two different procedures. The first was that of Hood,[56] while

(52) F. R. Atherton, H. I. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 382 (1945). The negative temperature coefficient of solubility of the barium salt of this compound is taken advantage of in its purification.

(53) D. Lipkin and B. S. Pitzele, unpublished results.

(54) This enzyme was a gift from Dr. John Josse, Syntex Institute for Molecular Biology, Stanford Industrial Park, Palo Alto, Calif. 94304.

(55) This colorimetric procedure is described in Technical Data Sheet TD 138 of the Fisher Scientific Co.

(56) A. Hood, U. S. Patent 2,712,548 (1955).

the second involved the use of DCC and tri-*n*-butylammonium phosphorofluoridate in an excess of methanol. Neither synthesis was completely satisfactory, although a pure sample was finally obtained by paper chromatography in solvent E. The sample was homogeneous as shown by electrophoresis in bicarbonate and formate buffers and by chromatography in solvents A and D. The sample when treated with 1 *N* hydrochloric acid at room temperature for 36 hr yielded monomethyl phosphate.

Anal. Calcd for $CH_3FLiO_3P \cdot 2H_2O$: P, 19.9. Found: P, 20.6.

Alkaline Hydrolysis of A-2′:3′-P, A-3′:5′-P, and A-5′-PF.—Three sets of conditions were employed: (1) 1 *N* potassium hydroxide at room temperature for 16 hr; (2) saturated barium hydroxide solution at room temperature for 8 hr; and (3) saturated barium hydroxide solution at 100° for 20 min. Conditions 1 and 2 are sufficient to hydrolyze A-2′:3′-P and A-5′-PF to A-2′- (and 3′-) P and A-5′-P, respectively, but not A-3′:5′-P. Condition 3 is necessary for hydrolysis of A-3′:5′-P to a mixture of A-3′-P and A-5′-P.[5b]

Trifluoroacetic Acid Degradations.—Samples of A-5′-P (4–7 mg) were dissolved in 0.4-ml portions of aqueous trifluoroacetic acid (60–100%). After a predetermined reaction time, one of the solutions was frozen in a Dry Ice bath and lyophilized. A solution of the residue in a small amount of water was subjected to paper chromatography in solvent A and to paper electrophoresis in both borate and formate buffers.

Registry No.—Hydrogen fluoride, 7664-39-3; A-3′-P, 84-21-9; A-2′-P, 130-49-4; A-5′-P, 61-19-8; A-5′-PF, 19375-33-8; MeA-5′-P, 13039-54-8; C-2′-P, 85-94-9; C-3′-P, 84-52-6; G-2′-P, 130-50-7; G-3′-P, 117-68-0; U-2′-P, 131-83-9; U-3′-P, 84-53-7; NR-5′-P, 1094-61-7; T-3′-P, 2642-43-5; T-5′-P, 365-07-1; dA-5′-P, 653-63-4; A-2′:3′-P, 634-01-5; A-3′:5′-P, 60-92-4; ATP, 56-65-5; ADP, 58-64-0.

Studies on Phosphorylation. IV. Selective Phosphorylation of the Primary Hydroxyl Group in Nucleosides[1]

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Nucleoside 5′-phosphates of a number of naturally occurring and synthetic purine and pyrimidine ribonucleosides and their 2′-deoxy and 2′-O-methyl derivatives were prepared in good yields by direct phosphorylation of their corresponding unblocked nucleosides with pyrophosphoryl chloride in *m*-cresol or *o*-chlorophenol. Similar treatment of purine and pyrimidine arabino- and gluconucleosides, and aristeromycin resulted in the selective phosphorylation of the primary hydroxyl groups to give the corresponding phosphates. α-Guanosine and 2′-deoxyadenosine gave the 5′-phosphates in relatively low yield. The 5′-phosphate and 3′,5′-cyclic phosphate were obtained from 9-β-D-xylofuranosyladenine. Acetonitrile, benzonitrile, ethyl acetate, methyl acrylate, ethyl benzoate and nitrobenzene, when used as solvents, gave satisfactory results in the direct phosphorylation reaction.

A new method was reported[2] from our laboratories for the preparation of naturally occurring ribonucleoside 5′-phosphates by protecting the 2′,3′-*cis*-glycol system of the corresponding nucleosides with borate followed by phosphorylation with pyrophosphoryl chloride. Several attempts to phosphorylate primary hydroxyl groups selectively without blocking secondary alcoholic functions of nucleosides have failed.[3–5] We now report on a new method for direct phosphorylation of unblocked nucleosides at the 5′ position.[6–8] When inosine was suspended in *m*-cresol and was treated with pyrophosphoryl chloride[9,10] in the absence of metaboric acid or boric anhydride followed by hydrolysis, inosine 5′-phosphate was obtained in almost quantitative yield. This method was then applied to many other nucleosides and a number of the corresponding 5′-phosphate derivatives were selectively obtained.

A general procedure is as follows. A nucleoside, suspended in *m*-cresol or *o*-chlorophenol (15–80-fold by weight), is treated with pyrophosphoryl chloride (2–15 molar excess) at 0–10° for 2–4 hr and then diluted with an ice–water mixture followed by extraction with ethyl ether or benzene. The nucleotide is adsorbed onto charcoal and the aqueous layer discarded. After elution from the charcoal the nucleotide is subjected to ion exchange chromatography (Dowex 1). The identification of the nucleotide thus obtained is made as follows: (i) elementary analyses and ultraviolet absorption spectra, (ii) comparison of its mobility on paper electrophoresis and on paper chromatography with authentic samples, (iii) treatment of the nucleotide with bull semen 5′-nucleotidase to give quantitative liberation of phosphoric acid, (iv) treatment with periodic acid, and (v) chemical shifts of the 5′-proton resonances.

Adenosine, inosine, 2-chloroinosine, 6-thioinosine, uridine, and cytidine gave the corresponding 5′-phosphates in 55–85% yield (Table I). In the case of guanosine, a larger quantity of solvent was necessary

(1) For papers II and III of this series, see M. Honjo, Y. Furukawa, and K. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1061 (1966), and M. Honjo, R. Marumoto, K. Kobayashi, and and Y. Yoshioka, *Tetrahedron Lett.*, 3851 (1966), respectively.

(2) K. Imai, T. Hirata, and M. Honjo, *Takeda Kenkyusho Nempo*, **23**, 1 (1964).

(3) G. R. Barker and G. E. Foll, *J. Chem. Soc.*, 3798 (1957).

(4) M. Ikehara, E. Ohtsuka, and Y. Kodama, *Chem. Pharm. Bull.* (Tokyo), **11**, 1456 (1963).

(5) M. Naruse and Y. Fujimoto, *Yakugaku Zasshi*, **86**, 37 (1966).

(6) Yoshikawa, *et al.*,[7] reported a novel process for the phosphorylation of the naturally occurring ribonucleosides to their 5′-phosphates after we had published a part of this work as a preliminary report.[8]

(7) M. Yoshikawa, T. Kato, and T. Takenishi, *Tetrahedron Lett.*, 5065 (1967).

(8) M. Honjo, T. Masuda, K. Imai, and S. Fujii, Abstracts of the 7th Meeting of the International Congress of Biochemistry, Tokyo, Aug 1967, IV, B-16.

(9) P. C. Crofts, I. M. Downie, and R. B. Heslop, *J. Chem. Soc.*, 3673 (1960).

(10) W. Koransky, H. Grunze, and G. Munch, *Z. Naturforsch.*, **17b**, 291 (1962).

TABLE I

PHOSPHORYLATION[a] OF NUCLEOSIDES WITH PYROPHOSPHORYL CHLORIDE IN *m*-CRESOL

Nucleoside (mg)	Solvent, ml	Pyrophosphoryl chloride, ml	Time, hr	Yield of phosphate of primary hydroxyl, %[b]
Inosine (536)	30	2.2	2	Quantitative
Inosine (268)	20[c]	1.0	2	Quantitative
2-Chloroinosine (2000)	130	13.0	2	Quantitative[d]
Guanosine (1000)	165	6.9	6	76
Cytidine (243)	15	0.5	2	93
α-Adenosine (161)	7.5	0.5	2	69
α-Guanosine (1020)	160	10.0	4	45[e]
Thymidine (290)	15	0.5	2	83
2′-Deoxyuridine (228)	15	0.6	2	76
2′-Deoxycytidine hydrochloride (26)	3	0.1	2	60
2′-Deoxyadenosine (75)	3	0.1	2	44
2′-O-Methyluridine (52)	2	0.1	2	80[f]
2′-O-Methylcytidine hydrochloride (59)	2	0.14	4	65[g]
1-β-D-Arabinofuranosylcytosine (906)	37	1.3	3	60
1-β-D-Arabinofuranosyluracil (244)	50	1.5	10	76
9-β-D-Glucopyranosyladenine (560)	60	1.5	6	60

[a] The reaction was done as described for adenosine. [b] Determined spectrophotometrically after paper electrophoresis [c] *o*-Chlorophenol was used. [d] M. Honjo, K. Imai, T. Furukawa, Y. Kanai, R. Marumoto, H. Honda, H. Aoki, and T. Hirata, *Takeda Kenkyusho Nempo*, **25**, 74 (1966). [e] Correct analysis ($C_{10}H_{12}N_5Na_2O_8P \cdot H_2O$) was obtained. The specific rotation was $[\alpha]^{24}D + 6.0°$ (*c* 1.0, water). [f] The specific rotation was $[\alpha]^{20}D + 15.7°$ (*c* 1.5, water). The concentration was calculated designating ϵ as 9950 at 260 mμ. [g] The specific rotation was $[\alpha]^{20}D + 42.9°$ (*c* 2.2, water). The concentration was calculated designating ϵ as 7550 at 260 mμ.

TABLE II

PHOSPHORYLATION[a] OF RIBONUCLEOSIDES WITH PYROPHOSPHORYL CHLORIDE IN NITRILES, ESTERS, AND NITROBENZENE

Nucleoside (mg)	Solvent (ml)	Pyrophosphoryl chloride, ml	Time, hr	Yield of 5′-phosphate, %[b]
Inosine (54)	Acetonitrile (3)	0.1	2	85
Adenosine (267)	Acetonitrile (10)	0.5	1	71
Uridine (24)	Acetonitrile (7)	0.2	2	82
Inosine (54)	Benzonitrile (3)	0.1	1	88
Adenosine (267)	Ethyl acetate (30)	0.5	1.5	82
Adenosine (27)	Methyl acrylate (3)	0.1	1	87
Inosine (27)	Ethyl benzoate (3)	0.1	1	79
Adenosine (54)	Nitrobenzene (3)	0.1	2	72

[a] The reaction was done as described for adenosine in *m*-cresol. [b] Determined spectrophotometrically after paper electrophoresis.

to obtain a good yield. The 5′-phosphate of α-adenosine[11] or α-guanosine[12] was obtained in lower yield.

Thymidine, 2′-deoxyuridine, 2′-deoxycytidine, 2′-O-methyluridine, and 2′-O-methylcytidine[13] were selectively phosphorylated[14-16] to their 5′-nucleotides in 50–75% yield. Similar treatment of 2′-deoxyadenosine, however, resulted in considerable cleavage of the glycosyl linkage and the 5′-phosphate was obtained only in 40% yield. 1-β-D-Arabinofuranosylcytosine, 1-β-D-arabinofuranosyluracil, 9-β-D-glucopyranosyladenine, and 9-[β-D-2′α,3′α-dihydroxy-4′β(hydroxymethyl)cyclopentyl]adenine (aristeromycin)[17] were also selectively phosphorylated at their primary hydroxyl groups. The products isolated consumed periodic acid in amounts of 1, 1, 2, and 1 mol/mol, respectively. The former three nucleoside phosphates had been synthesized previously, but either the procedures used were complicated or the yields were low or both.[18-25]

In the selective phosphorylation reaction, solvents play an importatnt role. Without any solvent, the 2′(3′),5′-diphosphates were obtained quantitatively.[26] Acetonitrile, benzonitrile, ethyl acetate, methyl acrylate, ethyl benzoate, or nitrobenzene may also be utilized as solvent in this reaction with satisfactory results (Table II). However, when the nitriles were employed as solvent, some cleavage of the glycosyl bond of purine nucleosides occurred. With esters as solvents, some formation of 2′(3′),5′-diphosphates were detected by paper electrophoresis. Although phosphorylation of nucleosides in nitrobenzene proceeded to the correspond-

(11) α-Adenosine 5′-phosphate, after deamination with nitrous acid, was hydrolyzed with the 5′-nucleotidase of *Agkistrodon halys blomhoffi* BOIE, more slowly than inosine 5′-phosphate.

(12) Y. Furukawa, K. Imai, and M. Honjo, *Tetrahedron Lett.*, 4655 (1968).

(13) Y. Furukawa, K. Kobayashi, Y. Kanai, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **13**, 1273 (1965).

(14) Some reports have appeared on the selective phosphorylation of thymidine,[15,16] 2′-deoxycytidine, and 2′-deoxyadenosine.[15]

(15) G. M. Tener, *J. Amer. Chem. Soc.*, **83**, 159 (1961).

(16) K. L. Agarwal and M. M. Dhar, *Experientia*, **21**, 432 (1965).

(17) T. Kishi, M. Muroi, T. Kusaka, M. Nishikawa, K. Kamiya, and K. Mizuno, *Chem. Commun.*, 852 (1967).

(18) P. T. Cardeilhac and S. S. Cohen, *Cancer Res.*, **24**, 1595 (1964).

(19) S. S. Cohen, *Progr. Nucleic Acid Res.*, **5**, 1 (1966).

(20) W. J. Wechter, *J. Med. Chem.*, **10**, 762 (1967).

(21) J. Smrt, *Collect. Czech. Chem. Commun.*, **32**, 3958 (1967).

(22) T. Ueda and A. Nomura, Abstracts of the 14th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1961, p 298.

(23) M. Privat de Garilhe, *Bull. Soc. Chim. Fr.*, 1485 (1968).

(24) G. R. Barker and G. E. Foll, *J. Chem. Soc.*, 3794 (1957).

(25) A. Nohara, K. Imai, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **14**, 491 (1966).

(26) M. Honjo, K. Imai, Y. Furukawa, H. Moriyama, K. Yasumatsu, and A. Imada, *Takeda Kenkyusho Nempo*, **22**, 47 (1963).

TABLE III
CHEMICAL SHIFTS[a] OF 2'-O-METHYLPYRIMIDINE NUCLEOSIDES AND THEIR 5'-PHOSPHATES

Compound	Chemical shift of $H_{6'}$, δ	$\Delta\delta$ (nucleotide–nucleoside)
Uridine 5'-phosphate	4.05	0.22
Uridine	3.83	
Uridine 2'(3')-phosphate	3.85	0.02
2'-O-Methyluridine 5'-phosphate	4.10	
		0.25
2'-O-Methyluridine	3.85	
2'-O-Methylcytidine 5'-phosphate	4.16	
		0.26
2'-O-Methylcytidine	3.90	

[a] Proton magnetic resonance spectra were determined using a Varian A-60 spectrometer, operating at 60 Mc/sec and are reported on the δ scale with tetramethylsilane as an external standard. The solvent was D_2O.

ing 5'-phosphates in 60–70% yield, in nitromethane the reaction yields were lower (20–40%).[27,28]

n-Hexane, cyclohexane, chlorobenzene, *n*-butyric acid, ethers, amines, dimethyl sulfoxide, carbon disulfide, alcohols, and formamides did not give satisfactory results in this reaction due either to solubility factors or to side reactions. As for phosphorylating reagents, phosphorus pentachloride and tetra-*p*-nitrophenyl pyrophosphate did not give selective phosphorylation.

Although direct phosphorylation occurred only to a small extent when 9-β-D-xylofuranosyladenine was treated with pyrophosphoryl chloride in *m*-cresol, the nucleoside was phosphorylated in acetonitrile to a mixture of nucleotides, separation of which was unsuccessful. After deamination with nitrous acid, the components were separated by ion-exchange chromatography (Dowex 1) and identified as the 5'-phosphate of 9-β-D-xylofuranosylhypoxanthine (16% yield) and its 3',5'-cyclic phosphate (31% yield). The 5'-phosphate was hydrolyzed to the nucleoside and phosphoric acid by bull semen 5'-nucleotidase. The 3',5'-cyclic phosphate showed the absence of a secondary dissociation of the phosphoryl group by potentiometric titration. This cyclic phosphate was resistant to the exonuclease of *Streptomyces aureus*,[29] although adenosine 3',5'-cyclic phosphate was completely hydrolyzed to adenosine 5'-phosphate by this enzyme.

The use of bull semen 5'-nucleotidase for identification of the position of phosphorylation of the mononucleotides of 2'-O-methyluridine and -cytidine was not possible since it has been demonstrated[30] that these compounds are resistant to deesterification by this enzyme. Jardetzky and Jardetzky[31] have shown that the chemical shifts of the 5' protons of some 5'-nucleotides are moved to lower field relative to their parent nucleosides. A similar situation was observed when the various 2'-O-methylated nucleosides and the corresponding nucleotides synthesized in this paper are compared (Table III). This fact indicates that the nucleotides obtained were 5'-mononucleotides.

(27) Haynes, *et al.*,[28] phosphorylated nicotinamide ribonucleoside directly with phosphoryl chloride in moist nitromethane to give the corresponding 5'-phosphate. The yield, however, was very low.

(28) L. J. Haynes, N. A. Hughes, G. W. Kenner, and A. R. Todd, *J. Chem. Soc.*, 3727 (1957).

(29) K. Ogata, Y. Nakao, S. Igarashi, E. Ohmura, Y. Sugino, M. Yoneda, and I. Suhara, *Agr. Biol. Chem.* (Tokyo), **27**, 110 (1963).

(30) M. Honjo, Y. Kanai, Y. Furukawa, Y. Mizuno, and Y. Sanno, *Biochim. Biophys. Acta*, **87**, 698 (1964).

(31) C. D. Jardetzky and O. Jardetzky, *J. Amer. Chem. Soc.*, **82**, 222 (1960).

Experimental Section

Adenosine 5'-Phosphate.—To a cooled suspension (0–10°) of adenosine (534 mg, 2 mmol) in *m*-cresol (30 ml) was added pyrophosphoryl chloride (1 ml, 7.2 mmol). The mixture, after being stirred for 2 hr at 0–10°, was diluted with an ice–water mixture (100 ml) and extracted with ethyl ether (40 ml). The aqueous layer was adjusted to pH 2 with 4 *N* sodium hydroxide, then adsorbed on a column of activated charcoal[32] (8 g). The column was washed with water; then the compounds adsorbed on the column were eluted with a mixture of ethanol, concentrated aqueous ammonia, and water (50:2:48). As shown by paper electrophoresis, the eluate contained adenosine (7%), adenosine 5'-phosphate (90%), and adenosine 2'(3'),5'-diphosphate (3%). After concentration to a small volume, the mixture (29,140 OD_{260} units) was applied on a Dowex 1-X8 (formate, 100–200 mesh) column (10 ml) and washed with water (395 ml). A fraction (23,400 OD_{260} units), eluted with 0.1 *N* formic acid (300 ml), was evaporated to dryness under reduced pressure. The crystalline residue (500 mg, 72% yield) was identified as adenosine 5'-phosphate by comparison with an authentic sample on paper electrophoresis and paper chromatography. An analytical sample was recrystallized from water, mp 198° dec uncor.

Anal. Calcd for $C_{10}H_{14}N_5O_7P$: C, 34.58; H, 4.06; N, 20.17; P, 8.92. Found: C, 34.81; H, 4.32; N, 19.93; P, 8.76.

6-Thioinosine 5'-Phosphate.[33,34]—6-Thioinosine (150 mg, 0.53 mmol) was phosphorylated in *m*-cresol (30 ml) with pyrophosphoryl chloride (0.5 ml, 3.6 mmol) as described for adenosine. The reaction mixture (9500 OD_{310} units) was applied on a Dowex 1-X8 (formate, 100–200 mesh) column (20 ml). The column was washed with 0.2 *M* ammonium bicarbonate (2000 ml); then the compounds were eluted with 0.3 *M* ammonium bicarbonate (2500 ml). Two fractions were eluted. The second fraction (2000 ml, 8500 OD_{310} units) was evaporated to dryness under reduced pressure. The residue was dissolved in water (15 ml) and the solution was passed through a Dowex 50-X8 (hydrogen, 100–200 mesh) column (5 ml). After the column was washed with water, the effluent and washings were combined and evaporated to dryness under reduced pressure. To the aqueous solution (1 ml) of the residue were added methanol (4 ml) and acetone (100 ml). The precipitate (150 mg) was purified by reprecipitation from a mixture of water, ethanol and acetone. Pale yellow, fine crystals (140 mg, 65% yield) were obtained, $[\alpha]^{22}D$ −58.5° (*c* 1.0, water). The product was homogeneous on paper electrophoresis (0.05 *M* sodium borate, pH 9.2; Whatman No. 1 paper at 22 V/cm) [mobility, 1.2 relative to inosine 5'-phosphate (1.0)].

Anal. Calcd for $C_{10}H_{13}N_4O_7PS \cdot C_2H_5OH$: C, 35.07; H, 4.67; N, 13.63; P, 7.56. Found: C, 34.88; H, 4.85; N, 13.55; P, 7.77.

Uridine 5'-Phosphate.—Uridine (488 mg, 2 mmol), *m*-cresol (21 ml), and pyrophosphoryl chloride (0.7 ml, 5 mmol) were treated as in the case of adenosine. Examination of the reaction mixture by paper electrophoresis showed that it contained uridine (14%), uridine 5'-phosphate (84%), and uridine 2'(3'),5'-diphosphate (2%). The mixture (16,700 OD_{260} units) was applied to a column (1.6 × 6 cm) of Dowex 1-X8 (formate, 100–200 mesh). The column was washed with water (420 ml) and uridine 5'-phosphate was eluted with 0.1 *N* formic acid containing 0.1 *M* ammonium formate (545 ml). The eluate (14,250 OD_{260} units) was desalted by charcoal treatment (5 g) and concentrated to 10 ml. Barium acetate (440 mg) and ethanol (20 ml) were added to the concentrate. The precipitate (723 mg) was purified by reprecipitation from water (10 ml)–ethanol (20 ml). Pure barium uridine 5'-phosphate (548 mg, 56% yield) was obtained as a white powder.

Anal. Calcd for $C_9H_{11}BaN_2O_9P \cdot 1.5H_2O$: C, 22.22; H, 2.90; N, 5.76; P, 6.38. Found: C, 22.39; H, 3.19; N, 5.51; P, 6.39.

Aristeromycin 6'-Phosphate.—Aristeromycin (530 mg, 2

(32) Shirasagi (Chromato-Tokusei), Takeda Chemical Industries, Ltd.

(33) The synthesis of 6-thioinosine 5'-phosphate was reported by Hampton and Maguire.[34]

(34) A. Hampton and M. H. Maguire, *J. Amer. Chem. Soc.*, **83**, 150 (1961).

mmol), *m*-cresol (30 ml), and pyrophosphoryl chloride (2 ml, 14.4 mmol) were treated as in the case of adenosine. The mixture (29,000 OD_{260} units) was applied to a column (2.5 × 12 cm) of Dowex 1-X8 (formate, 100–200 mesh). The column was washed with water (400 ml) and aristeromycin 6′-phosphate was eluted with 0.1 *N* formic acid (340 ml). The eluate (23,750 OD_{260} units) was evaporated to dryness under reduced pressure. To the residue was added ethanol to give a white powder (545 mg, 75% yield), mp 186–188° uncor. The product was homogeneous on paper electrophoresis [mobility, 0.89 relative to adenosine 5′-phosphate (1.0) in sodium borate (0.05 *M*, pH 9.2)] and on paper chromatography [R_f 0.74 in isobutyric acid–0.5 *N* aqueous ammonia (10:6)]: $\lambda_{max}^{0.1\ N\ HCl}$ 260.5 mμ (ε 14,500), $\lambda_{min}^{0.1\ N\ HCl}$ 234 mμ; $\lambda_{max}^{H_2O}$ 262 mμ (ε 14,800), $\lambda_{min}^{H_2O}$ 232 mμ; $\lambda_{max}^{0.1\ N\ NaOH}$ 263 mμ (ε 14,300), $\lambda_{min}^{0.1\ N\ NaOH}$ 228 mμ; $[\alpha]^{24}D$ −34.6° (c 1.0, water).

Anal. Calcd for $C_{11}H_{16}N_5O_6P\cdot H_2O$: C, 36.36; H, 4.99; N, 19.28; P, 8.54. Found: C, 36.30; H, 4.99; N, 18.87; P, 8.48.

9-β-D-Xylofuranosylhypoxanthine 5′-Phosphate and 9-β-D-Xylofuranosylhypoxanthine 3′,5′-Cyclic Phosphate.—To a suspension of 9-β-D-xylofuranosyladenine[35] (361 mg, 1.35 mmol) in acetonitrile (20 ml) was added pyrophosphoryl chloride (1.4 ml, 10 mmol) at 0–5°. The mixture was stirred for 2 hr at this temperature and then was poured into a mixture of ice and water (130 ml). The mixture was adjusted to pH 2 with sodium hydroxide and treated with activated charcoal (5 g) as described above. The eluate containing 5′-phosphate (34%) and 3′,5′-cyclic phosphate (66%) of 9-β-D-xylofuranosyladenine (examined by paper electrophoresis) was concentrated to dryness under reduced pressure. The residue was dissolved in 2 *N* acetic acid (100 ml) and was treated with sodium nitrite (8 g) at 37° for 40 hr. The mixture, after desalting by charcoal treatment (8 g), was concentrated and applied to a Dowex 1-X8 (chloride, 100–200 mesh) column (2 × 41 cm). The column was first washed with water (990 ml) and the nucleotides were then eluted successively with 0.003 *N* hydrochloric acid containing 0.02 *M* sodium chloride and 0.003 *N* hydrochloric acid containing 0.04 *M* sodium chloride.

The first fraction (2100 ml, 3990 OD_{250} units, 28% yield) was worked up as described for uridine. The barium salt of 9-β-D-xylo-furanosylhypoxanthine 5′-phosphate was obtained as a white powder (114 mg, 16% yield) which was homogeneous on paper electrophoresis [mobility, 0.90 relative to inosine 5′-phosphate (1.0) in sodium borate (0.05 *M*, pH 9.2)] and on paper chromatography [relative mobility 1.1 compared to inosine 5′-phosphate (1.0) in isobutyric acid–0.5 *N* aqueous ammonia (10:6)]: $\lambda_{max}^{0.1\ N\ HCl}$ 249 mμ (ε 10,500); $\lambda_{max}^{H_2O}$ 248.5 mμ (ε 11,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 253.5 mμ (ε 11,800); $[\alpha]^{25}D$ −21.0° (c 0.5, water).

Anal. Calcd for $C_{10}H_{11}BaN_4O_8P\cdot 2H_2O$: N, 10.78; P, 5.97. Found: N, 10.88; P, 6.23.

The second fraction (3415 ml, 7370 OD_{250} units, 49% yield) was worked up as described above. The barium salt of 9-β-D-xylofuranosylhypoxanthine 3′,5′-cyclic phosphate was isolated as a white powder (180 mg, 31% yield) which was homogeneous on paper electrophoresis [mobility 0.69 relative to inosine 5′-phosphate (1.0) in sodium borate (0.05 *M*, pH 9.2)] and on paper chromatography [relative mobility 1.2 compared to inosine 5′-phosphate (1.0) in isobutyric acid–0.5 *N* aqueous ammonia (10:6)]: $\lambda_{max}^{0.1\ N\ HCl}$ 250 mμ (ε 11,100); $\lambda_{max}^{H_2O}$ 249 mμ (ε 11,100), $\lambda_{min}^{H_2O}$ 223 mμ; $\lambda_{max}^{0.1\ N\ NaOH}$ 254 mμ (ε 12,300), $\lambda_{min}^{0.1\ N\ NaOH}$ 231 mμ; $[\alpha]^{25}D$ −44.3° (c 1.0, water).

Anal. Calcd for $C_{10}H_{10}BaN_4O_7P\cdot 2H_2O$: C, 27.67; H, 3.25; N, 12.91; P, 7.15. Found: C, 27.33; H, 3.34; N, 12.63; P, 7.25.

Registry No.—Adenosine 5′-phosphate, 61-19-8; 6-thioinosine 5′-phosphate, 53-83-8; uridine 5′-phosphate, 58-97-9; aristeromycin 6′-phosphate, 19471-36-4; barium salt of 9-β-D-xylofuranosylhypoxanthine 5′-phosphate, 19458-99-2; barium salt of 9-β-D-xylofuranosylhypoxanthine 3′,5′-cyclic phosphate, 19459-00-8.

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(35) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

Structure and Stereochemistry of Reduction Products of Abietic-Type Resin Acids[1]

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Products formed by catalytic hydrogenation of abietic, neoabietic, and levopimaric acid are correlated with those obtained by reduction with lithium in liquid ammonia. Structural and stereochemical assignments are presented for all known and several new dihydroabietic acids on the basis of hydroxylation–cleavage reactions, lactonization behavior, results on hydrogenation, and spectral data including nmr, far-uv, ORD, and CD measurements. A marked difference in the equilibrium position of the γ- and δ-lactones derived from 13α- and 13β-dihydroabietic acids is noted and used to define or confirm the configuration at C-13 in these acids. Newly characterized compounds include 9,5-friedoabietan-18:10-olide (**15b**) (13α-dihydroabietic γ-lactone) and the following acids: 7-abieten-18-oic (**7**), 8(14)-abieten-18-oic (**8**), 13-abieten-18-oic (**9**), 8-abieten-18-oic (**14**), 13(15)-abieten-18-oic (**27**), and 8,13(15)-abietadien-18-oic acid (**31**).

In connection with work on the synthesis[4] of the tricyclic diterpene hydrocarbon fichtelite (18-norabietane[5]), and as an extension of earlier studies[6] on the lithium–ethylamine reduction of dehydroabietic acid, we had occasion to investigate the structure and

(1) Based on the Ph.D. Thesis of J. N. M., The University of Kansas, Sept 1965, and revised from the presentation given before the Division of Organic Chemistry at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965 (Abstracts, p 17p; see Abstracts of Second Midwest Regional Meeting of the American Chemical Society, Lawrence, Kan., Oct 1966, p 46). Financial support for earlier portions of this work from the National Science Foundation (G-19936), from the University of Kansas Center for Research in Engineering Science (CRES-40B), and from the Alfred P. Sloan Foundation, is gratefully acknowledged.

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(3) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

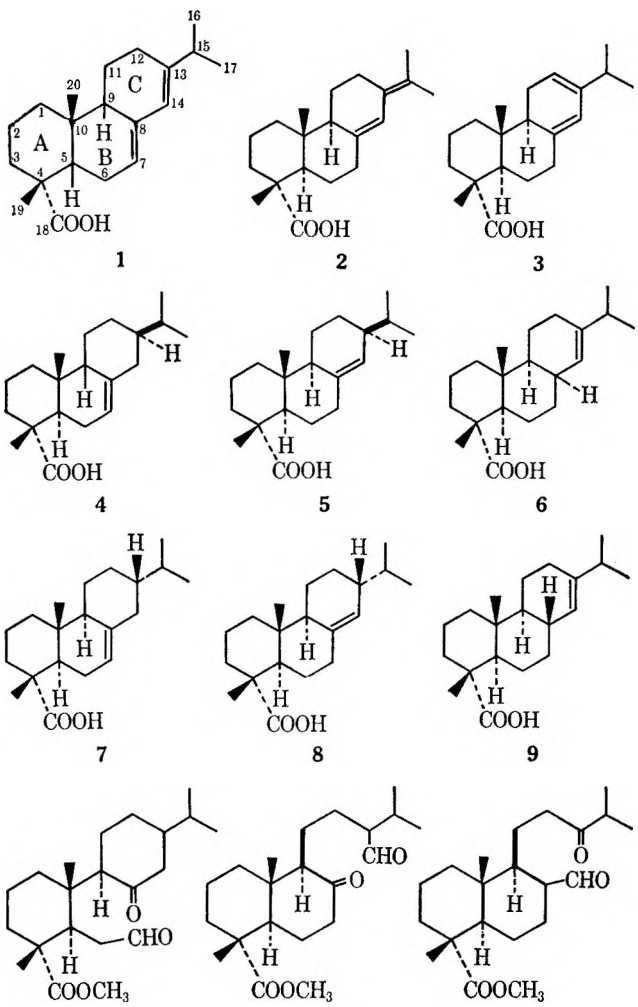
(4) (a) A. W. Burgstahler and J. N. Marx, *Tetrahedron Lett.*, 3333 (1964); *J. Org. Chem.*, **34**, 1562 (1969). (b) *Cf.* N. P. Jensen and W. S. Johnson, *ibid.*, **32**, 2045 (1967).

stereochemistry of products formed by reduction of abietic (**1**), neoabietic (**2**), and levopimaric (**3**) acid (Chart I). Other workers have shown that catalytic hydrogenation of these three resin acids yields various dihydro and tetrahydro acids, some of which are known to be mixtures.[7,8] Lithium–ammonia reduction of abietic acid has also been reported.[4,9]

Under neutral or basic conditions, partial catalytic hydrogenation of abietic acid would be expected to favor approach to the less hindered α side of the molecule to produce dihydro acids **4**, **5**, and **6**. In fact, the two known dihydroabietic acids arising directly from such partial hydrogenation are **4** and **5**.[10–13] By contrast, lithium–ammonia reduction, with its preference for axial protonation,[14] would be expected to yield mainly acids **7**, **8**, and **9**. In our work we have found that this reduction affords not only these three acids but also acid **5**. The major product is the 13α-8(14)-ene acid **8**, obtained previously in impure form by Royals and coworkers,[9] who, however, had assigned a 7-ene structure to it. As isolated from the reduction mixture by crystallization, **8** is contaminated by *ca.* 15% persistent isomeric impurity, separable by chromatography of the methyl esters on silver nitrate impregnated alumina, analogous to tlc separations of other resin acid esters.[15] The 8α-13-ene structure **6** has been proposed[8] and provisionally accepted[16,17] for this minor component; however, our results indicate that it is actually the previously unknown 8β-13-ene acid **9**.

The second most abundant product of the reduction of abietic acid with lithium in ammonia is the 13β-8(14)-ene acid **5**. The remaining minor product, the 13α-7-ene acid **7**, is a new compound, which was isolated as a cocrystallizing mixture with **9**, readily separable by chromatography on silver nitrate–alumina. The formation of acids **8** and **5** as principal products of the reduction also accords with our additional observation that the action of lithium in ethylamine on a related system, 3,5-cholestadiene, yields mainly 4-cholestene. Likewise, by analogy with the sodium–alcohol reduction of 2,4-cholestadiene to 4-cholestene,[18] lithium–ammonia reduction of levopimaric acid (and also neoabietic acid) was found to give mainly acids **8** and **5**.[19]

CHART I



(5) The numbering and systematic nomenclature follow the recent proposals (third revision, Oct 1968) of a group chaired by Dr. J. W. Rowe, U. S. Department of Agriculture, Forest Service, Forest Products Laboratory, Madison, Wis. *Cf.* R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 50 (1965). The parent abietane skeleton as proposed by E. Fujita, T. Fujita, and H. Katayama [*Chem. Commun.*, 968 (1967)] possesses the *trans-anti-trans* configuration with a 13α-isopropyl group. Inverted configurations are designated by the position number and the correct stereochemistry just before the skeletal name. The order of groups on ring methylene position is determined by the sequence rule [R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956)].

(6) A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, **86**, 96 (1964).

(7) For references to the earlier work, see J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, 1952, Chapter 5.

(8) For a recent, independent assignment of the configurations of the tetrahydroabietic acids, see J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966). We thank Professors Huffman and Herz for sending us a copy of their manuscript prior to publication.

(9) (a) E. E. Royals, W. C. Bailey, and R. M. Kennedy, *ibid.*, **23**, 151 (1958); (b) W. G. Bailey, Ph.D. Thesis, Emory University, 1956; (c) R. M. Kennedy, Ph.D. Thesis, Emory University, 1957. We thank Dr. Royals for additional experimental details concerning this work.

(10) Apart from the bond isomerization product **13** (Chart II), only these two dihydroabietic acids **4** and **5** have been isolated in pure state from the hydrogenation of abietic acid. Lombard[11] had correctly assigned structure **4** to the one with mp 166°, $[\alpha]_D$ −26°, which Velluz and coworkers[12] later mistakenly formulated as **9**. The other acid, mp 151°, $[\alpha]_D$ +42°, is also formed by hydrogenation of neoabietic and levopimaric acid. Although Velluz[12] assigned structure **6** to this acid, our data indicate that it is **5**. Recently, it has been observed[18] that partial hydrogenation of 12α-hydroxyabietic acid yields dihydro-12α-hydroxy products analogous to **4** and **5**.

(11) R. Lombard, *Bull. Soc. Chim. Fr.*, [V] **9**, 833 (1942); [V] **11**, 526 (1944). R. Lombard and J. Ebelin, *ibid.*, 316 (1951); 438 (1952); 930 (1953).

(12) L. Velluz, G. Muller, A. Petit, and J. Mathieu, *ibid.*, 401 (1954).

(13) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(14) (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 3; (b) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(15) D. F. Zinkel and J. W. Rowe, *J. Chromatog.*, **13**, 74 (1964).

(16) B. E. Cross and P. L. Myers, *J. Chem. Soc., C*, 471 (1968). Evidently the sample of **8** used by these authors was contaminated with **5** as well as **9**, since their products of osmium tetroxide hydroxylation included the 8α,14α-glycol of **5** as well as the 8α,14α-glycol of **8** and the 13β,14β-glycol of **9** (see Experimental Section). We cordially thank Professor Cross for kindly providing samples and making comparisons of our products with theirs. He has also informed us (letter, July 30, 1968) that his more recent evidence agrees with our assignment of structure **9** rather than **6** to the persistent 13-ene contaminant of **8**. See also ref 17.

(17) Although a minor epoxide isolated from the reaction of *m*-chloroperbenzoic acid with impure acid **8** was evidently derived from the 8α-13-ene isomer **6**, as claimed,[8] new work has recently been reported (J. W. Huffman and J. A. Alford, 5th International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968) which confirms our conclusion that the principal contaminant of **8** has structure **9** and not **6**.

(18) H. E. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 575 (1937).

(19) The formation of **5** and **8** by chemical reduction of levopimaric acid (**3**) provides further direct chemical evidence for the 9α configuration in this acid: (a) W. G. Dauben and R. M. Coates, *ibid.*, **28**, 1698 (1963); (b) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963); (c) A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Amer. Chem. Soc.*, **83**, 4660 (1961).

Proof of Structure. A. Position of the Double Bond.—Chemical evidence for the location of the double bonds in the foregoing dihydroabietic acids was obtained by hydroxylation of the corresponding methyl esters with osmium tetroxide, followed by lead tetraacetate cleavage of the resulting glycol esters. In each case, these operations gave a ketoaldehyde ester whose nmr spectrum allowed the position of the double bond to be assigned with certainty. Thus the 8β-13-ene acid **9** afforded a ketoaldehyde ester which must have structure **12.** The isopropyl methyl doublet was shifted downfield, in agreement with the formation of an alkyl isopropyl ketone.[20] The C-10 methyl was nonshielded, and the aldehyde proton gave rise to a doublet at τ 0.47, in accord with the presence of an equatorial aldehyde function.[21] That epimerization had not occurred during the cleavage reaction was shown by the fact that no deuterium incorporation was observed when the reaction was conducted in acetic acid-1-*d*. All the data, therefore, are in agreement with the assignment of structure **9** to this acid.[17]

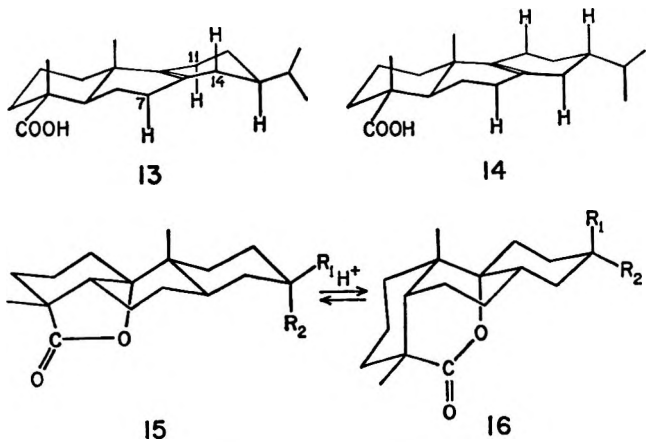
Acids **5** and **8** gave rise to ketoaldehyde esters **11a** and **11b,** respectively, whose nmr spectra showed the isopropyl methyl resonance in the normal position. However, the C-10 methyl signal was shifted upfield by *ca.* 0.2 ppm, owing to the fact that this methyl group lies in the shielding cone of the carbonyl group.[22] In agreement with their formulation as α-disubstituted aldehydes, the nmr spectra of these cleavage products exhibited the aldehyde proton signal as doublets (J = 2 Hz).

Unlike **11a** and **11b,** the ketoaldehyde esters **10a** and **10b** derived from acids **4** and **7,** respectively, displayed normal chemical shifts, both for their isopropyl and for their C-10 methyl resonances. However, the aldehyde proton signal appeared as a triplet with J = 2 Hz. This result requires the presence of two protons on the α carbon and is consistent only with cleavage of a 7-ene structure.

In contrast to the foregoing results, ozonolysis of the acid now known to have structure **8,** has been reported[9] to give a product derived from a 7-ene structure. In our work, we found that ozonization of moderately pure acid **8** gave a mixture of products, only about half of which appeared to be the result of "normal" cleavage of an 8(14)-ene. None of the reported[9] monomeric keto anhydride could be isolated, and any which may have been present would have had to arise by bond rearrangement during ozonolysis[23] or from contamination of **8** by **7** (or **4**).

B. Configuration at C-13.—For determination of the configuration at C-13 in the 7-ene and 8(14)-ene acids, the well-known dihydroabietic acid lactonization reaction proved especially useful. By treatment with HBr in acetic acid, the dihydro acids **4** and **5** formed by partial hydrogenation[11,12] of abietic-type dienoid acids are converted into a common dihydro acid whose previous[12] formulation as the 13β-8-ene acid **13** (Chart II) has been confirmed.[24] Similar treatment of acid **8** has also been reported[9] to give an analogous product, which we have found to be a mixture containing the 13α-7-ene acid **7** (20–25%) and the expected 13α-8-ene acid **14** (75–80%). Apparently the 8-ene structure is less stable in **14** than in **13,** although the reason (evidently conformational in nature[14b]) is not clear.

CHART II



a, R_1 = isopropyl; R_2 = H
b, R_1 = H; R_2 = isopropyl
c, R_1 = R_2 = H

Acid **13** on further treatment with HBr in acetic acid or with cold sulfuric acid gives γ-lactone **15a,**[7] whose structure and stereochemistry have been unequivocally determined.[25] Although it has also been reported[9] that this same compound results from lactonization of acid **8** (impure), but in low yield, we have found that a new γ-lactone, **15b,** is the major direct product. Minor amounts of lactone **15a** apparently arise, at least in part, from 13β contaminants (such as **5**) present in all but the most highly purified preparations of acid **8.** It has also been noted[26] that prolonged treatment of **15a** (or its dihydroabietic acid precursors) with sulfuric acid gives rise to δ-lactone **16a.** Moreover, a different δ-lactone, **16b,** results from further acid treatment[9] of **15b** or its precursors. However, the ratio at equilibrium of γ- to δ-lactone is very different in the two sets of isomers. At 25° it is *ca.* 55:45 of lactones **15a** and **16a,** and *ca.* 1:99 of lactones **15b** and **16b.**

These differences in the equilibrium position of the two sets of lactones can be accounted for by reasoning similar to that presented previously.[24,25b,27] At equilibrium (at 25°), the unknown podocarpane (13-deisopropylabietane) prototype has been estimated[25b] to contain 95.7% δ-lactone **16c** and only 4.3% γ-lactone **15c,** corresponding to a free-energy difference of 1.8 kcal/mol. Since an axial isopropyl group in a cyclohexane ring is *ca.* 2.1 kcal/mol less stable at 25° than an equatorial one,[28] a β-isopropyl group in the present

(20) *Cf.* isopropyl methyl doublet centered at τ 8.95 in 3-methyl-2-butanone (Sadtler Nuclear Magnetic Resonance Spectra, Vol. 3, No. 1885).

(21) *Cf.* 19-norabietan-18-al (equatorial aldehyde), τ 0.37 (J = 3 Hz),[4a] and 18-norabietan-19-al (axial aldehyde), τ −0.20 (J < 1 Hz),[4a] in which there is a similar geometrical relationship to the C-10 methyl.

(22) The C-10 methyl in 6-keto steroids shows an almost identical upfield shift; *cf.* N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 20. See also ref 8 and 30.

(23) An example of such a bond shift during ozonolysis is reported by C. R. Enzell and B. R. Thomas, *Tetrahedron Lett.*, 225 (1965).

(24) W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30,** 1881 (1965).

(25) (a) L. A. Subleskey and T. F. Sanderson, *J. Amer. Chem. Soc.*, **76,** 3512 (1954); (b) L. J. Gough, T. F. Sanderson, V. I. Stenberg, and E. Wenkert, *J. Org. Chem.*, **25,** 1269 (1960). For additional proof of the configuration at C-8, see ref 24.

(26) Le-Van Thoi, *Bull. Soc. Chim. Fr.*, 761 (1955); *cf.* ref 24.

(27) E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.*, **81,** 688 (1959).

(28) N. L. Allinger and L. A. Freiberg, *J. Org. Chem.*, **31,** 894, 4327 (1966).

TABLE I

PROTON CHEMICAL-SHIFT VALUES FOR ABIETIC-TYPE RESIN ACIDS[a,b]

Acid	C-4 Methyl	C-10 Methyl	Isopropyl methyls (J = 5–7 Hz)	Olefinic protons
Abietadien-18-oic				
Abietic (1)	8.71	9.13	8.97	4.22, 4.66
Neoabietic (2)	8.77	9.16	8.26[c]	3.71
Levopimaric (3)	8.80	9.05[d]	8.98	4.39, 4.78
Palustric (8,13-diene)	8.77	8.92	8.96	4.58
8,13(15)-diene (31)	8.83	9.00	8.34[c]	
Abieten-18-oic				
13β-7-ene (4)	8.75	9.15	9.09, 9.14[e,f]	4.74
13α-7-ene (7)	8.75	9.17	9.14[e]	4.73
13β-8(14)-ene (5)	8.86	9.21	9.11, 9.16[e,f]	4.56
13α-8(14)-ene (8)[g]	8.86	9.22	9.12, 9.16[e,f]	4.67
8β-13-ene (9)	8.82	9.15	9.03	4.91
13β-8-ene (13)[h]	8.79	9.02	9.11	
13α-8-ene (14)	8.81	9.01	9.12	
8β-13(15)-ene (27)	8.83	9.14	8.35[c]	
Abietan-18-oic[g]				
8α,13β (17)	8.80	8.90	9.10	
8β,13β (18)	8.84	9.17	9.13[e]	
8β,13α (19)	8.83	9.19	9.14[e]	

[a] Determined in carbon tetrachloride solution on Varian A-60 and HA-100 nmr spectrometers at 250-sec sweep time/500-Hz sweep width with internal tetramethylsilane as reference. [b] *Cf.* ref 24, 29, and 30. [c] Isopropylidene singlet. [d] Reflects folded B/C conformation (*cf.* ref 19c). [e] Assignment verified by double-resonance decoupling of the C-15 proton on the HA-100 instrument by irradiation at *ca.* τ 8.5. [f] Pair of doublets (resolved only in the 100-MHz spectrum). [g] *Cf.* ref 8. [h] *Cf.* ref 24.

TABLE II

FAR-ULTRAVIOLET ABSORPTION OF METHYL ABIETEN-18-OATES[a]

Parent abieten-18-oic acid	λ_{max}, nm (ϵ_{max})	λ_{min}, nm (ϵ_{min})
13β-7-ene (4)	204.0 (6,500)	195 (5,600)
13α-7-ene (7)	203.5 (6,800)	194 (6,200)
13β-8(14)-ene (5)[b]	200.5 (10,700)	
13α-8(14)-ene (8)	206.5 (8,700)	197 (7,700)
13β-8-ene (13)[c]	195.0 (9,400)	
13α-8-ene (14)	196.5 (7,800)	
8β-13-ene (9)	190.5 (9,500)	
8β-13(15)-ene (27)	197.0 (12,300)	

[a] Measured in Phillips Petroleum Co. Spectro Grade isooctane in 0.1-cm quartz cells from 220 to 186 nm on a Cary Model 14 recording spectrophotometer with continuous nitrogen purge; scan speed 30 nm/min; optical density range 0–1.0. All readings are corrected for solvent blank. Our values for two previously published reference compounds follow: 4-cholestene, λ_{max} 193.3 nm (ϵ 10,200) [lit.[31] λ_{max} 193 nm (ϵ 10,000)]; 5α-lanost-8-en-3β-yl acetate, λ_{max} 200 nm (ϵ 8200) [lit.[31] λ_{max} 200 nm (ϵ 8330)]. [b] For methyl 8(14)-pimaren-18-oate, λ_{max} 201.4 nm (ϵ 9880). [c] For methyl 8-pimaren-18-oate, λ_{max} 193.5 nm (ϵ 8860).

system helps to favor the otherwise less stable γ-lactone by 2.1 minus 1.8, or 0.3 kcal/mol. This gives a calculated equilibrium composition of 62% **15a** and 38% **16a**. On the other hand, an α-isopropyl group increases the stability of the ring-C inverted δ-lactone by 2.1 plus 1.8, or 3.9 kcal/mol, which corresponds to 99.8% **16b** in equilibrium with 0.2% **15b**. In both cases, the predicted values lie close to those observed experimentally.

Thus, the lactonization causes little or no epimerization at C-13, and its application to the various dihydroabietic acids proved to be a convenient method of determining or verifying the configuration at this center. In each case the result was consistent with the assignments shown in Chart I. As would be expected, the reaction proceeded more slowly with the 8β-13-ene acid **9** than with the other dihydro acids and, interestingly, gave almost exclusively the 13α-isopropyl lactones **15b** and **16b**.

C. Spectral Evidence.—The nmr spectra of the acids (Table I) are consistent with the positions assigned to the double bonds. In acid **9** the 13,14 double bond (*cf.* abietic, levopimaric, and palustric acid) causes the isopropyl methyl doublet to be shifted downfield from where it appears in the other isomers. In the 7-ene acids **4** and **7**, the C-4 methyl resonance is likewise shifted downfield from its position in the spectra of the other isomers. This effect evidently arises from conformational changes introduced into ring B by a 7,8 double bond. In any event, it is also present in the spectrum of abietic acid (**1**),[29] 9-hydroxyabietic acid,[24] 9-hydroxy-13β-abiet-7-en-18-oic acid,[24] isopimaric acid,[30] and the 14-keto-7-ene acid derived from acid **8** by dehydrochlorination and hydrolysis of its nitrosyl chloride addition product[9] (see Experimental Section). Acids **5** and **8** with an 8,14 double bond, would be expected to have "normal"[30] C-10 methyl shifts. The appearance of the isopropyl

(29) As determined by us (Table I). J. C. W. Chien [*J. Amer. Chem. Soc.*, **82**, 4762 (1960)] does not report this shift, but his values, determined under different conditions, are difficult to correlate. This has also been noted by by J. D. McChesney, Ph.D. Thesis, Indiana University, 1965, p 24 (see also ref 30a below).

(30) (a) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965). (b) J. W. ApSimon, W. G. Craig, P. V. Demarco, W. D. Mathieson, and W. B. Whalley, *Tetrahedron*, **23**, 2375 (1967).

signals as a pair of doublets in the 100-MHz spectra of these two isomers indicates a nonequivalent magnetic environment which molecular models suggest would probably be associated with an 8,14 double bond.

Further spectral support for the assignments of the positions of the double bonds in the dihydroabietic acids is seen in the far-ultraviolet (far-uv) absorption of the methyl esters (Table II). In all cases, the absorption characteristics are comparable with those of appropriate steroid or terpene analogs.[31] The λ_{max} of the methyl ester of acid **5** is perhaps a little lower than expected, but a conformation of ring C allowing the isopropyl group to become pseudoequatorial could possibly account for it. This might also explain the close similarity of the nmr spectrum of **5** with that of acid **8**, in which a pseudoequatorial isopropyl group is almost certainly present.

The ORD (Figure 1) and CD curves of the dihydroabietic acids also support the assigned structures. Thus, in agreement with predictions based on chirality considerations,[32] and by analogy with the sign of the Cotton effect of 17β-hydroxy-4-estrene (+) and 17β-hydroxy-5-estrene (−),[32] acids **5** and **8** exhibit positive Cotton effects, while acids **4** and **7** display negative ones.[33] The curve of acid **9** might at first sight appear to indicate a positive Cotton effect, similar to that of 17β-acetoxy-5β-androst-3-ene[32] and 5β-cholest-3-ene,[34] thereby implying a B/C-*cis* ring junction (formula **6**) rather than a *trans* one (formula **9**). Actually, however, the circular dichroism of this acid shows that the sign of the Cotton effect is negative, like that of 5α-cholest-3-ene,[32] which also has a positive rotation at 230 nm before dipping to the first extremum of a negative Cotton effect (*cf.* positive background in the ORD curves of the saturated acids **17**, **18**, and **19**[35]). Molecular models also indicate that the strong positive Cotton effect of acid **5** is best accounted for[32] with ring C in a conformation requiring the 13β-isopropyl group to be pseudoequatorial. The marked difference in the ORD curves of **13** and **14** can be rationalized if the 13β-isopropyl group in **13** is allowed to become equatorial. Then all of the three allylic pseudoaxial hydrogens (7α, 11α, and 14β) form right-handed helices with the double bond and therefore contribute toward a positive Cotton effect.[32] In **14**, with an equatorial 13α-isopropyl group, only the 7α hydrogen exerts a positive contribution, while the now pseudoaxial 11β and 14α hydrogens make a negative one, thus causing the Cotton effect to be weakly negative.

Relation to Tetrahydroabietic Acids.—The structural and stereochemical assignments of the various dihydroabietic acids are also consistent with the results of catalytic hydrogenation of these acids over platinum in acetic acid (Table III). The products are the three known tetrahydroabietic acids, mp 168, 182, and 202°,[7,8,12] which are readily identified by the glpc

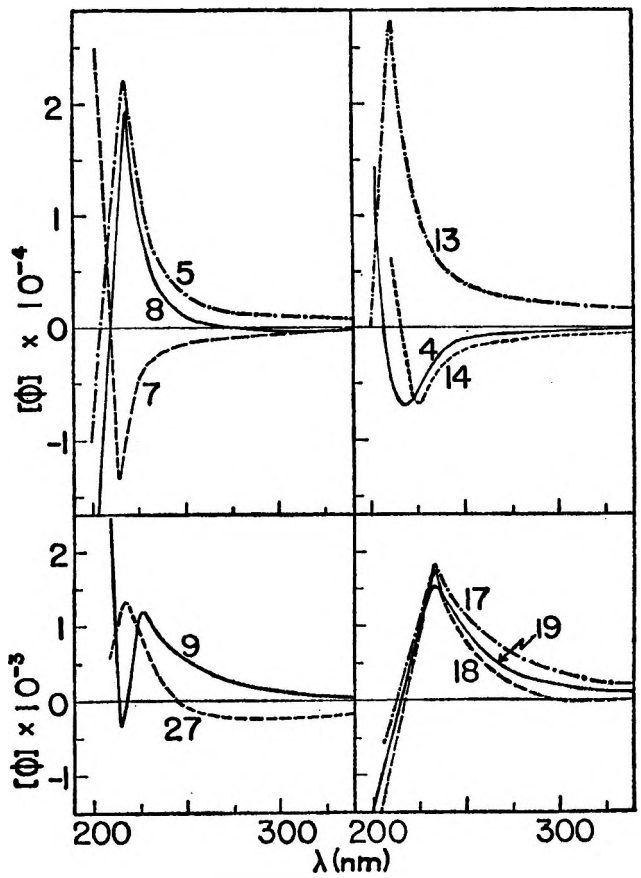


Figure 1.—Optical rotatory dispersion (in *n*-hexane) of reduced abietic-type resin acids. (For circular dichroism data, see Experimental Section.)

TABLE III
TETRAHYDRO ACIDS FROM HYDROGENATION OF ABIETIC-TYPE RESIN ACIDS[a]

Starting acid	Percent of tetrahydroabietic acid formed[b] 17 (mp 168°)	18 (mp 202°)	19 (mp 182°)
1	25	33	35[c]
2	25	34	40[c]
3	28	34	34[c]
4	66	28	6
5	34	62	4
7	0	0	100
8	0	10	90
9	0	6	94
13	39	55	6
14	2	5	93[d]
27	4	16	80
31	25	27	48

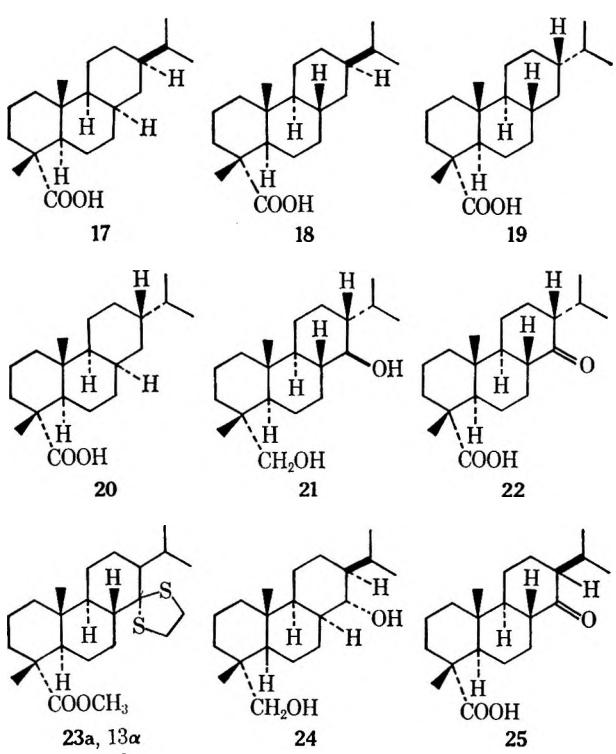
[a] Microscale (3–5 mg) hydrogenations were conducted at 25° (1 atm) over prereduced platinum oxide (30 mg) in glacial acetic acid (10 ml) and were complete in 3–20 min. [b] Determined by glpc of the methyl esters on 20% DEGS as described in ref 36. Peak area calculations were verified with a Du Pont 310 curve resolver. [c] Dehydroabietic (8,11,13-abietatrien-18-oic) acid constituted most of the remainder of the product. Acids **1**, **2**, and **3** were at least 95–98% pure according to glpc of their methyl esters. The other starting acids were chromatographically homogeneous. [d] A similar product composition resulted from hydrogenation of a 4:1 mixture of **14** and **7** over 5% rhodium on alumina at 150° in ethanol at 2000 psi.

(31) R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962).
(32) A. Yogev, D. Amar, and Y. Mazur, *Chem. Commun.*, 339 (1967).
(33) Although the plain (longer wavelength) portions of the ORD curves of 4- and 5-eholestene [C. Djerassi, W. Clossen, and A. E. Lippman, *J. Amer. Chem. Soc.*, **78**, 3163 (1956)] have been cited in connection with those of analogous dihydropimaric and dihydroisopimaric acids [A. J. Bose, *Chem. Ind.* (London), 1628 (1959); 1104 (1960)], the signs of the Cotton effects[32] of these steroids are actually opposite to those of the more apposite 19-nor steroids mentioned above [*cf.* M. Legrand and R. Viennet, *C. R. Acad. Sci., Paris, Ser. C*, **262**, 1290 (1965)].
(34) Determined by us on a sample kindly supplied by Dr. Ruth Lack from Professor C. W. Shoppee's collection [C. W. Shoppee, D. E. Evans, and G. H. R. Summers, *J. Chem. Soc.*, 97 (1957)].
(35) J. D. Renwick and P. M. Scopes, *ibid.*, *C*, 1949 (1968).

retention values[36] of their methyl esters and in part by their nmr spectra.[8] From Table III it is seen that, although minor amounts of epimerization occurred at C-13, hydrogenation of acids **7**, **8**, and **14** with a 13α-isopropyl group afforded mainly the tetrahydro acid of mp 182°, in accord with the 13α-isopropyl configuration that has been proposed[4a,8] for the latter. Hydrogenation of acids **4**, **5**, and **13**, on the other hand, gave mainly the 168 and 202° acids, in agreement with previous findings of Velluz and coworkers[12] and the assignment of a 13β-isopropyl configuration to these two tetrahydro acids.[1,8] The hydrogenation of the 8β-13-ene acid **9** to a mixture containing essentially only the 182 and 202° acids further indicates that the latter two acids belong to the B/C-*trans* series and shows that the 168° acid is the 13β-B/C-*cis* isomer **17**.

This last conclusion is confirmed by the significant downfield shift of the C-10 methyl resonance in the nmr spectrum (Table I) of the 168° acid compared with the corresponding shifts in the other two tetrahydro acids.[8] Such steric deshielding in **17** is caused by the axial 12β and 14β hydrogens. The comparatively low melting point is also in agreement with the folded structure required by **17**. The formation of this acid as the major product from high pressure hydrogenation of abietic acid over Raney nickel[11] is likewise expected (α side, all-*cis* reduction). Hence the 202° acid has the 8β,13β structure **18**, and the 182° acid has the 8β,13α structure **19**. The latter assignment was made in our preliminary report,[4a] while the other two were later made independently by Huffman, *et al.*,[8] and by two of us.[1]

CHART III



Several unsuccessful attempts were made to obtain the as yet unknown fourth 9α isomer, 8α-abietan-18-oic acid (**20**), the least stable member of the series (B/C-*cis* fusion and axial isopropyl group). It was hoped that, under some conditions, hydrogenation of either **7** or **14** would occur from the α side, as in the case of **4** and **13**, but evidently the blocking effect of the α-isopropyl group as it becomes axial in **20** is sufficient to prevent this. Even high pressure hydrogenation of a mixture of **7** and **14** over rhodium on alumina[37] failed to give detectable amounts of a new tetrahydro acid.

As a further chemical confirmation of its formulation as **19** and in connection with its use in the synthesis of fichtelite,[4a] a multistep, stereoselective preparation of the 182° tetrahydro acid was also carried out. Reduction–hydroboration[38] of acid **8** gave diol **21**, whose stereochemistry was assigned on the basis of the C-14 proton signal, which appeared as a triplet, J = 9–10 Hz, characteristic of an axial proton coupled to two adjacent axial protons.[39] Oxidation of diol **21** with Jones reagent gave the corresponding keto acid **22**, an alternative route to which has been reported by Huffman, *et al.*[8] This acid is stable to base and therefore has the all-*trans* configuration shown.[4a,8] Interestingly, it is extremely reluctant[4a,16] to form a 2,4-dinitrophenylhydrazone, evidently for steric reasons. Removal of the keto function of **22** to give the tetrahydro acid **19** was accomplished *via* esterification with diazomethane, thioketal formation to give **23**, and Raney nickel desulfurization, followed by hydrolysis. Some epimerization at C-13 occurred during the thioketal formation,[8] although under mild conditions most of the product retained the original configuration, as would be expected.[40] The desulfurization reaction was also not completely specific, since 5–10% of the C-13 epimeric acid **18** and up to 20% of the 13α-8-ene acid **14** could be detected by glpc of the reaction mixture. In contrast to this stereoselective route to **19**, Wolff–Kishner reduction of keto acid **22** caused complete epimerization at C-13 to give **18**, as has been independently observed by Huffman, *et al.*[8] Similar isomerization has been noted in the Wolff–Kishner reduction of even less hindered ketones, such as 9,10-diketoperhydroanthracene.[41]

For comparison purposes, a similar sequence of reactions was carried out on acid **5**. Reduction–hydroboration gave mainly diol **24**, whose nmr spectrum shows a deshielded C-10 methyl resonance as well as the expected *trans*-diaxial coupling (triplet, J = 10 Hz) of the C-14 proton. The β-side attack of diborane on acid **8** and the α-side attack on acid **5** is evidently controlled by the configuration at C-13 in the respective compounds. Jones oxidation of diol **24** was attended by clean epimerization at C-8 but not at C-13, to yield **25**, which corresponds to recent independent findings of Huffman and Alford.[17] The structure of **25** follows from the negative ORD curve of its methyl ester (like

(36) F. H. M. Nestler and D. F. Zinkel, *Anal. Chem.*, **39**, 1118 (1967).

(37) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, pp 979–982.

(38) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964); *cf.* ref 16.

(39) A. I. Scott, D. W. Young, S. A. Hutchinson, and N. S. Bhacca, *Tetrahedron Lett.*, 849 (1964); E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Amer. Chem. Soc.*, **86**, 2218 (1964); W. Herz, D. Melchior, R. N. Mirrington, and P. J. S. Pauwells, *J. Org. Chem.*, **30**, 1873 (1965).

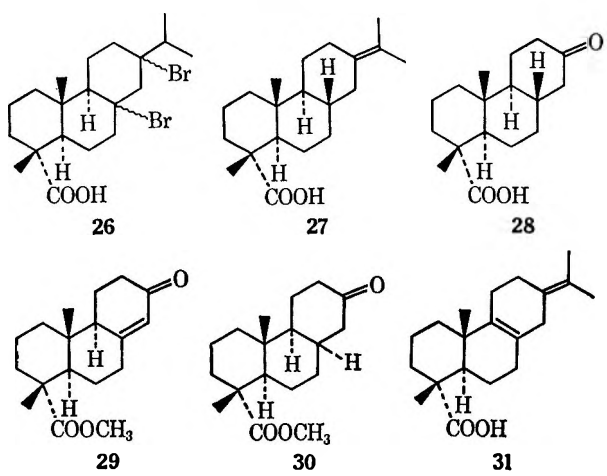
(40) R. E. Ireland and J. A. Marshall, *ibid.*, **27**, 1620 (1962).

(41) R. K. Hill, J. G. Martin, and W. H. Stouch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961); R. L. Clarke, *ibid.*, **83**, 965 (1961); N. S. Crossley and H. B. Henbest, *J. Chem. Soc.*, 4413 (1960); C. Djerassi, T. T. Grosnickle, and L. B. High, *J. Amer. Chem. Soc.*, **78**, 3166 (1956); see also ref 14b.

that of **22**[8]), the unhindered nature of the carbonyl group as judged by its ready formation of a 2,4-dinitrophenylhydrazone, the incorporation of one deuterium atom when diol **24** was oxidized with deuterated Jones reagent, and its conversion in good yield into tetrahydro acid **18** by the thioketal–desulfurization sequence.

Further Correlations. Acids 27 and 31.—Independent chemical evidence for the 8β configuration of **19** was obtained from a determination of the structure of the dihydroabietic acid formed by the action of sodium in cold ethanol[42] on abietic acid dihydrobromide (**26**, Chart IV). On the basis of the following evidence, this product of reductive elimination is the 8β-13(15)-ene acid **27.** The nmr spectrum (Table I) indicates the presence of an isopropylidene group (*cf.* neoabietic acid). Catalytic hydrogenation (Table III) afforded mainly acid **19,** implying a common stereochemistry at C-8 in the two compounds. Ozonolysis gave acetone and the tricyclic keto acid **28.** This keto acid was also obtained from the methyl ester of neoabietic acid (**2**) by partial ozonolysis[6,43] to **29,** followed by reduction with lithium in ammonia and oxidation of the resulting diol.[44] The B/C-*trans* ring junction in **28,** and hence in **27** and **19,** follows from the well-established stereochemical course of the metal–ammonia reduction of analogous 3-keto steroidal 4-enes and related compounds[14] and by the fact that the methyl ester of **28** exhibits a strong positive Cotton effect in its ORD, like that of 5α-cholestan-3-one.[45] Catalytic hydrogenation of **29** over palladium in ether furnished a mixture containing a 4:7 ratio of the methyl ester of **28** and the 8α epimer **30** (*cf.* related reduction of 4-cholesten-3-one to 5β-cholestan-3-one[46]).

CHART IV



Finally, from the mother liquors of the preparation of acid **27,** we were able to isolate a new isomer of abietic acid having the 8,13(15)-diene structure **31.** Readily purified as the methyl ester, this acid is the principal product if the sodium–alcohol reduction is conducted at elevated temperatures or if only sodium ethoxide in ethanol is used.[47] The structure follows from the nmr spectrum (Table I), which indicates the presence of an isopropylidene group and a downfield shift of the C-10 methyl signal, suggestive of the presence of unsaturation in the 8,9 position (*cf.* the C-10 methyl signal in the spectra of acids **13** and **14**). The absence of an olefinic proton signal and the presence of strong absorption at τ 8.06 (secondary allylic protons) and 7.40 (doubly allylic protons), coupled with the lack of conjugated diene absorption in the uv, allow only the 8,13(15)-diene structure **31** for this compound.

In accord with this assignment, hydrogenation of **31** over platinum in acetic acid resulted in the absorption of 2 mol of hydrogen with the formation of a mixture (Table III) of acids **17, 18,** and **19,** thereby proving that the original carbon skeleton was still intact. Isomerization with hydrochloric acid in ethanol[48] converted **31** in high yield into abietic acid (**1**). It is of interest that, in the formation of **31** by bisdehydrobromination of abietic acid dihydrobromide with base, no appreciable amount of conjugated dienic product could be detected.

Experimental Section[49]

Lithium–Ammonia Reduction of Abietic Acid. A. 8(14)-Abieten-18-oic Acid (8) and 13-Abieten-18-oic Acid (9).—By the method of Royals and coworkers,[9] reduction of 200 g (0.445 mol) of the diamylamine salt (mp 136–137.5°, $[\alpha]_D$ −60°) of abietic acid (**1**)[50] with 15 g (2.16 g-atoms) of lithium shot[51] was conducted at −35° in 2 l. of distilled anhydrous liquid ammonia. The blue color was allowed to persist for 4 hr before addition of ethanol. Isolation of the acidic product afforded, after four recrystallizations from acetone, 38 g (28%) of impure **8**: mp 190–195°; $[\alpha]_D$ −26° (lit. mp 197–198°, $[\alpha]_D$ −24°;[4b] mp 197–197.5°, $[\alpha]_D$ −24.7°[9]). Fractional crystallization of the mother liquors gave an additional 10 g of product with the same melting point and rotation (total yield 35%). Integration of the olefinic peaks in the nmr spectrum (*cf.* Table I) indicated the presence of *ca.* 85% **8** together with 15% **9.** This proportion of isomers was confirmed by glpc of the methyl esters (diazomethane). Four additional crystallizations from acetone gave material of mp 195–197.5°, $[\alpha]_D$ −25°, with little change in the nmr spectrum and glpc behavior. Efforts to achieve purification through the diamylamine salt, mp 116–117°, were unsuccessful; however, column chromatography of the methyl esters (1-g scale) on silver

(42) T. Hasselstrom and J. D. McPherson, *J. Amer. Chem. Soc.*, **61,** 1228 (1939).

(43) G. C. Harris and T. F. Sanderson, *ibid.*, **70,** 339 (1948); *cf.* S. W. Pelletier, K. N. Iyer, C. W. J. Chang, and A. Ogiso, *Tetrahedron Lett.*, 3819 (1968).

(44) This transformation of **29** to **28** has also been carried out by Dr. A. Afonso in the laboratories of Professor Ernest Wenkert. We thank Professor Wenkert for communicating his results to us for inclusion in this paper (see Experimental Section).

(45) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 43.

(46) H. Grasshof, *Hoppe-Seyler's Z. Physiol. Chem.*, **223,** 249 (1934).

(47) For possibly related results, see T. Hasselstrom and J. D. McPherson, *J. Amer. Chem. Soc.*, **61,** 2247 (1939); also p 426 of ref 7.

(48) V. M. Loeblich, D. E. Baldwin, and R. V. Lawrence, *ibid.*, **77,** 2823 (1955); see also ref 6 and 24.

(49) Melting points were determined in open capillaries with a Hershberg melting point apparatus calibrated against standard substances. Thin layer chromatography (tlc) was performed on microscope slides covered with silica gel G (Merck). Gas–liquid partition chromatography (glpc) was conducted at 200° on DEGS and SE-30/EGiP columns as described in ref 36, which also gives retention data for the methyl esters of the various dihydro- and tetrahydroabietic acids described herein. Sodium D-line rotations were measured on 1–2% solutions in ethanol at 25° with a Perkin-Elmer Model 141 polarimeter. Except where noted, optical rotatory dispersion (ORD) and circular dichroism (CD) curves were determined at 28° in *n*-hexane (1.0-cm cell) on a Cary Model 60 recording spectropolarimeter. Ultraviolet spectra were recorded in ethanol (or isooctane for the data in Table II) on a Cary Model 14 spectrophotometer. Infrared spectra were taken in carbon tetrachloride solution with a Perkin-Elmer Model 137 Infracord. Nmr spectra were determined in carbon tetrachloride solution on a Varian A-60 or HA-100 instrument with tetramethylsilane as internal reference. Ether solutions were dried over anhydrous magnesium sulfate. Petroleum ether refers to the fraction with bp 35–45°. Combusion analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(50) Obtained from WW gum resin by the procedure of G. C. Harris and T. F. Sanderson, "Organic Syntheses," Col. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 1.

(51) P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, **77,** 2804 (1955); *cf.* L. R. Worden and A. W. Burgstahler, *J. Chem. Educ.*, **45,** 425 (1968).

nitrate impregnated alumina (gradient elution with ether–petroleum ether), similar to the tlc method of Zinkel and Rowe,[15] was effective. The oily ester, $[\alpha]_D$ −34°, of **8** was eluted first, and on hydrolysis with refluxing 15% potassium hydroxide it afforded pure **8**: mp 199–200° (from acetone); $[\alpha]_D$ −32°; ORD (*c* 0.10) $[\Phi]_{400}$ −205°, $[\Phi]_{315}$ −270°, $[\Phi]_{275}$ ±0°, $[\Phi]_{250}$ +1050°; ORD (*c* 0.010) $[\Phi]_{230}$ +6000°, $[\Phi]_{218}$ +19,500°, $[\Phi]_{210}$ ±0°, $[\Phi]_{203}$ −16,000°; CD (*c* 0.00435) $[\Theta]_{245}$ ±0, $[\Theta]_{210}$ +37,000, $[\Theta]_{197}$ ±0.

The second component from the chromatographic separation was the methyl ester, $[\alpha]_D$ +5.5°, of **9** (*cf.* part C below). Hydrolysis with alcoholic base gave pure **9**, which, after recrystallization from ligroin, had mp 146–147°; $[\alpha]_D$ +6°; ORD (*c* 0.10) $[\Phi]_{400}$ +30°, $[\Phi]_{300}$ +105°, $[\Phi]_{260}$ +525°; ORD (*c* 0.010) $[\Phi]_{227}$ +1200°, $[\Phi]_{215}$ −300°, $[\Phi]_{210}$ +2500°; CD (*c* 0.0135) $[\Theta]_{260}$ ±0, $[\Theta]_{221}$ +2200, $[\Theta]_{208}$ −4900, $[\Theta]_{197}$ ±0.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.74; H, 10.65.

B. 13β-Abiet-8(14)-en-18-oic Acid (5).—The combined mother liquors from the reduction were diluted to 200 ml with hot acetone and mixed with 50 ml of diamylamine. After the solution had been cooled to −20°, the resulting mixture of salts was collected and the filtrate was concentrated to provide an additional crop. The solid product after recrystallization from acetone melted at 105–110°. Acidification of the mother liquors with cold 3 *N* hydrochloric acid and extraction with ether furnished a solid whose nmr spectrum showed only the one olefinic proton peak (τ 4.56) present in **5** (*cf.* Table I). Three crystallizations of this product from acetone–water furnished 15 g (11% from abietic acid diamylamine salt) of **5** as prisms: mp 144–147°; $[\alpha]_D$ +40° (lit. mp 143–145°, $[\alpha]_D$ +43.9°;[11] mp 151°, $[\alpha]_D$ +42°;[12] mp 146°, $[\alpha]_D$ +43°;[52] mp 149°, $[\alpha]_D$ +43°[53]). After further purification through the cyclohexylamine salt, mp 205–206°, a sample had mp 148.5–150°; $[\alpha]_D$ +42°; ORD (*c* 0.10) $[\Phi]_{400}$ +355°, $[\Phi]_{300}$ +1050°; ORD (*c* 0.010) $[\Phi]_{230}$ +8500°, $[\Phi]_{217}$ +22,000°, $[\Phi]_{205}$ ±0°, $[\Phi]_{200}$ −10,000°; CD (c 0.00525) $[\Theta]_{260}$ ±0, $[\Theta]_{209}$ +17,000, $[\Theta]_{195}$ ±0. The methyl ester had mp 84–85°, $[\alpha]_D$ +33°, as reported.[11]

In the preparation (1-g scale) of **5** by low pressure hydrogenation[11,29,63] of neoabietic acid (**2**)[54] over 10% palladium on carbon in ethanol, nmr analysis indicated that at least two other isomers were formed. Acid **5** with mp 140–144° was isolated in 15% yield after three crystallizations from acetone–water. In the similar preparation of **5** by partial hydrogenation[11,29] of levopimaric acid (**3**)[65] over the same catalyst in ethanol, considerable disproportionation to dehydroabietic acid occurred unless the reduction was conducted at −10 to −15° (ice–salt bath). The nmr spectrum of the crude product obtained under these conditions indicated that **5** was formed almost exclusively, but the yield of product with mp 141–144° (after three crystallizations) was only 25%.

C. 7-Abieten-18-oic Acid (7).—Regeneration of the free acids from the solid diamylamine salt mixture (mp 105–110°) of part B above, followed by recrystallization from acetone, gave a mixture of **7** **8**, and **9** (nmr analysis). The mother liquors contained much abietic acid and were discarded. Four crystallizations of the solid acid mixture from acetone afforded 10 g of impure **8**, mp 190–195°. Fractional crystallization of the residues, with nmr analysis as a guide for combining fractions, gave 4.5 g of crystalline product, mp 161–162°, $[\alpha]_D$ −8°, containing **7** and **9** in the ratio 9:11, according to glpc of their methyl esters. By column chromatography on silver nitrate–alumina, the methyl ester, mp 39.5–40°, $[\alpha]_D$ −26°, of **7** was eluted first, followed closely by the methyl ester, $[\alpha]_D$ +3.5°, of **9** (*cf.* part A above). Hydrolysis of its crystalline methyl ester furnished pure acid **7**: mp 180–182°; $[\alpha]_D$ −24°; ORD (*c* 0.10) $[\Phi]_{400}$ −170°, $[\Phi]_{300}$ −480°, $[\Phi]_{250}$ −1400°; ORD (*c* 0.010) $[\Phi]_{230}$ −3100°, $[\Phi]_{214}$ −13,500°, $[\Phi]_{205}$ ±0°, $[\Phi]_{202}$ +25,000°; CD (*c* 0.0042) $[\Theta]_{260}$ ±0, $[\Theta]_{224}$ +5700, $[\Theta]_{205}$ −33,000, $[\Theta]_{192}$ ±0.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.02; H, 10.54.

For comparison and spectral purposes, an authentic sample of the C-13 epimer of **7** [**13β-abiet-7-en-18-oic acid (4)**] was kindly supplied by Professor Leon Velluz.[12] This sample had mp 162.5–164°; $[\alpha]_D$ −14.5° (lit. mp 166°, $[\alpha]_D$ −26°;[11] mp 164°, $[\alpha]_D$ −16°[12]); ORD (*c* 0.10) $[\Phi]_{400}$ −160°, $[\Phi]_{300}$ −400°, $[\Phi]_{250}$ −980°; ORD (*c* 0.015) $[\Phi]_{230}$ −4500°, $[\Phi]_{217}$ −6800°, $[\Phi]_{205}$ ±0°, $[\Phi]_{202}$ +14,000°; CD (*c* 0.0075) $[\Theta]_{260}$ ±0, $[\Theta]_{227}$ +1100, $[\Theta]_{207}$ −17,500, $[\Theta]_{191}$ ±0.

Lithium–Ammonia Reduction of Levopimaric and Neoabietic Acid.—To a stirred solution of 1.0 g (3.3 mmol) of levopimaric acid (**3**)[65] in 60 ml of 1:1 ether–ammonia was added 0.2 g of lithium shot.[51] After 3 hr, 5 ml of methanol was added, and the ammonia was allowed to evaporate. Acidification of the residue with cold 3 *N* hydrochloric acid and extraction with ether gave a product whose nmr spectrum resembled that of the one derived from abietic acid except for the lack of a peak at τ 8.75, thus showing the absence of **7**. Olefinic proton peaks at τ 4.56, 4.67, and 4.91 indicated the presence of **5**, **8**, and **9** (*cf.* Table I). After precipitation of the diamylamine salts (two crops), followed by regeneration of the free acids in the filtrate, there was obtained 0.16 g of **5**, identified by its nmr spectrum and melting point (140–144°, after two crystallizations from acetone–water). Regeneration of the acids from the crude mixture of solid diamylamine salts, followed by four recrystallizations from acetone, furnished 0.30 g of the acid **8**–**9** mixture, mp 190–195°. The material in the mother liquors was not examined further.

Reduction of neoabietic acid (**2**)[54] by the same procedure afforded a mixture whose nmr spectrum was similar to that of the crude reduction product of levopimaric acid. Acids **5** and **8**–**9** were isolated in approximately the same yields as above. Glpc of the methyl esters of the total product mixture of all three reductions indicated that the acids isolated were the only ones present, in addition to recovered starting material. Any peak corresponding to the methyl ester of **6**, if present, was very minor or was obscured by one of the other peaks.

Lithium–Ethylamine Reduction of 3,5-Cholestadiene.—A stirred solution of 0.50 g (1.35 mmol) of 3,5-cholestadiene, mp 79–80°, $[\alpha]_D$ −120°,[56] in 40 ml of ethylamine was treated with small amounts of lithium shot[51] until the blue color persisted for several minutes. A few drops of *t*-amyl alcohol were introduced to discharge the color, and then more lithium was added to restore it. This operation was repeated three times. The neutral product recovered by evaporation, dilution with water, and extraction with petroleum ether crystallized from acetone in fine needles: mp 79–81°; $[\alpha]_D$ +69° ($CHCl_3$); yield 0.41 g (82%). The recorded values[57] for 4-cholestene are mp 83°; $[\alpha]_D$ +76°. Treatment with bromine in ethyl acetate, followed by crystallization of the product from cold ethyl acetate–methanol, afforded a dibromide with mp 116–117°; $[\alpha]_D$ +37° (lit.[57] mp 117°; $[\alpha]_D$ +39° for 4-cholestene dibromide).

A similar reduction of 2,4-cholestadiene,[58] mp 67–68°, $[\alpha]_D$ +165°, furnished a comparable yield of hydrocarbon whose melting point and spectral properties indicated that it also was mainly 4-cholestene.

Hydroxylation–Cleavage Experiments. A. Ketoaldehyde Esters 11a and 11b from Acids 5 and 8.—A solution of 210 mg (0.66 mmol) of the methyl ester, mp 84–85°, of **5** and 180 mg (0.71 mmol) of osmium tetroxide in 10 ml of dry pyridine was allowed to stand overnight at 25°. The brown solution was then diluted with water and extracted with ether. After removal of the ether, the osmate ester was dissolved in 10 ml of dioxane and treated with hydrogen sulfide,[59] and the mixture was concentrated under reduced pressure. Chromatography of the residue of 8 g of silica gel and elution with ether furnished 200 mg (90%) of glycol ester formulated as **methyl 8α,14α-dihydroxy-13β-abietan-18-oate,**[17] which crystallized from methanol–petroleum ether in fine needles: mp 165–166°; $[\alpha]_D$ −12°; nmr (pyridine) τ 6.17 (d, J = 10 Hz, C-14 H), 6.36 (methoxyl), 8.76 (C-4 methyl), 8.98 (deshielded C-10 methyl), and 9.06 (d, J = 7 Hz, isopropyl); nmr ($CDCl_3$) τ 6.28 (methoxyl), 6.42 ($W_{1/2}$ = 10 Hz, C-14 H), 8.79 (C-4 methyl), 8.97 (deshielded C-10 methyl), and 9.05 and 9.14 (overlapping isopropyl doublets, J = 6 Hz). Except for the melting point, these properties correspond closely with those recorded by Cross and Myers for the glycol ester mistakenly identified as "IXb" in their paper.[16]

(52) G. Brus, P. Legendre, and J. Grainier, *Bull. Soc. Chim. Fr.*, 955 (1947).

(53) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959).

(54) Isolated from WW gum resin by the procedure of V. M. Loeblich and R. V. Lawrence, *J. Org. Chem.*, **21**, 610 (1956).

(55) Isolated from pine oleoresin by the procedure of V. M. Loeblich, D. E. Baldwin, R. T. O'Connor, and R. V. Lawrence, *J. Amer. Chem. Soc.*, **77**, 6311 (1955); *cf.* W. D. Lloyd and G. W. Hedrick, *Org. Syn.*, **45**, 64 (1965).

(56) J. C. Eck, R. L. Van Peursem, and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, **61**, 171 (1939).

(57) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 253.

(58) E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

(59) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.49; H, 10.33.

Hydrolysis of the ester with refluxing alcoholic potassium hydroxide furnished the corresponding acid, **8α,14α-dihydroxy-13β-abietan-18-oic acid,** which crystallized from ethanol–ethyl acetate–petroleum ether in fine needle clusters: mp 234–235°; $[\alpha]_D$ −15° (*cf.* mp 229–232°, $[\alpha]_D$ −17°, recorded by Cross and Myers[16] for their glycol acid derived from the above ester).

A solution of 80 mg of the ester and 100 mg of lead tetraacetate in 3 ml of acetic acid was stirred at 25° for 2 hr. One drop of ethylene glycol was added, and after 10 min the product was isolated by dilution of the mixture with water and extraction with ether. The resulting oily ketoaldehyde ester **11a** (**methyl 8,14-dioxo-8,14-seco-13*S*-abietan-18-oate**) was homogeneous by tlc and showed ir absorption at 3.7 and 5.8–5.9 μ and nmr peaks at τ 0.22 (d, J = 2 Hz, aldehyde H), 6.28 (methoxyl), 8.82 (C-4 methyl), 9.04 (d, J = 5.5 Hz, isopropyl), and 9.25 (shielded C-10 methyl).

By the same procedure, the methyl esters of 157 mg (0.52 mmol) of the **8**–**9** mixture, mp 194–197°, furnished 125 mg (74%) of glycol ester formulated as **methyl 8α,14α-dihydroxyabietan-18-oate,**[16] which likewise crystallized from methanol–petroleum ether in fine needles: mp 147–148° (lit.[16] mp 148–149°); $[\alpha]_D$ −45°; nmr (in pyridine) peaks at τ 6.28 (d, J = 3 Hz, C-14 H), 6.40 (methoxyl), 8.69 (C-4 methyl), 8.94 and 9.02 (overlapping isopropyl doublets, J = 6.5 Hz), and 9.10 (C-10 methyl); nmr in $CDCl_3$ as recorded by Cross and Myers.[16] Melting point and ir comparison through the courtesy of Professor Cross confirmed the identity with glycol ester "Xc" in his paper.[16]

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.37; H, 10.42.

Hydrolysis of the ester with refluxing alcoholic potassium hydroxide furnished the corresponding acid, **8α,14α-dihydroxyabietan-18-oic acid,** which crystallized from ether–petroleum ether in fine needles: mp 162–164°; $[\alpha]_D$ −42° (lit.[16] mp 151–154°, $[\alpha]_D$ −39.5°).

Cleavage of the ester with lead tetraacetate gave the corresponding ketoaldehyde ester **11b** (**methyl 8,14-dioxo-8,14-seco-abietan-18-oate**) as an oil: ir 3.7 and 5.8–5.9 μ; nmr τ 0.43 (d, J = 2 Hz, aldehyde H), 6.28 (methoxyl), 8.83 (C-4 methyl), 9.04 (d, J = 5.5 Hz, isopropyl), and 9.25 (shielded C-10 methyl).

Ozonolysis of 0.30 g (1.0 mmol) of the **8**–**9** mixture, mp 194–197°, in the manner described by Kennedy,[9c] gave a mixture of keto acids whose nmr spectrum displayed a peak at τ 9.25 (C-10 methyl) with *ca.* half the area of the peak at 8.83 (C-4 methyl). Treatment of the crude product with refluxing acetic anhydride for 2 hr gave a mixture of anhydrides whose ir spectrum exhibited bands at 5.53, 5.70 (shoulder), 5.77, and 5.85 μ. Efforts to isolate a pure product by chromatography on silica gel led to extensive loss of material.

Oxidation of **11b** with Jones reagent[60] gave a comparison sample of the monomethyl ester of the keto diacid resulting from "normal" cleavage at C-8–C-14. The material was characterized by an nmr spectrum which was essentially the same as that of **11b** except for the disappearance of the aldehyde proton signal at τ 0.43. Treatment with acetic anhydride as above gave what appeared to be the expected dimeric keto ester anhydride, characterized by ir absorption at 5.55, 5.78, and 5.85 μ, and an essentially unchanged nmr spectrum.

B. Ketoaldehyde Esters 10a and 10b from Acids 4 and 7.—Hydroxylation as in A above of the methyl ester prepared from 76 mg (0.25 mmol) of **4** (sample kindly supplied by Professor Leon Velluz[12]) afforded 60 mg (76%) of the corresponding glycol ester formulated as **methyl 7α,8α-dihydroxy-13α-abietan-18-oate**: nmr at τ 6.34 (methoxyl), 6.53 ($W_{1/2}$ = 7 Hz, C-7 H), 7.11 (OH), 8.83 (C-4 methyl), 8.96 (deshielded C-10 methyl), and 9.12 (d, 6.5 Hz, isopropyl). This product was not characterized further but was oxidized directly with lead tetraacetate to give ketoaldehyde ester **10a** (**methyl 7,8-dioxo-7,8-seco-13β-abietan-18-oate**): nmr τ 0.37 (t, J = 2 Hz, aldehyde H), 6.34 (methoxyl), 8.80 (C-4 methyl), 9.00 (d, J = 6 Hz, isopropyl), and 9.10 (C-10 methyl) (last two assignments tentative).

A similar hydroxylation-cleavage of 30 mg (0.1 mmol) of the methyl ester, mp 39.5–40°, of **7** gave 15 mg of ketoaldehyde ester **10b** (**methyl 7,8-dioxo-7,8-secoabietan-18-oate**): τ 0.33 (t, J = 2 Hz, aldehyde H), 6.33 (methoxyl), 8.83 (C-4 methyl), 9.08 (d, J = 6 Hz, isopropyl), and 9.10 (C-10 methyl) (last two assignments tentative).

C. Ketoaldehyde Ester 12 from Acid 9.—From the osmium tetroxide hydroxylation of 100 mg (0.3 mmol) of the methyl ester of chromatographically pure **9**, mp 146–147°, there was obtained 40 mg of recovered starting material and 28 mg of crystalline glycol ester, mp 93–98°, which, although homogeneous by tlc, could not be recrystallized from any solvent. This ester was identical by ir and nmr comparison with that derived from the 188° glycol acid mistakenly identified as "XIIb" in the paper by Cross and Myers[16] and is formulated as predominantly **methyl 13,14β-dihydroxyabietan-18 oate** on the basis of the nmr spectrum: τ 6.33 (methoxyl), 6.82 (d, J = 9 Hz, C-14 H), 8.81 (C-4 methyl), 9.07 and 9.12 (pair of doublets, J = 7 Hz, isopropyl), and 9.10 (C-10 methyl). Cleavage of 25 mg of this product with 32 mg of lead tetraacetate was conducted in 1 ml of acetic acid-1-*d* for 2.5 hr at 25°. The mixture was then evaporated to dryness *in vacuo*, triturated with carbon tetrachloride, and filtered, and the solvent was removed, giving 18 mg of oily ketoaldehyde ester **12** (**methyl 13,14-dioxo-13,14-seco-abietan-18-oate**), homogeneous by tlc, whose nmr spectrum indicated that it was essentially deuterium free, with peaks at τ 0.47 (d, J = 3.5 Hz, aldehyde H), 6.35 (methoxyl), 8.86 (C-4 methyl), 8.95 (d, J = 7 Hz, isopropyl attached to carbonyl[20]), and 9.09 (nondeshielded C-10 methyl).

14-Oxo-7-abieten-18-oic Acid from the Nitrosyl Chloride Addition Product of Acid 8.—By reaction with nitrosyl chloride in acetic acid–ethyl acetate at 5°, acid mixture **8**–**9**, mp 194–197°, was converted in 30% yield into the reported α-chloro oxime, mp 176–177°.[9] Heating this product with pyridine at 90° for 30 min afforded the α,β-unsaturated oxime, as described.[9] After purification through the cyclohexylamine salt, mp 193–194°, this had mp 191–192°; λ_{max} 239 nm (ε 5500) [lit.[9] mp 192.5–193°, λ_{max} 239 nm (ε 6600)]; nmr signals at τ 3.90 (broad, oxime H), 4.70 (olefinic H), 8.73 (C-4 methyl), 9.12 (C-10 methyl), and 9.15 (d, J = 6 Hz, isopropyl). These data indicate that this product is the oxime of 14-oxo-7-abieten-18-oic acid.

Hydrolysis of the unsaturated oxime with 3 *N* sulfuric acid in refluxing 80% ethanol gave a difficultly purified keto acid whose spectral properties suggested that it contained increasing amounts of the isomeric 8-ene acid as the reaction proceeded. After hydrolysis for 2 hr the keto acid isolated as the cyclohexylamine salt (mp 192–195°) had λ_{max} 243 nm (ε 4400); nmr τ 4.70 (olefinic H) and 8.73 (C-4 methyl); ORD[61] (*c* 0.20, in methanol) $[\Phi]_{500}$ +180°, $[\Phi]_{330}$ +750°, $[\Phi]_{315}$ +700°; ORD (*c* 0.0055, in hexane) $[\Phi]_{265}$ +8500°, $[\Phi]_{247}$ ±0°, $[\Phi]_{230}$ −7800°, $[\Phi]_{220}$ −3000°. After hydrolysis for 4 hr the product (as the cyclohexylamine salt) had λ_{max} 248 nm (ε 4800) [lit.[9] λ_{max} 249 nm (ε 6400)], and the nmr spectrum showed considerable diminution of the peaks at τ 4.70 and 8.73, suggesting extensive isomerization of the double bond from the 7,8 to 8,9 position (*cf.* acid isomerization of **8** to a mixture of **7** and **14**).

Epoxidation of Methyl 13-Abieten-18-oate.—A solution of 106 mg (0.33 mmol) of the oily methyl ester of chromatographically pure **9** and 110 mg (0.64 mmol) of *m*-chloroperbenzoic acid in 5 ml of chloroform was stirred at 25° for 0.5 hr. Recovery of the neutral fraction afforded 108 mg of solid epoxide which, although homogeneous by tlc, recrystallized from methanol to give a product with mp 93–100°. The nmr spectrum exhibited signals at τ 6.34 (methoxyl), 7.64 (C-14 H, slightly broadened), 8.86 (C-4 methyl), 9.16 (C-10 methyl), and a pair of doublets centered at 9.07 and 9.11 (J = 6.5 Hz, isopropyl). (These values differ from those reported by Huffman, *et al.*,[8,17] for an epoxide apparently derived from the 8α-13-ene acid **6** present in a preparation of **8** melting at 187–194°.) A sample recrystallized from ether for analysis had mp 87–94°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.55; H, 10.33.

Isomerization of Acids 5 and 8. A. 13β-Abiet-8-en-18-oic Acid (13).—As an alternative to the reported[12] isomerization of **5** to **13** with hydrogen bromide in acetic acid (which we found to yield bromine-containing products), a modification of the procedure of Edwards and Howe,[53] suggested to us by Professor Ernest Wenkert from work of Dr. A. Afonso,[44] was employed. A solu-

(60) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin. *J. Chem. Soc.*, 2548 (1953).

(61) We thank Dr. Ulrich Weiss and Mr. David W. Hudson, NIAMD, National Institutes of Health, Bethesda, Md., for this determination.

tion of 1.0 g (3.3 mmol) of **5** (mp 144–147°) and 0.1 g of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 1 hr. After the solution had been washed with water, the product was recovered by evaporation of the solvent and crystallization from acetone to yield 0.84 g (84%) of **13** as platelets: mp 181–183°; $[\alpha]_D$ +120° (lit. mp 175°, $[\alpha]_D$ +125°;[11] mp 185°, $[\alpha]_D$ +125°;[12] mp 185–187°[62]). The nmr spectrum was devoid of olefinic proton absorption, and the methyl ester was homogeneous by glpc. A recrystallized sample had mp 183–185°; $[\alpha]_D$ +124°; ORD (*c* 0.10) $[\Phi]_{400}$ +860°, $[\Phi]_{300}$ +2100°; ORD (*c* 0.0050) $[\Phi]_{230}$ +8500°, $[\Phi]_{210}$ +27,000°, $[\Phi]_{200}$ ±0°; CD (*c* 0.0027) $[\Theta]_{235}$ ±0, $[\Theta]_{199}$ +26,500, $[\Theta]_{188}$ +17,000. The diamylamine salt crystallized from acetone in flattened needles, mp 117–118°.

B. 8-Abieten-18-oic Acid (14).—Application of the above procedure to the **8–9** mixture, mp 194–197°, afforded a similar yield (80%) of isomerized product which, after two crystallizations from acetone, had mp 173–176°; $[\alpha]_D$ +6° (lit.[9c] mp 174.5–176°, $[\alpha]_D$ +8°). However, the nmr spectrum and glpc of the methyl ester showed that this product contained *ca.* 20–25% **7** and only 75–80% desired 8-ene acid **14**. Separation was effected by chromatography of the methyl esters on silver nitrate impregnated alumina,[15] with the ester of **14** being eluted before that of **7**. Hydrolysis of the purified ester furnished pure **14** which crystallized from acetone as short needles: mp 164–166° with resolidification and remelting at 172–174°; $[\alpha]_D$ +6°; ORD (*c* 0.10) $[\Phi]_{400}$ −380°, $[\Phi]_{300}$ −780°, $[\Phi]_{250}$ −2000°; ORD (*c* 0.0125) $[\Phi]_{225}$ −6700°, $[\Phi]_{217}$ ±0°, $[\Phi]_{210}$ +6900°; CD (*c* 0.0125) $[\Theta]_{245}$ ±0, $[\Theta]_{215}$ −7300, $[\Theta]_{200}$ −2500.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.53; H, 10.64.

The diamylamine salt crystallized from acetone in long thin needles, mp 124–125.5°.

C-13 Epimeric Dihydroabietic γ- and δ-Lactones 15 and 16.—Treatment of 0.10 g of **13** with 3 ml of a saturated solution of hydrogen bromide in glacial acetic acid for 18 hr at 25°, or with 2 ml of 18 *M* sulfuric acid (*d* 1.84) for 1 hr at 0°, gave a mixture showing a strong ir band at 5.65 μ (γ-lactone) and lesser peaks at 5.80 (δ-lactone) and 5.90 μ (acid). Two recrystallizations of the neutral fraction from acetone furnished 45 mg (45%) of 13β-dihydroabietic γ-lactone **15a** (**9,5-friedo-13β-abietan-18:10-olide**): mp 129.5–131°; $[\alpha]_D$ −3° (lit.[7,12] mp 130–131°; $[\alpha]_D$ −2°, −6°); nmr signals at τ 8.95 (C-4 methyl), 9.11 (d, *J* = 6 Hz, isopropyl), and 9.15 (C-9 methyl). When allowed to stand in concentrated sulfuric acid for 24 hr at 25°, **15a** was converted into a mixture of γ- and δ-lactones in a ratio of *ca.* 55:45, determined by the relative ir absorption at 5.65 and 5.80 μ[24,27] and confirmed by glpc (see below). Hydrolysis of this mixture with potassium hydroxide in refluxing *n*-butyl alcohol[9] furnished 13β-dihydroabietic δ-lactone **16a** (**5β,13β-abietan-18:9-olide**) in 35% yield. When crystallized from methanol this formed small plates: mp 147–149°; $[\alpha]_D$ +42° (lit. mp 151–152°, $[\alpha]_D$ +42.6°;[24] mp 149°, $[\alpha]_D$ +43°[26]); ir 5.80 μ; nmr as recorded by Herz and Wahlborg.[24] When allowed to stand in concentrated sulfuric acid for 24 hr at 25°, **16a** gave the same 55:45 ratio of γ- and δ-lactones obtained from **15a**.

For preparation of γ-lactone **15b**, a solution of 1.0 g (3.3 mmol) of acid **14** (containing 25% acid **7**) in 20 ml of chloroform, was stirred with 0.6 ml of 18 *M* sulfuric acid for 10 min at 0°. The ir spectrum of the product indicated the presence of 20% γ-lactone and 80% unchanged acid. With longer reaction times a δ-lactone band at 5.80 μ began to appear in the spectrum. Crystallization from acetone–water separated the bulk of unchanged acid. Chromatography of the mother liquor residues on 15 g of neutral alumina (activity grade II) afforded, by elution with ether, 0.16 g (16%) of 13α-dihydroabietic γ-lactone **15b** (**9,5-friedoabietan-18:10-olide**), which crystallized from methanol in needles: mp 101–102°; $[\alpha]_D$ −45°; ir 5.65 μ; nmr τ 8.93 (C-4 methyl), 9.05 (C-9 methyl), and 9.08 (d, *J* = 6 Hz, isopropyl).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.60; H, 10.52.

When allowed to stand in 5 ml of 18 *M* sulfuric acid for 24 hr at 25°, 0.50 g of **15b** gave a mixture of γ- and δ-lactones in a ratio of *ca.* 1:99, whereas contact with sulfuric acid for 1 hr at 0° produced a 40:60 ratio, as reported.[9] Selective removal of residual γ-lactone by saponification as above in the isolation of **16a** gave 13α-dihydroabietic δ-lactone **16b** (**5β-abietan-18:9-olide**), which showed carbonyl absorption only at 5.80 μ. Further purification by chromatography on 10 g of neutral alumina and elution with ether afforded 0.38 g (76%) of **16b** as a colorless oil, $[\alpha]_D$ −38° (lit.[9] $[\alpha]_D$ −43°), which could not be induced to crystallize. The principal nmr peaks appeared at τ 8.80 (C-4 methyl), 8.92 (C-10 methyl), and 9.06 (d, *J* = 5.5 Hz, isopropyl). Sulfuric acid equilibration of this product for 24 hr at 25° produced the 1:99 mixture of γ- and δ-lactones obtained from **15b**.

The percentage equilibrium ratios (by ir analysis[24]) of γ-lactone to δ-lactone from sulfuric acid treatment at 25° of some of the other dihydroabietic acids investigated in this study were as follows: acid **4**, 55:45; acid **7–9** mixture (mp 161–162°), 5:95; acid **8–9** mixture (mp 194–197°), 5:95; acid **27** (see later), 10:90. By glpc at 200° on DEGS, **15a**, **15b**, **16a**, and **16b** were separated cleanly and exhibited the following retention times relative to methyl pimarate: 4.78, 2.39, 3.35, and 3.51, respectively. On SE-30/EGiP, the values relative to the same standard were 1.97, 1.23, 1.47, and 1.58.

Reduction–Hydroboration of Acids 8 and 5. A. Abietane-14β,18-diol (21).—To an ice-cold solution of 0.4 g of lithium aluminum hydride and 1.0 g (3.3 mmol) of acid **8–9** mixture, mp 190–195°, in 30 ml of dry ether was added 2.0 ml of boron trifluoride etherate in 30 ml of ether over a period of 3 hr.[38] The mixture was allowed to warm to 25° and was then stirred for 6 hr. Saturated sodium sulfate solution was slowly added until hydrolysis was complete and the mixture had turned white. Solid sodium sulfate was then added, and the coagulated salts were separated by filtration. The ether filtrate was evaporated, and the solid residue was dissolved in 70 ml of 80% ethanol containing 1.0 g of sodium hydroxide. To this was added slowly, with stirring, 6.0 ml of 30% hydrogen peroxide, and the mixture was refluxed overnight. The oily product obtained on extraction with chloroform was dissolved in hot benzene, causing crystallization to occur. After completion of crystallization at room temperature (further cooling led to the formation of very stable gels with the solvent), there was obtained 0.65 g (65%) of diol **21** as prisms, mp 172–174°. A recrystallized sample had mp 173–175°; $[\alpha]_D$ +11°; nmr spectrum (pyridine) τ 6.51 (AB quartet, *J* = 11 Hz, C-4 hydroxymethyl[63]), 6.87 (t, *J* = 9 Hz, C-4 H), 9.00 and 9.12 (overlapping isopropyl doublets, *J* = 6.5 Hz), 9.09 (C-4 methyl), and 9.15 (C-10 methyl).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 78.08; H, 11.72.

In agreement with the proposed structure and configuration, the nmr spectrum of the oily diacetate of **21**, prepared by acetylation with acetic anhydride in pyridine, showed signals at τ 5.50 (t, *J* = 10 Hz, C-4 H), 6.31 (AB quartet, *J* = 11 Hz, C-4 acetoxymethyl[63]), 8.03 and 8.05 (acetate methyls), 9.12 (C-4 methyl), 9.15 (d, *J* = 7 Hz, isopropyl), and 9.17 (C-10 methyl).

B. 13β-Abietane-14α,18-diol (24).—Application of the foregoing reduction–hydroboration procedure to 1.0 g (3.3 mmol) of **5**, mp 144–147°, furnished 0.60 g (60%) of a diol which formed stable gels with most crystallization solvents. Partial purification by chromatography on 20 g of silica gel and elution with ether, followed by crystallization from ether, afforded **24** as a microcrystalline solid which softened at 115° and melted at 155–157°: nmr signals at τ 6.27 (t, *J* = 6.5 Hz, C-14 H), 6.71 (AB quartet, *J* = 10 Hz, C-4 hydroxymethyl[63]), 8.96 (deshielded C-10 methyl), 9.06 and 9.12 (overlapping isopropyl doublets, *J* = 6.5 Hz), and 9.18 (C-4 methyl).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 77.94; H, 11.89.

The nmr spectrum of the oily diacetate of **24** showed peaks at τ 4.85 (t, *J* = 9 Hz, C-14 H), 6.30 (AB quartet, *J* = 11 Hz, C-4 acetoxymethyl[63]), 8.05 and 8.07 (acetate methyls), 8.93 (deshielded C-10 methyl), 9.05 and 9.11 (overlapping isopropyl doublets, *J* = 6 Hz), and 9.19 (C-4 methyl).

A later minor fraction from chromatography of the mother liquors from the hydroboration reaction had mp 125–127°, but this was not examined further.

Oxidation of Diols 21 and 24. A. 14-Oxoabietan-18-oic Acid (22).—To a stirred solution of 1.0 g (3.3 mmol) of **21** in 60 ml of acetone at 0° was added 6.0 ml of Jones reagent.[60] A green

(62) C. Tabacik-Wlotzka, M. Mousseron, and A. Chafaï, *Bull. Soc. Chim. Fr.*, 2299 (1963).

(63) A. Gaudemer, J. Polonsky, and E. Wenkert, *ibid.*, 407 (1964), and references cited therein.

precipitate formed rapidly and gradually coagulated to a hard mass. After 8 hr at 25°, the mixture was treated with 5 ml of methanol and then with 100 ml of water, with stirring and heating, to digest the precipitate. The crude keto acid **22**, collected by filtration, weighed 0.87 g (81%): mp 251–254°. Recrystallization from methanol gave colorless rectangular platelets: mp 257–259°; $[\alpha]_D$ +19°. Huffman, *et al.*,[8] record mp 256–257°, $[\alpha]_D$ +21°, for a sample prepared from the β-epoxide[9] of **8**.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.98; H, 10.06.

Esterification with diazomethane gave the methyl ester of **22**, which crystallized from methanol in needles: mp 80–81°; $[\alpha]_D$ +14°; nmr as recorded by Huffman, *et al.*[8]

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.19; H, 10.11.

Neither acid **22** nor its methyl ester formed a semicarbazone or 2,4-dinitrophenylhydrazone under the usual conditions. (Cross and Myers[16] report formation of the latter derivative from the ester after reaction for 14 days.) Neither the acid nor ester was epimerized by sodium methoxide in refluxing methanol or 5% hydrochloric acid in diglyme at 100°. The ORD[61] of **22** in methanol was the same as that recorded by Huffman, *et al.*,[8] for an ethanol solution.

B. 14-Oxo-13β-abietan-18-oic Acid (25).—Application of the foregoing oxidation to 0.40 g of **24** furnished 0.35 g of crude **25**, which partially solidified but could not be obtained crystalline. The nmr spectrum showed peaks at τ 8.84 (C-4 methyl), 9.09 and 9.15 (overlapping isopropyl doublets, J = 7 Hz), and 9.13 (C-10 methyl). The 2,4-dinitrophenylhydrazone of the methyl ester (diazomethane) formed readily but melted over the range 100–112°. When seeded with a sample prepared as described below, the methyl ester of **25** crystallized from methanol–water in fine needles: mp 79–79.5°; $[\alpha]_D$ −92°; nmr τ 6.35 (methoxyl), 8.83 (C-4 methyl), 9.09 and 9.14 (overlapping isopropyl doublets, J = 7 Hz), and 9.16 (C-10 methyl); ORD (*c* 0.0435) $[\Phi]_{400}$ −690°, $[\Phi]_{319}$ −2300°, $[\Phi]_{313}$ −1650°, $[\Phi]_{309}$ −1850°, $[\Phi]_{283}$ +230°; CD (*c* 0.0435) $[\theta]_{330}$ ±0, $[\theta]_{297}$ −1550, $[\theta]_{220}$ +1850.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.15; H, 10.42.

As an alternative route to the methyl ester of **25**, 1 ml of boron trifluoride etherate was added dropwise to a stirred solution of 0.44 g (1.47 mmol) of the methyl ester (mp 83–85°) of **5** and 0.2 g of sodium borohydride in 10 ml of dry diglyme cooled to 0°. The mixture was stirred for 3 hr at 25°, and 5 ml of 10% sodium hydroxide and 5 ml of 30% hydrogen peroxide were added. Stirring was continued for an additional 3 hr, water was added, and the neutral product was isolated by extraction with chloroform. Crystallization from methanol gave 0.28 g (57%) of **methyl 14α-hydroxy-8α,13β-abietan-18-oate** as fine needles: mp 137–137.5°; nmr ($CDCl_3$) τ 6.35 (methoxyl), 6.54 (hydroxyl), 8.82 (C-4 methyl), 9.00 (deshielded C-10 methyl), and 9.10 and 9.20 (pair of doublets, isopropyl, J = 7 Hz).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.72; H, 10.85.

Oxidation of 0.23 g (0.97 mmol) of the foregoing product in 10 ml of acetone at 0° by dropwise addition of Jones reagent[60] until the orange color persisted for 5 min afforded 0.15 g (65%) of recrystallized methyl ester of **25**, mp 79–79.5° (see above). When conducted with Jones reagent prepared with D_2SO_4 and D_2O (with precautions to exclude moisture in the work-up with D_2O), the oxidation yielded a keto ester containing one deuterium atom, as was determined by comparison of the mass spectrum with that of a nondeuterated sample.

Methyl 14-Oxoabietan-18-oate Ethylenethioketal (23a).—A solution of 0.50 g (1.5 mmol) of the methyl ester of **22** in 2.0 ml of ethanedithiol and 0.6 ml of boron trifluoride etherate was prepared at 0° and allowed to stand overnight at 20°. Extraction of the solidified mixture with benzene, repeated washing with 5% sodium hydroxide solution, and recrystallization of the product from methanol–benzene gave 0.56 g (91%) of thioketal **23a** as feathery needles: mp 205.5–206.5°; $[\alpha]_D$ −33° ($CHCl_3$); nmr (*cf.* Huffman, *et al.*[8]) τ 6.33 (methoxyl), 6.79 (ethylenethioketal protons), 8.84 (C-4 methyl), 9.15 (C-10 methyl), and a pair of doublets centered at 9.01 and 9.08 (J = 6.5 Hz, isopropyl).

Anal. Calcd for $C_{23}H_{38}O_2S_2$: C, 67.27; H, 9.33; S, 15.62. Found: C, 67.31; H, 9.25; S, 15.48.

In larger batches, the formation of **23a** was attended by considerable epimerization[8] (mainly at C-13 to give **23b**), as shown by the lower melting point (195–202°) of the product and by its subsequent conversion into samples of **19** containing significant amounts of the C-13 epimer **18** (see below).

Methyl 14-Oxo-13β-abietan-18-oate Ethylenethioketal (23b).—By the procedure used to prepare **23a**, 0.11 g of the methyl ester of **25** (mp 77–79°) was converted in comparable yield into **23b**, which crystallized from benzene in needle clusters: mp 192–195° (lit.[8] mp 192–193°); nmr spectrum as recorded by Huffman, *et al.*,[8] for a sample isolated from the mother liquors of **23a**.

Anal. Calcd for $C_{23}H_{38}O_2S_2$: C, 67.27; H, 9.33. Found: C, 67.45; H, 9.61.

Abietan-18-oic Acid (19). A. From Thioketal 23a.—A stirred suspension of *ca.* 25 g of Raney nickel catalyst (W-2) and 1.30 g (3.15 mmol) of **23a**, mp 205.5–206.5°, in 300 ml of absolute ethanol was refluxed overnight. The neutral product was purified by chromatography on 25 g of neutral alumina (elution with 1:1 ether–petroleum ether). There was obtained 0.86 g (85%) of an oil which when seeded with a sample of the methyl ester of **19**, prepared as described below, crystallized slowly from methanol at −10 to −20°: mp 45–46°; $[\alpha]_D$ +7° (lit. mp 44–45°;[64] $[\alpha]_D$ +7.2°[11]). Glpc showed the crystalline ester (0.55 g, 55%) to be homogeneous, but the crude material averaged about 5–10% methyl ester of **18** and up to 20% methyl ester of **14**, depending on the activity of the Raney nickel. Saponification of the crystalline ester gave 0.47 g (90%) of **19** as prisms from acetone: mp 180–182°; $[\alpha]_D$ +6° (lit. mp 180–181°, $[\alpha]_D$ +10°;[8] mp 185.5–186°, $[\alpha]_D$ −2.3°;[9] mp 185–186°, $[\alpha]_D$ +12.4°;[11] mp 183–184°, $[\alpha]_D$ +6°;[64] mp 179–181°, $[\alpha]_D$ +6.2°[65]); ORD (*c* 0.288) $[\Phi]_{400}$ +60°, $[\Phi]_{300}$ +205°, $[\Phi]_{233}$ +1550°, $[\Phi]_{217}$ ±0°, $[\Phi]_{200}$ −1500°; CD (*c* 0.288) $[\theta]_{250}$ ±0, $[\theta]_{217}$ +3100, $[\theta]_{190}$ ±0.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.51; H, 10.99.

B. From Acid 8 by Hydrogenation.—A solution of 1.0 g (3.3 mmol) of acid mixture **8–9**, mp 194–197°, in 30 ml of acetic acid–ethyl acetate (1:1) was hydrogenated over 0.2 g of platinum oxide during 30 min. The resulting solid gave a negative test with tetranitromethane, and the nmr spectrum showed no detectable signal at τ 8.90 (absence of **17**; see Table I). Glpc of the methyl ester of the crude product from several runs or from hydrogenation of pure **8**, mp 199–200°, indicated the presence of *ca.* 90% **19** and 10% **18** but no **17** (Table III). Crystallization of the crude acid from acetone gave 0.81 g (80%) of **19** as prisms: mp 179.5–181°, raised to 180–181.5° by recrystallization; $[\alpha]_D$ +6°. Further purification by means of the diamylamine salt, mp 127–127.5°, gave material with mp 181.5–182°, $[\alpha]_D$ +6°. The methyl ester (mp 45–46°, $[\alpha]_D$ +7°) crystallized from methanol at −10 to −20°.

For spectral and comparison purposes, an authentic sample of **8α,13β-abietan-18-oic acid (17)** was prepared as follows. A solution of 3.0 g (0.01 mol) of abietic acid (**1**)[60] in 30 ml of absolute ethanol was hydrogenated over 10 g of W-2 Raney nickel catalyst at 200° and 3000 psi for 8 hr.[11] The nmr spectrum (Table I) of the total reduction product and glpc of its methyl ester on DEGS indicated that **17** was the predominant product. Three crystallizations from methanol furnished 1.05 g (35%) of **17** as needles: mp 165–167°; $[\alpha]_D$ +17° (lit. mp 164°, $[\alpha]_D$ +21°;[8] mp 165–166°, $[\alpha]_D$ +28.3°;[11] mp 168°, $[\alpha]_D$ +23°;[12] mp 163–164.5°, $[\alpha]_D$ +26°;[66] mp 168–170°, $[\alpha]_D$ +19°[67]); ORD (*c* 0.237) $[\Phi]_{400}$ +175°, $[\Phi]_{300}$ +370°, $[\Phi]_{233}$ +1840°, $[\Phi]_{215}$ ±0°, $[\Phi]_{205}$ −750°; CD (*c* 0.237) $[\theta]_{250}$ ±0, $[\theta]_{215}$ +1900, $[\theta]_{190}$ ±0. The methyl ester crystallized from methanol in stout needles: mp 95–97°; $[\alpha]_D$ +13° (lit. mp 97–98°, $[\alpha]_D$ +11°;[8] mp 99°, $[\alpha]_D$ +21.3°;[11] mp 96°, $[\alpha]_D$ +15°;[12] mp 99°, $[\alpha]_D$ +20°[66]).

For preparation of an authentic sample of **13β-abietan-18-oic acid (18)**, a solution of 1.0 g (3.3 mmol) of **5**, mp 144–147°, in 25 ml of acetic acid was hydrogenated over prereduced platinum oxide as reported previously.[12] The nmr spectrum of the crude product and glpc of its methyl esters (Table III) indicated that **18** and **17** were present in the ratio of 2:1, along with minor amounts of **19**. After six recrystallizations from acetone, there was obtained 0.28 g (27%) of pure **18** as prisms: mp 200–201°; $[\alpha]_D$ +8° (lit. mp 201–201.5°, $[\alpha]_D$ +8°;[8] mp 202°, $[\alpha]_D$ +7°[12]); ORD (*c* 0.201) $[\Phi]_{400}$ −8°, $[\Phi]_{300}$ ±0°, $[\Phi]_{233}$ +1800°, $[\Phi]_{215}$ ±0°, $[\Phi]_{205}$ −1500°; CD (0.201) $[\theta]_{245}$ ±0, $[\theta]_{216}$ +2200, $[\theta]_{195}$ ±0. The methyl ester after crystallization from wet methanol had

(64) E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.*, **60**, 921 (1938).

(65) L. Ruzicka and St. Kaufmann, *Helv. Chim. Acta*, **24**, 1389 (1941). See also other references cited on p 384 in ref 7.

(66) L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, **60**, 159 (1938).

(67) L. Ruzicka and H. Schinz, *Helv. Chim. Acta*, **6**, 662 (1923).

mp 74–76° (lit. mp 75–77°,[8] 77°[12]). Application of the Huang-Minlon modification[68] of the Wolff–Kishner reduction to the methyl ester of **22** gave this same tetrahydro acid, as also observed by Huffman, *et al.*[8]

Desulfurization of ethylenethioketal **23b** (mp 190–192°) furnished the methyl ester of **18** with a purity greater than 90% according to analysis by glpc (ester of **19** apparent major impurity).

13(15)-Abieten-18-oic Acid (27).—Abietic acid dihydrobromide (**26**), mp 172–174°, was prepared by the method of Hasselstrom and McPherson.[42] The product (**27**) of mild sodium–alcohol reduction was obtained by the following modification of the published procedure.[42] To an ice-cold solution of 15 g of sodium dissolved in 600 ml of absolute ethanol, 10.0 g (0.022 mol) of abietic acid dihydrobromide was added (insoluble), followed by 15 g of sodium in 0.1-g pieces, with cooling and stirring. After 2 hr the ice bath was removed and the mixture was allowed to stir overnight at 20°. After dilution with 3 l. of water the mixture was extracted with two 200-ml portions of petroleum ether (discarded) and acidified to pH 2 with 6 *N* hydrochloric acid. Further extraction with three 200-ml portions of ether, followed by drying over anhydrous sodium sulfate, treatment with Norit, filtration, and evaporation of the solvent, furnished impure **27** as colorless plates from acetone: mp 180–205°; yield 1.165 g (18%). Three crystallizations gave material with mp 210–216°; $[\alpha]_D$ −15° (changed by further crystallization to mp 218–220°; $[\alpha]_D$ −18°) (lit.[42] mp 217.5–218.5°; $[\alpha]_D$ −23°); ORD (*c* 0.20) $[\Phi]_{400}$ −140°, $[\Phi]_{300}$ −250°, $[\Phi]_{245}$ ±0°, $[\Phi]_{230}$ +650°; ORD (*c* 0.040) $[\Phi]_{217}$ +1350°, $[\Phi]_{210}$ +650°; CD (0.00735) $[\Theta]_{250}$ ±0, $[\Theta]_{208}$ +5500, $[\Theta]_{200}$ ±0. The methyl ester had mp 129.5–130.5° (lit.[42] mp 131.5–132.5°).

13-Oxopodocarpan-18-oic Acid (28). A. From Acid 27.—Ozone (5% in dry oxygen) was bubbled slowly through a solution of 200 mg (0.66 mmol) of **27** in 40 ml of ethyl acetate at −78° until the solution turned blue. The solution was then flushed with nitrogen, allowed to warm to room temperature, and stirred under hydrogen over 10% palladium on carbon. Three crystallizations of the resulting solid from methanol gave 85 mg (46%) of **28** as needles: mp 158–159°; $[\alpha]_D$ +16°; nmr τ 8.82 (C-4 methyl) and 9.08 (C-10 methyl).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.43; H, 9.36.

Ozonolysis of the methyl ester of **27** gave the methyl ester of acid **28** (see part B below), whose yellow 2,4-dinitrophenylhydrazone crystallized from methanol–water: mp 192–194°.

Hydroxylation with osmium tetroxide in the manner described for the methyl ester of **5** converted 96 mg (0.3 mmol) of the methyl ester of **27** into 57 mg (54%) of the corresponding glycol ester, characterized by nmr signals at τ 6.38 (methoxyl), 7.60 (OH), 8.82 (C-4 methyl), 8.87 (C-15 methyls), and 9.16 (C-10 methyl). Cleavage with lead tetraacetate gave the methyl ester of **28**, with identical infrared and nmr spectra. The 2,4-dinitrophenylhydrazone had mp and mmp 192–194°.

B. From Neoabietic Acid (2).—To a solution of 200 mg (0.69 mmol) of **29** (mp 123–125°, prepared by partial ozonolysis of methyl neoabietate[6,43]) in 40 ml of dry ether and 50 ml of liquid ammonia was added 0.5 g of lithium shot[51] in portions with stirring. After 15 min, 10 ml of ethanol was added to discharge the blue color. The product recovered after evaporation of the ammonia and extraction from water with ether and then chloroform was apparently mostly diol in nature (ir absorption at 2.8 and 3.0 μ but none in the 5.7–6.2-μ region). This material was stirred with 0.5 ml of Jones reagent[50] in 10 ml of acetone for 3 hr. Isolation of the acidic product by dilution with water, extraction with ether, and crystallization from methanol gave 65 mg (34%) of needles of acid **28**, mp 158–159°, undepressed on admixture with the preparation obtained above. The ir and nmr spectra of the acid as prepared by the two routes were also indistinguishable. Treatment of the mother liquors from the crystallization of the oxidation product with diazomethane and then with 2,4-dinitrophenylhydrazine reagent gave the yellow 2,4-dinitrophenylhydrazone, mp and mmp 192–194° (after three recrystallizations), of the methyl ester of **28**, as described above.

In an alternative procedure (by Dr. A. Afonso[44]), the crude acid from application of the above sequence to 370 mg (1.28 mmol) of **29** was esterified with diazomethane and chromatographed on 12 g of neutral alumina (activity grade II). Elution with benzene–hexane (1:1) gave 230 mg (62%) of the methyl ester of acid **28**, which crystallized from aqueous methanol: mp 98–104°; $[\alpha]_D$ +18°; ORD (0.10) $[\Phi]_{400}$ +85°, $[\Phi]_{312}$ +3300°, $[\Phi]_{280}$ +900°; ORD (*c* 0.010) $[\Phi]_{235}$ +18,000°, $[\Phi]_{220}$ ±0°, $[\Phi]_{210}$ −23,000°; CD (*c* 0.010) $[\Theta]_{330}$ ±0, $[\Theta]_{298}$ +1550, $[\Theta]_{265}$ +1200, $[\Theta]_{216}$ +16,500, $[\Theta]_{196}$ ±0.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.59; H, 9.51.

Hydrogenation of 0.1 g (0.35 mmol) of **29** over 50 mg of 10% palladium on carbon in 15 ml of ether[46] at 30° (1 atm) was complete in 20 min and furnished a solid, mp 65–75°, whose nmr spectrum indicated the presence of predominantly B/C-*cis* product **30** (deshielded C-10 methyl resonance at τ 8.92) along with the methyl ester of **28**. Glpc on SE-30/EGiP showed that **30** and the methyl ester of **28** were present in the ratio of 7:4, with retention times of 1.64 and 1.40, respectively, relative to methyl pimarate.

8,13(15)-Abietadien-18-oic Acid (31).—The acids remaining in the mother liquors from the preparation of **27** were converted into the methyl esters with diazomethane. After three crystallizations of the very impure product from methanol, well-formed needles were deposited, which, after two further crystallizations, had mp 104.5–106°; $[\alpha]_D$ +161°; yield 0.60 g (9% from **26**). The nmr spectrum indicated that no olefinic protons were present, thus showing that the substance was the methyl ester of the nonconjugated diene acid **31**. The uv spectrum showed λ_{max} 194.5 nm (ϵ 30,800).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.38; H, 9.95.

Saponification of the ester with 10% potassium hydroxide in ethylene glycol at 180° gave the corresponding acid, **31**, which crystallized from acetone–water in small needles: mp 162–165°; $[\alpha]_D$ +165°; ORD (*c* 0.30) $[\Phi]_{400}$ +1250°, $[\Phi]_{300}$ +3200°; ORD (*c* 0.010) $[\Phi]_{250}$ +7300°, $[\Phi]_{230}$ +18,000°, $[\Phi]_{215}$ ±0°; CD (0.010) $[\Theta]_{260}$ ±0, $[\Theta]_{222}$ +18,500, $[\Theta]_{200}$ ±0.

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.58; H, 10.13.

By nmr analysis **31** was the major product when the reaction was conducted at elevated temperatures or if the addition of sodium to the sodium ethoxide suspension of **26** was omitted. For isomerization to abietic acid (**1**), a solution of 20 mg of **31** in 5 ml of 5% hydrochloric acid in ethanol was refluxed overnight under nitrogen. This led to the characteristic uv absorption spectrum of abietic acid:[6,48] λ_{max} 235 nm (ϵ 21,100), 241.5 (22,500), and 250 (15,100).

Registry No.—**4,** 19407-36-4; **5,** 19407-37-5; **7,** 19407-38-6; **8,** 19407-39-7; **9,** 19402-25-6; **11a,** 19402-26-7; **11b,** 19402-27-8; **14,** 19402-28-9; **15b,** 19402-29-0; **19,** 19402-30-3; **21,** 19426-92-7; **22,** 19426-93-8; **22** methyl ester, 19426-94-9; **23a,** 19426-95-0; **23b,** 14519-73-4; **24,** 19426-97-2; **25** methyl ester, 19426-98-3; **25** methyl ester (2,4-dinitrophenylhydrazone), 19427-03-3; **27,** 19402-31-4; **28,** 19402-32-5; **31,** 19402-33-6; **31** methyl ester, 19402-34-7; methyl 8α,14α-dihydroxy-13β-abietan-18-oate, 19426-99-4; methyl 8α,14α-dihydrohyabietan-18-oate, 19427-00-0; methyl 14α-hydroxy-8α,13β-abietan-18-oate, 19427-01-1; epoxide of mp 87–94° ($C_{21}H_{34}O_3$), 19427-02-2.

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(68) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

Synthesis of Fichtelite and Related Derivatives of Abietane[1]

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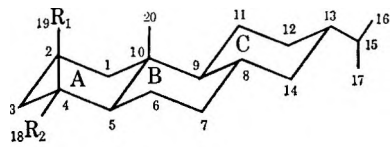
Stereoselective routes to fichtelite (18-norabietane, **1a**) and its C-4 epimer (19-norabietane, **1b**) from abietic acid *via* abietan-18-oic acid (**1c**) are described. The latter acid on conversion into 19-nor-4(18)-abietene (**3**) followed by hydrogenation or hydroboration and reduction yields principally fichtelite, whereas oxidation of the hydroboration product to 18-norabietan-19-al (**1h**) followed by epimerization and reduction affords 19-norabietane. Similar transformations are reported for ring-C aromatic (8,11,13-abietatriene) analogs, together with nmr spectral correlations and a synthesis of the parent hydrocarbon abietane (**1m**).

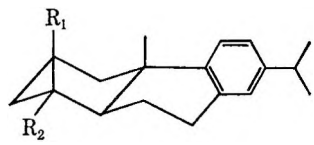
Despite considerable investigation since the isolation of the fossil resin hydrocarbon fichtelite (18-norabietane, **1a**)[3] was reported in 1841,[4] nearly a century elapsed before even the molecular formula, $C_{19}H_{34}$, was established.[5] The apparent origin of fichtelite from abietic-type resin acids, evident from its occurence with the dehydrogenation product retene (1-methyl-7-isopropylphenanthrene),[6] suggested a norabietane structure which was confirmed by X-ray data.[7] However the stereochemistry, particularly at C-4, remained speculative.[8] Some years ago, a total synthesis of a hydrocarbon mixture that may have contained *dl*-fichtelite was reported by Sterling and Bogert.[5]

In the present study, fichtelite and its C-4 epimer **1b** were synthesized stereoselectively from abietic acid (7,13-abietadien-18-oic acid) by reactions which demonstrate that fichtelite has the 4β-methyl configuration shown in **1a**. Subsequent to the preliminary account of our work,[9] Johnson and coworkers[10,11] reported a simplified version of the same route and also a "biogenetic-like polycyclization" leading to *dl*-fichtelite.

In our synthesis, abietan-18-oic acid (**1c**)[12] was converted into 19-nor-4(18)-abietene (**3**), which was then selectively reduced to 18-norabietane (**1a**, fichtelite) or to 19-norabietane (**1b**). Although **1c** can be obtained directly from abietic acid by catalytic hydrogenation over platinum in acetic acid,[12,13] the yield is low and the product is difficult to purify. A more convenient method is by hydrogenation of 8(14)-abieten-18-oic acid, prepared readily by reduction of abietic acid with lithium in ammonia.[12,14]

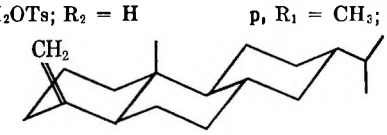


1

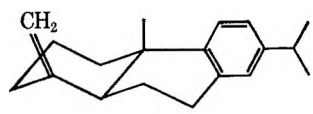


2

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = CO_2H$
d, $R_1 = CH_3$; $R_2 = N^+(CH_3)_3I^-$
e, $R_1 = CH_3$; $R_2 = N(CH_3)_2O$
f, $R_1 = CH_2OH$; $R_2 = H$
g, $R_1 = CH_2OTs$; $R_2 = H$
h, $R_1 = CHO$; $R_2 = H$
i, $R_1 = H$; $R_2 = CHO$
j, $R_1 = H$; $R_2 = CH_2OH$
k, $R_1 = H$; $R_2 = CH_2OTs$
m, $R_1 = R_2 = CH_3$
n, $R_1 = CH_3$; $R_2 = CH_2OH$
p, $R_1 = CH_3$; $R_2 = CHO$



3



4

Transformation of **1c** into **3** was patterned after the Hofmann elimination sequence described by Zeiss and Martin[15] for the conversion of dehydroabietic acid (**2c**) *via* methiodide **2d** into the ring-C aromatic analog **4**. Although it has been reported[16] that pyrolysis of N-oxide **2e** offers a superior route to **4**, we found that the original procedure of Zeiss and Martin involving the action of potassium carbonate in refluxing ethanol on methiodide **2d** gave up to 85% over-all yield (from **2c**) of olefinic products containing **4** (*ca.* 80%) and the corresponding 3- and 4-enes (20%). When applied to

(1) From the Ph.D. Thesis of J. N. M., The University of Kansas, Sept 1965. Financial support for this work from the National Science Foundation (G-19936), The University of Kansas Center for Research in Engineering Science (CRES-40B), and the Alfred P. Sloan Foundation is gratefully acknowledged.

(2) (a) Alfred P. Sloan Research Fellow, 1961–1964. (b) Predoctoral Fellow, U. S. Public Health Service, 1964–1965.

(3) (a) The abietane numbering and systematic nomenclature follow recent proposals (third revision, Oct 1968) of a group chaired by Dr. J. W. Rowe, U. S. Department of Agriculture, Forest Service, Forest Products Laboratory, Madison, Wis. (b) *Cf.* R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 50 (1965). (c) See also E. Fujita, T. Fujita, and H. Katayama, *Chem. Commun.*, 968 (1967); Abstracts of Papers, 5th International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968, p 323.

(4) C. Bromeis, *Ann.*, **37**, 304 (1841).

(5) For review, see E. C. Sterling and M. T. Bogert, *J. Org. Chem.*, **4**, 20 (1939); see also, J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, University Press, Cambridge, England, 1952, pp 337–338. For recent work on the occurrence of fichtelite, see papers by A. I. Skrigan cited in *Chem. Abstr.*, **55**, 18889e (1961); **62**, 10664a (1965).

(6) L. Ruzicka and E. Waldmann, *Helv. Chim. Acta*, **18**, 611 (1935).

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(8) L. F. Fieser and M. Fieser, "Topics in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1963, p 199.

(9) A. W. Burgstahler and J. N. Marx, *Tetrahedron Lett.*, 3333 (1964).

(10) N. P. Jensen and W. S. Johnson, *J. Org. Chem.*, **32**, 2045 (1967). We are grateful to Professor Johnson and Dr. Jensen for sending us a copy of their paper prior to publication.

(11) W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Amer. Chem. Soc.*, **88**, 3860 (1966); W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *ibid.*, **90**, 5872 (1968).

(12) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 1550 (1969); *cf.* J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *ibid.*, **31**, 4128 (1966). We thank Professors Huffman and Herz for sending us a copy of their manuscript before publication.

(13) L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, **5**, 315 (1922).

(14) E. E. Royals, W. C. Bailey, and R. W. Kennedy, *J. Org. Chem.*, **23**, 151 (1958); R. W. Kennedy, Ph.D. Thesis, Emory University, 1957; University Microfilm 58-5153.

(15) H. H. Zeiss and W. B. Martin, Jr., *J. Amer. Chem. Soc.*, **75**, 5935 (1953); *cf.* A. W. Burgstahler, Ph.D. Thesis, Harvard University, 1952.

(16) J. W. Huffman and R. F. Stockel, *J. Org. Chem.*, **28**, 506 (1963).

TABLE I

PROTON CHEMICAL-SHIFT VALUES FOR ABIETANE AND 8,11,13-ABIETATRIENE DERIVATIVES[a]

Abietane series			8,11,13-Abietatriene series		
Compd	C-10 methyl, τ	Other peaks,[b] τ (J, Hz)	Compd	C-10 methyl, τ	Other peaks,[c] τ (J, Hz)
1a	9.18	C-4 methyl at 9.05 (d, J = 4)	**2a**	8.83	C-4 methyl at 8.96 (d, J = 7)[d]
1b	9.25	C-4 methyl at 9.10 (d, J = 3)	**2b**	8.89	C-4 methyl at 9.03 (d, J = 5)[d]
1f	9.33	CH_2OH at 6.40 ($W_{1/2}$ = 10)	**2f**	8.97	CH_2OH at 6.28 ($W_{1/2}$ = 11)
1g	9.35	CH_2OTs at 6.00 ($W_{1/2}$ = 16)	**2g**	8.98	CH_2OTs at 5.92 ($W_{1/2}$ = 16)
1h	9.32	CHO at −0.20 (d, J < 1)	**2h**	8.97	CHO at −0.21 (d, J < 1)
1i	9.20	CHO at 0.37 (d, J = 3)	**2i**	8.86	CHO 0.26 (d, J = 3)
1j	9.22	CH_2OH at 6.41 ($W_{1/2}$ = 6)	**2j**	8.87	CH_2OH at 6.31 ($W_{1/2}$ = 5)
1k	9.27	CH_2OTs at 6.00 ($W_{1/2}$ = 8)	**2k**	8.92	CH_2OTs at 5.93 ($W_{1/2}$ = 7)
1m	9.17	C-4 methyls at 9.15, 9.16[e]	**2m**	8.84	C-4 methyls at 9.05, 9.05[f,g]
1n	9.16	CH_2OH at 6.85 (q, J = 10), C-4 methyl at 9.25	**2n**	8.83	CH_2OH at 6.80 (q, J = 11), C-4 methyl at 9.18
1p	9.12	CHO at 0.85, C-4 methyl at 8.96[e]	**2p**	8.80	CHO at 0.73, C-4 methyl at 8.86[f]

[a] Determined in carbon tetrachloride solution on a Varian A-60 or HA-100 nmr spectrometer with tetramethylsilane as internal reference. [b] Isopropyl doublet centered at τ 9.14 ± 0.02 ($J \sim$ 5.5–7.0 Hz). [c] Isopropyl doublet centered at τ 8.78 ± 0.02 ($J \sim$ 6–7 Hz). [d] Similar values have been found for the corresponding nor-8,11,13-podacarpatriene by J. dePaiva Campello (M.S. Thesis, Indiana University, June 1966). We cordially thank Professor Ernest Wenkert for this information. [e] *Cf.* ref 3c. [f] *Cf.* ref 23. [g] Prepared from **2c** essentially by the method of W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 928 (1942); *cf.* E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963); glpc, r_{Pim} (see ref 25) = 0.55.

acid **1c**, the sequence afforded **3** of comparable purity in 70% over-all yield.[17]

By analogy with similar structures,[18] **3** would be expected to undergo hydrogenation predominantly from the α side to produce the axial 4β-methyl product **1a**. In fact, hydrogenation of **3** over platinum in acetic acid afforded a mixture containing mostly **1a**, which was shown to be identical with a sample of natural fichtelite.[19] To confirm the 4β-methyl configuration of fichtelite, the 4α-methyl epimer **1b** was prepared. Hydroboration–oxidation of olefin **3** gave mainly 18-norabietan-19-ol (**1f**) plus some fichtelite, evidently by protonolysis of the intermediate organoborane.[20] Subsequent conversion of **1f** into fichtelite by tosylation to **1g**, displacement with *n*-butyl mercaptide, and desulfurization demonstrated that both hydrogenation and hydroboration of **3** follow the same stereochemical course. The axial configuration of the C-4 substituent was assigned on the basis of the fact that mild oxidation of **1f** with Jones reagent[21] gave an aldehyde (**1h**) which was isomerized by acid to the equatorial 4α epimer **1i**. The two aldehydes, **1h** and **1i**, were found to have readily distinguishable nmr spectra (Table I), and each was uncontaminated with the other within the limits of detectability.

A mixture of **1h** and **1i**, along with other products, resulted from boron trifluoride rearrangement of the epoxide prepared by the action of *m*-chloroperbenzoic acid on **3**. Wolff–Kishner reduction of **1i** or, alternatively, its reduction to alcohol **1j**, followed by conversion into the tosylate (**1k**) and the *n*-butyl thio ether, and desulfurization then furnished hydrocarbon **1b**. The latter, obtained as an oil, $[\alpha]_D$ +5°, has infrared (ir) and nmr spectra that are different from those of fichtelite. In particular, the C-10 methyl signal appears at higher field in the nmr spectrum (Table I) of **1b** than it does in that of **1a**, as would be expected for relief of the 1,3-diaxial interactions present in **1a** but not **1b**.[22,23] Thus it is firmly established that fichtelite is 18-norabietane (**1a**) and that its formation in nature by reduction and decarboxylation of abietic-type resin acids[5] occurs with retention of the β-methyl configuration at C-4.

In the 8,11,13-abietatriene series, hydrogenation of olefin **4** similarly furnished predominantly the 4β-methyl epimer **2a**, as judged by the nmr spectrum (Table I). Nitration gave a ring-C dinitro derivative not identical with that (mp 133–134°) obtained by Perold and Jeger[19b] from fichtelite by partial dehydrogenation and subsequent nitration. This result implies that the stereochemistry of their product differs from that of the parent hydrocarbon.

Application of the hydroboration–isomerization–reduction sequence to **4** gave the 4α-methyl hydrocarbon **2b**, whose ir spectrum differs markedly from that of **2a** but corresponds closely to that of the dehydrogenation product of fichtelite published by Perold and Jeger.[19b]

(17) An alternative, one-step route to **4** by treatment of **2c** with lead tetraacetate has been reported [J. W. Huffman and P. G. Arapakos, *ibid.*, **30**, 1604 (1965)], but we found the reaction to be rather unselective, with **4** constituting less than half of the olefinic products. Jensen and Johnson,[10] however, successfully utilized this method in their synthesis of fichtelite from 8(14)-abieten-18-oic acid. Recently, nitrous acid deamination of 4α-amino-18-nor-8,11,13-abietatriene has been reported [R. N. Seelye and W. B. Watkins, *Tetrahedron Lett.*, 1271 (1968)] to give a 45% yield of alkenes containing 65% **4**, whose nmr spectrum is also recorded by these authors.

(18) *Inter alia*, J. A. Marshall and N. Cohen, *J. Amer. Chem. Soc.*, **87**, 2773 (1965); A. S. Bawdekar and G. R. Kelkar, *Tetrahedron*, **21**, 1521 (1965). An example of the opposite result has been reported for a 4-methylene-9β,-19-cyclosteroidal alkaloid [K. S. Brown, Jr., and S. M. Kupchan, *J. Amer. Chem. Soc.*, **86**, 4430 (1964)], but molecular models show that the compound has a conformation quite different from that of **3**.

(19) (a) We cordially thank Professor O. Jeger for this sample of natural fichtelite. (b) *Cf.* G. W. Perold and O. Jeger, *Helv. Chim. Acta*, **32**, 1085 (1949).

(20) This side reaction is not normally encountered in a basic peroxide medium. *Cf.* H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 62–66. It should also be noted that treatment of the organoborane with acetic or propionic acid yielded little or no hydrocarbon.

(21) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(22) G. Slomp, Jr., and B. R. McGarvey, *J. Amer. Chem. Soc.*, **81**, 2200 (1959).

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The dinitro derivative of **2b** prepared on one occasion had mp 151–153°, but in other preparations it had mp 130–131°.[24] The latter is in agreement with the melting point reported by Perold and Jeger for their dinitro derivative, indicating that epimerization had occurred at C-4 in their aromatization of ring C of fichtelite.

Incidental to the synthesis of fichtelite, we also prepared the "parent" hydrocarbon abietane (**1m**), mp 38–38.5°, by reduction of acid **1c** to abietan-18-ol (**1n**), oxidation to aldehyde **1p**, and Wolff–Kishner reduction. This same route has since been reported by Fujita and coworkers[3c] in connection with their studies on the structure and chemistry of the diterpene enmein.

Experimental Section[25]

19-Nor-4(18)-abietene (3).—The preparation of this olefin on a 1-g scale from **1c**, mp 181–182°[12] (preferably purified through the methyl ester, mp 45–46°[12,26]), was patterned after "Method a" of Zeiss and Martin[16] for the analogous conversion of **2c** into **4**. The intermediate base, **4α-methylamino-18-norabietane**, was characterized as the **hydrochloride**, mp 265–265.5° dec, after recrystallization from ethanol–ethyl acetate.

Anal. Calcd for $C_{20}H_{38}ClN$: C, 73.24; H, 11.37; Cl, 10.81. Found: C, 73.29; H, 11.40; Cl, 10.40.

Crude **3** from the Hofmann elimination was obtained as an oil in 70% over-all yield from acid **1c**. Although the ir spectrum showed the expected exocyclic methylene absorption at 6.1 and 11.2 μ, glpc and nmr analysis indicated that it was a mixture of double-bond isomers containing *ca.* 80% **3**. The major contaminant appeared to be 19-nor-3-abietene (nmr signal at τ 4.75; glpc r_{Pim} 0.40). Chromatography on silver nitrate impregnated alumina[12] and elution with petroleum ether–ether (10:1) furnished a homogeneous sample of **3**: glpc r_{Pim} 0.42; $[\alpha]_D$ +66°; $n^{26}D$ 1.5102; and principal nmr peaks at τ 5.25, 5.51 (=CH_2), 9.14 (d, J = 6.5 Hz, isopropyl), and 9.33 (shielded C-10 methyl).

Anal. Calcd for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.45; H, 12.27.

Olefin **3** was also prepared by the method of Huffman and Stockel,[16] but the yield was lower. Cope elimination of amine oxide **1e** was extremely facile and occurred largely during formation. The tertiary base, **4α-dimethylamino-18-norabietane**, was characterized as the yellow **picrate**, mp 192–193°, after recrystallization from ethanol–ether.

Anal. Calcd for $C_{27}H_{42}N_4O_7$: C, 60.65; H, 7.92; N, 10.48. Found: C, 60.64; H, 7.74; N, 10.20.

18-Norabietane (Fichtelite, 1a). A. By Hydrogenation.—A solution of 0.50 g (1.9 mmol) of crude **3** in 15 ml of acetic acid was stirred at 25° with 0.1 g of prereduced platinum oxide under 1 atm of hydrogen. After 10 min, the reaction was complete, and the product was recovered by extraction and passage through alumina with petroleum ether. When seeded in methanol with natural fichtelite,[19] it gave 230 mg (44%) of elongated plates or flattened needles of **1a**: mp 32–37° (after four crystallizations the melting point was 42–45°; after four more it was 45–46°); $[\alpha]_D$ +19° (lit. mp 46°, $[\alpha]_D$ +18°;[5] mp 45.8–46.1°, $[\alpha]_D$ +19°[10]); ORD (*c*, 0.10 in hexane) $[\Phi]_{400}$ +80°, $[\Phi]_{300}$ +280°, $[\Phi]_{250}$ +400°, $[\Phi]_{225}$ +825°. The mixture melting point with authentic fichtelite was 45–46°. The ir spectrum (solution and KBr disk), nmr spectrum (Table I), X-ray powder diffraction pattern,[27] and glpc behavior (r_{Pim} 0.36) were identical with those of natural fichtelite.

Anal. Calcd for $C_{19}H_{34}$: C, 86.94; H, 13.06. Found: C, 87.23; H, 12.74.

B. By Hydroboration.—To an ice-cold solution of 0.35 g of lithium aluminum hydride and 1.11 g (4.23 mmol) of crude **3** in 25 ml of dry ether was added 1.2 ml of boron trifluoride etherate in 20 ml of ether over a period of 30 min. The mixture was stirred for 2 hr at 25° and then treated with saturated sodium sulfate solution and solid anhydrous sodium sulfate. The solids were separated and the ether replaced by 40 ml of tetrahydrofuran. To the resulting solution 20 ml of 10% sodium hydroxide and 15 ml of 30% hydrogen peroxide were added, and the two phases were stirred rapidly for 5 hr at 25°. After dilution with water and extraction with ether, the mixture furnished 1.10 g of an oily product which was chromatographed on 30 g of silica gel (Grace, 100 mesh, activated). Elution with petroleum ether–benzene (2:1) afforded 0.17 g (15%) of hydrocarbon mixture, R_f 0.80 (6:1), whose recrystallization behavior and analysis by glpc and nmr showed that it was mainly fichtelite. Direct hydrolysis of the organoborane product with acetic acid or propionic acid was unsuccessful. **18-Norabietan-19-ol (1f)**, undoubtedly containing minor amounts of product derived from isomeric contaminants in **3**, was eluted from the column with benzene–ether (19:1) as a viscous oil: yield 0.91 g (77%); R_f 0.26 (6:1); ir bands at 2.8 and 3.0 μ. This product was characterized by its nmr spectrum (Table I) and ***p*-toluenesulfonate (1g)**. The latter was prepared by reaction of 183 mg (0.65 mmol) of **1f** and 200 mg of *p*-toluenesulfonyl chloride in 10 ml of dry pyridine with stirring overnight at 20°. Extraction of the neutral fraction with ether and three crystallizations from petroleum ether yielded 150 mg (53%) of prisms of **1g**: mp 109–109.5°; ir bands at 7.3, 8.4, and 8.5 μ.

Anal. Calcd for $C_{26}H_{40}O_3S$: C, 72.19; H, 9.32. Found: C, 72.47; H, 9.54.

For conversion into the *n*-butyl thio ether, 110 mg (0.25 mmol) of **1g** was refluxed overnight with a solution of 0.3 ml of *n*-butyl mercaptan in 20 ml of *t*-butyl alcohol containing 0.05 g of dissolved potassium. After extraction with chloroform and thorough washing with 1 *N* sodium hydroxide, the resulting mixture was separated by chromatography on basic alumina into olefin **3** and the desired thio ether, R_f 0.42 (1:0). The latter substance (40 mg, 53% yield) was desulfurized with 1 g of W-2 Raney nickel in ethanol (overnight reflux). The resulting hydrocarbon crystallized from methanol when seeded with fichtelite and had essentially identical ir and nmr spectra. Recrystallization furnished 5 mg (17%) of fichtelite, mp 35–40° (mmp 35–45°), which by glpc analysis was 90% pure.

18-Norabietan-19-al (1h) and 19-Norabietan-18-al (1i).—To a stirred solution containing 0.60 g (2.14 mmol) of alcohol **1f** in 20 ml of acetone cooled to 0° was added 0.60 ml of Jones reagent[21] at such a rate that the solution remained orange. After 5 min, 5 ml of methanol was added to consume excess reagent. The mixture was then concentrated under reduced pressure and the neutral fraction isolated by extraction with ether and chromatography on 12 g of silica gel. Elution with benzene–petroleum ether (1:3) furnished 270 mg (45%) of **1h** as a colorless oil, R_f 0.65 (6:1), with ir bands at 3.7 and 5.8 μ. The nmr spectrum (Table I) indicated that it was substantially free of of the C-4 epimeric aldehyde **1i** (see below). A sample purified by short-path distillation had bp (bath temperature) 150–160° (0.05 mm).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.26; H, 11.48.

For epimerization to **1i**, 0.25 g (0.87 mmol) of **1h** was heated for 1 hr at 60° with 1 ml of 2 *N* hydrochloric acid in 10 ml of diglyme under nitrogen. After recovery by extraction with

(24) Initially, the 131° melting point was found for preparations of the dinitro derivative of **2b** contaminated with **2a**. Recently, this melting point has been confirmed for preparations derived from pure **2b** (private communication from Professor J. W. Huffman, to whom we are most grateful for bringing this fact to our attention).

(25) Melting points were determined in open capillaries with a Hershberg melting point apparatus calibrated against standard substances. Thin layer chromatography (tlc) was performed on microscope slides covered with silica gel G (Merck). R_f values were determined with cyclohexane–ethyl acetate (proportions in parenthesis). Gas–liquid partition chromatography (glpc) was conducted at 200° on a 6-ft 9% SE-30/1% EGip column, to which retention values relative to methyl pimarate (r_{Pim} = 1.00) are referred. [*Cf.* F. H. M. Nestler and D. F. Zinkel, *Anal. Chem.*, **39**, 1118 (1967). We are deeply grateful to Dr. Zinkel for most of the glpc data recorded herein.] Except where noted otherwise, D-line rotations were measured in ethanol (1–2% solution) with a Perkin-Elmer Model 141 polarimeter. ORD data were obtained in ethanol on a Cary Model 60 recording spectropolarimeter with a 1.0-cm cell. Infrared spectra were recorded in carbon tetrachloride solution on a Perkin-Elmer Model 137 Infracord. Nmr spectra were determined in carbon tetrachloride solution on a Varian A-60 or a HA-100 spectrometer with tetramethylsilane as internal reference. Petroleum ether refers to the fraction with bp 35–45°. Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(26) E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.*, **60**, 921 (1938).

(27) We thank Professor Paul W. Gilles and Dr. Gordon Lewis of this department for this determination.

ether and repeated washing with water (to remove the diglyme), the product (0.20 g, 80%) had essentially the same tlc behavior as **1h**, but the nmr spectrum (Table I) revealed the absence of the aldehyde and C-10 methyl resonances of **1h** and their replacement by those of **1i**. The sample purified by short-path distillation had bp 150–160° (0.05 mm).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.39; H, 11.54.

As an alternative route to **1i**, a solution of 1.00 g (3.8 mmol) of crude **3** in 15 ml of chloroform was added to 1.0 g (5.8 mmol) of *m*-chloroperbenzoic acid at 20°. Tlc indicated that the olefin had reacted completely in less than 10 min. The solution was washed with 1% sodium hydroxide, dried, and evaporated to yield 1.05 g (99%) of epoxide, R_f 0.30. For rearrangement to the aldehyde, 0.96 g of the crude epoxide in 20 ml of benzene was treated with 5 drops of boron trifluoride etherate, whereupon the solution turned golden red. After hydrolysis the mixture was extracted and the product was chromatographed on 20 g of silica gel. Elution with petroleum ether–benzene (4:1) gave nonconjugated olefinic material, R_f 0.80 (6:1). Further elution with a 1:1 mixture of the same solvents afforded 0.39 g (41%) of a mixture **1h** and **1i**, present in a 1:1 ratio, as determined by the nmr spectrum. Acid isomerization converted the mixture into **1i** as above.

19-Norabietane (1b). A. By Wolff–Kishner Reduction.—A solution of 130 mg (0.47 mmol) of **1i**, 1 ml of anhydrous hydrazine, and 1 g of potassium hydroxide in 15 ml of diethylene glycol was heated with stirring at 140–160° for 2 hr under nitrogen and then at 210° for 4 hr. After recovery of the product by dilution of the mixture with water and extraction with ether, it was chromatographed on 10 g of acidic alumina, giving in the petroleum ether fractions 75 mg (60%) of hydrocarbon **1b** as an oil: $n^{25}D$ 1.5005; $[\alpha]D$ +5°; R_f 0.75 (1:0); and glpc r_{Pim} 0.40. The nmr spectrum (Table I) indicated the absence of fichtelite (**1a**), but about 10% was present according to glpc. The analytical sample was prepared by short-path distillation: bp (bath temperature) 145–150° (0.5 mm).

Anal. Calcd for $C_{19}H_{34}$: C, 86.94; H, 13.06. Found: C, 86.72; H, 13.01.

B. *Via* **19-Norabietan-18-ol (1j).**—Reduction of 276 mg (1.0 mmol) of **1i** with 0.1 g of lithium aluminum hydride in ether afforded, after elution with benzene–ether (19:1) from 5 g of silica gel, 175 mg (63%) of **1j** as a viscous oil: R_f 0.25 (6:1); ir bands at 2.8 and 3.0 μ. Like **1f**, this product was characterized by its nmr spectrum (Table I) and ***p*-toluenesulfonate (1k)** which, however, could not be obtained crystalline. Tosylation of the entire alcohol product by the procedure applied to **1f** furnished 140 mg (51%) of oily **1k**, of which 50 mg was purified for analysis by chromatography on 5 g of silica gel. Tosylate ir bands were present at 7.3, 8.4, and 8.5 μ.

Anal. Calcd for $C_{26}H_{40}O_3S$: C, 72.19; H, 9.32. Found: C, 72.55; H, 9.62.

The other portion (90 mg) of **1k** was allowed to react with 0.3 g of potassium *n*-butyl mercaptide in 10 ml of *t*-butyl alcohol (overnight reflux). Chromatography of the product on 5 g of acidic alumina furnished 60 mg (97%) of impure thio ether, R_f 0.43 (1:0), by elution with benzene–petroleum ether (1:2). Olefin **3** could not be detected by nmr analysis of the material in earlier fractions. Desulfurization of the thio ether with 1 g of W-2 Raney nickel, followed by elution from 5 g of acidic alumina with petroleum ether, afforded 30 mg of **1b** (55% from the tosylate): $[\alpha]D$ +3°; $n^{25}D$ 1.5000; R_f 0.75 (1:0). The ir and nmr spectra were identical with those of **1b** obtained by route A above. Glpc analysis (r_{Pim} 0.40) indicated a comparable purity.

Abietane (1m).—Reduction of 0.64 g (2.0 mmol) of the methyl ester (mp 45–46°) of acid **1c**[12] with 0.3 g of lithium aluminum hydride in 20 ml of tetrahydrofuran (overnight stirring at 25°) afforded 0.55 g (94%) of **abietan-18-ol (1n)**, which, after crystallization from methanol, had mp 32–35° (lit.[3c] mp 33–34°). For oxidation to aldehyde **1p**, 0.50 g (1.7 mmol) of **1n** in 25 ml of a stirred solution in acetone cooled to 0° was treated dropwise during 3 min with 0.8 ml of Jones reagent.[21] After 5 min, 2 ml of methanol was added and the mixture was diluted with water and extracted with ether. From the washed and dried ether extracts there was obtained 0.45 g (90%) of oily **abietan-18-al (1p)** having the expected ir absorption at 3.7 and 5.8 μ.[3c] The **2,4-dinitrophenylhydrazone** crystallized from ethanol and then carbon tetrachloride in fine yellow spores, mp 172–173°.

Anal. Calcd for $C_{26}H_{38}N_4O_4$: C, 66.36; H, 8.14; N, 11.90. Found: C, 66.32; H, 7.90; N, 12.18.

The **semicarbazone** crystallized from chloroform–ethyl acetate–ethanol as fine needles, mp 245–247°.

Anal. Calcd for $C_{21}H_{37}N_3O$: C, 72.58; H, 10.73; N, 12.09. Found: C, 72.69; H, 10.71; N, 11.93.

For conversion into **1m**, 0.35 g (1.0 mmol) of the semicarbazone was mixed with 2.0 g of powdered potassium hydroxide and the mixture was heated to 225–250° for 5 min, when decomposition appeared to be complete. The cooled residue was taken up in water and extracted with petroleum ether to yield 0.18 g of a nearly colorless product, mp 33–35°. After passage through 10 g of acidic alumina with petroleum ether, this afforded 85 mg (31%) of **1m**, mp 34–36°, as translucent plates from ether–ethanol. Recrystallization furnished 65 mg (23%) of pure **abietane (1m)**: mp 38–38.5°; $[\alpha]D$ (CCl_4) −8.5° {lit.[3c] mp 37–38°; $[\alpha]D$ (*n*-hexane) −5°}; $n^{20}D$ 1.5042 (supercooled melt); ORD (*c*, 0.25 in hexane) $[\Phi]_{400}$ −35°, $[\Phi]_{250}$ −85°, $[\Phi]_{210}$ −170° (lit.[3c] "plain negative curve"); glpc r_{Pim} 0.51.

Anal. Calcd for $C_{20}H_{36}$: C, 86.88; H, 13.12. Found: C, 86.76; H, 13.21.

Experiments in the Ring-C Aromatic Series. A. 18-Nor-8,11,13-abietatrien-19-ol (2f) and 19-Nor-8,11,13-abietatrien-18-ol (2j).—Since work in this series served primarily to develop suitable reaction conditions for the synthesis of **1a** and **1b**, various intermediates were characterized for the most part simply by spectral means. Hydroboration of olefin **4**[15] by the procedure used to obtain **1f** afforded **2f** in comparable yield as a viscous oil. The **3,5-dinitrobenzoate** of **2f**, prepared by reaction with freshly distilled 3,5-dinitrobenzoyl chloride in pyridine at room temperature for 1 hr, crystallized from methanol in faintly yellow clusters: mp 107–109°; C-10 methyl signal at τ 8.82.

Anal. Calcd for $C_{26}H_{30}N_2O_6$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.58; H, 6.29; N, 6.12.

Oxidation of **2f** to **2h** was conducted with Jones reagent[21] as in the preparation of **1h**. Acid isomerization of **2h** furnished **2i**, which formed a deep yellow **2,4-dinitrophenylhydrazone** that crystallized from ethanol in fine needle clusters, mp 152–154°.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.78; H, 6.60; N, 12.27.

Reduction of **2i** with lithium aluminum hydride gave **2j** as an oil whose **3,5-dinitrobenzoate**, prepared as above, crystallized from methanol in fine pale yellow needles: mp 126–128°; C-10 methyl signal at τ 8.76; mmp 79–85° with the 3,5-dinitrobenzoate of **2f**.

Anal. Calcd for $C_{26}H_{30}N_2O_6$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.75; H, 6.77; N, 5.84.

Hydroxylation of **4** with osmium tetroxide in the manner described by Huffman and Stockel[16] gave a glycol, mp 119–120° (lit.[16] mp 101–102°), which was rearranged with 98% formic acid as described by these authors. (In one run the glycol had mp 101–102°, but this result could not be duplicated.) Chromatography of the formic acid product on silica gel afforded roughly equal amounts of an unsaturated hydrocarbon fraction by elution with petroleum ether–benzene (4:1) and an aldehyde-containing fraction by elution with benzene–petroleum ether (1:1). The latter comprised *ca.* equal amounts of **2h** and **2i** (by nmr analysis), contaminated with a small amount of nonaldehydic material (ir absorption at 5.75 μ). This sequence was not applied to **3**.

B. 12,14-Dinitro Derivatives of 18-Nor-8,11,13-abietatriene (2a) and 19-Nor-8,11,13-abietatriene (2b).—Oily hydrocarbon **2a** (r_{Pim} 0.42[28]), prepared from **4** by either of the two methods by which **1a** was obtained from **3**, was nitrated by the procedure of Perold and Jeger.[19b] After purification by chromatography on neutral alumina and elution with benzene–petroleum ether (1:1), the nitration product crystallized from methanol in light yellow needles: mp 176–177.5°; R_f 0.84 (0:1); nmr signal at τ 2.40 (C-11 aromatic H), 8.64 (d, J = 7 Hz, isopropyl), 8.75 (C-10 methyl), and 8.96 (d, J = 7 Hz, C-4 methyl).

Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.51, H, 7.60; N, 8.09.

Hydrocarbon **2b** (r_{Pim} 0.48[29]), also an oil, was prepared by the thio ether route used to obtain **1b** and was nitrated as above. Chromatography gave a light yellow solid, R_f 0.84 (0:1), which,

(28) Infrared partly similar to Figure 4, ref 19b.

(29) Infrared as in Figure 3, ref 19b.

after two crystallizations from methanol, had mp 151–153° (other preparations,[24] mp 130–131°); nmr signals at τ 2.52 (C-11 aromatic H), 8.64 (d, J = 7 Hz, isopropyl), 8.82 (C-10 methyl), and 9.02 (d, J = 5 Hz, C-4 methyl).

Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 66.13; H, 7.81; N, 8.05.

Registry No.—**1a**, 2221-95-6; **1b**, 19402-16-5; **1f**, 1451-69-0; **1g**, 3749-83-5; **1h**, 19402-19-8; **1i**, 19407-09-1; **1j**, 19407-10-4; **1k**, 19407-11-5; **1m**, 19407-12-6; **1n**, 15821-26-8; **1p**, 19407-14-8; **1p** (2,4-dinitrophenylhydrazone), 19407-15-9; **1p** (semicarbazone), 19407-16-0; **2a**, 19407-17-1; **2a** (12,14-dinitro derivative), 19407-40-0; **2b**, 19407-18-2; **2b** (12,14-dinitro derivative), 19407-41-1; **2f**, 19407-19-3; **2f** (3,5-dinitrobenzoate), 3858-39-7; **2g**, 19407-21-7; **2h**, 19407-22-8; **2i**, 19407-23-9; **2i** (2,4-dinitrophenylhydrazone), 19407-24-0; **2j**, 19407-25-1; **2j** (3,5-dinitrobenzoate), 1451-73-6; **2k**, 19407-27-3; **2m**, 19407-28-4; **2n**, 19426-88-1; **2p**, 13601-88-2; **3**, 19407-30-8; 4α-methylamino-18-norabietane hydrochloride, 19407-31-9; 4α-dimethylamino-18-norabietane picrate, 19407-32-0.

Photochemistry of Isothiochroman-4-one[1-3]

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Irradiation of isothiochroman-4-one in cyclohexane (high pressure mercury lamp, Pyrex 7740 filter) produced thiochroman-3-one (21%). Under similar conditions 7-methoxy-, 8-methyl-, 3-methyl-, and 3,3-dimethylisothiochroman-4-one rearranged to 6-methoxy- (40%), 5-methyl- (30%), 2-methyl- (30%), and 2,2-dimethylthiochroman-3-one (37%), respectively. 1,2,3,4-Tetrahydro-1-keto-3-thiaphenanthrene failed to undergo the rearrangement reaction. Irradiation of 5-methyl-2,3-dihydro-2H,6H-thiopyran-3-one under similar conditions resulted in rearrangement to 2-(2-prop-1-enyl)-1-thietan-3-one (28–35%). The pathway for the photochemical conversion of isothiochroman-4-ones into thiochroman-3-ones is discussed.

Photochemistry.—The ultraviolet (uv) spectra of β-keto sulfides show evidence for charge transfer in the excited state as well as perturbation of the n,π^* state of the carbonyl group.[5-7] Various interpretations of the spectral data have been discussed.[5-8] These effects are not observed in the spectra of β-keto sulfones.[9]

Only two reports have appeared on the photochemistry of β-keto sulfides. Schönberg, Fateen, and Omran[10] obtained radical coupling products (*e.g.*, bidesyl) in the photolysis of desyl aryl sulfides, and La Count and Griffin[11] found that phenacyl benzyl sulfide failed to give the thietanol product from α-hydrogen atom abstraction as did the oxygen analog, phenacyl benzyl ether.

Initial studies confirmed the indication that simple, acyclic β-keto sulfides undergo photochemical reaction involving homolytic cleavage of the α-carbon–sulfur bond. Photolysis of 2-*t*-butylmercaptocyclohexanone (**1**) in cyclohexane for 2 hr produced three products[12] corresponding to 22% of the starting material. Less than 10% **1** remained. The products were identified as di-*t*-butyl disulfide, cyclohexenone, and cyclohexanone and were formed in a ratio of 5:1.4:1. Photolysis in methanol gave the same products in somewhat better yield plus a small amount of 3-*t*-butylmercaptocyclohexanone which was probably formed from Michael addition of *t*-butylmercaptan to cyclohexanone.

In view of the product distribution resulting from β cleavage to radical pairs, it was decided to investigate systems in which the two functionalities were contained in the same ring system. The unsaturated system, isothiochroman-4-one (**2**), was selected. Irradiation of 0.2–0.4% solutions of **2** in cyclohexane or Genetron 113 (1,1,2-trichloro-1,2,2-trifluoroethane) with a Hanovia, Type L, 450-W mercury arc immersion lamp with a Pyrex filter, produced thiochroman-3-one (**5**) in yields of 19–21% and 1-thiaindane in 6% yield. The remainder of the starting material is converted into an amorphous polymeric material which gradually precipitated from the reaction mixture. In a similar fashion 7-methoxyisothiochroman-4-one (**3**) and 8-methylisothiochroman-4-one (**4**) were converted into 6-methoxythiochroman-3-one (**6**) and 5-methylthiochroman-3-one (**7**) in yields of 30 and 40%, respectively. These two examples establish that the sulfur atom in the thiochroman-3-one products is attached to

2, R = R′ = H
3, R = H; R′ = CH_3O
4, R = CH_3; R′ = H

5, R = R′ = H
6, R = H; R′ = CH_3O
7, R = CH_3; R′ = H

the aryl carbon atom which held the carbonyl function in the starting isothiochroman-4-ones. Photolysis of

(1) This work was previously reported in communication form.[2]

(2) W. C. Lumma, Jr., and G. A. Berchtold, *J. Amer. Chem. Soc.*, **89**, 2761 (1967).

(3) This research has been supported by National Science Foundation Grants No. GP-5761 and GP-7831.

(4) To whom inquiries should be sent. Alfred P. Sloan Fellow, 1963–1967.

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(7) G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962).

(8) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, p 55.

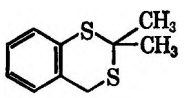
(9) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 231 (1949).

(10) A. Schönberg, A. K. Fateen, and S. Omran, *ibid.*, **78**, 1224 (1956).

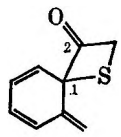
(11) R. B. La Count and C. E. Griffin, *Tetrahedron Lett.*, 1549 (1965).

(12) A complex mixture of high boiling material was also isolated, but the constituents were not characterized.

3-methylisothiochrom-4-one (**8**) and 3,3-dimethylisothiochroman-4-one (**9**) produced 2-methylthiochroman-3-one (**10**) and 2,2-dimethylthiochroman-3-one (**11**) in yields of 30 and 37%, respectively, thereby establishing that C-3 in the starting materials became C-2 in the products. (A product assigned structure **12** was also isolated from the photolysis of **9** in 6% yield.) This was also established by the photolysis of deuterated **2** prepared by base-catalyzed exchange with D_2O.

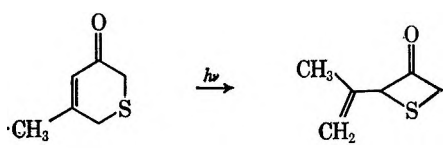


12



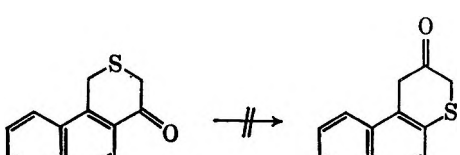
13

These results combined with the appearance of a weak absorption band at 1770 cm^{-1} in the infrared (ir) spectrum of solutions of **2** which had been irradiated for short periods of time suggest that **13** might be the initial photoproduct in the reaction. Excitation of the carbonyl group or the triene moiety in **13** could then result in cleavage of bond 1 and subsequent rearrangement to starting material or cleavage of bond 2 and rearrangement to product. Evidence for the intermediacy of **13** was obtained from the photolysis of 5-methyl-2,3-dihydro-2H,6H-thiopyran-3-one (**14**) which produced the thietanone **15** in yields of 28–35%. The stability of **15** under the conditions of the reaction suggests that excitation of the triene moiety of **13** is responsible for further rearrangement.



14 **15**

Irradiation of **2** with a 3500-Å[13] source resulted in the slow formation of polymeric material. Compound **3** was not produced but an absorption band appeared at 1770 cm^{-1} in the spectrum of the solution suggesting the formation of intermediate **13**. Since this suggests the 3500-Å source will effect n,π^* excitation of **2** to form **13** but does not supply sufficient energy to excite the triene moiety in **13**[14] relative to other processes, it became of interest to investigate the photochemistry of **16** which, by analogy with 2-acetonaphthalene, should have a π,π^* triplet of lower energy than its n,π^* triplet.[15] Irradiation of **16** with either of the



16 **17**

previously described light sources did not produce **17**; amorphous polymer was the only product observed. Although other explanations are possible, it appears most likely that an n,π^* configuration may be necessary for the observed photochemical rearrangement.

Preparation of the Keto Sulfides.—The synthesis of **1** was accomplished from the reaction of sodium *t*-butylmercaptide with 2-chlorocyclohexanone in ethanol. The synthesis of **2**[16–19] and several methyl-substituted analogs[19,20] by the Friedel–Crafts cyclization of the corresponding arylmethylmercaptoacetic acids or acid chlorides has been reported previously. The isothiochroman-4-ones **2** and **4** were prepared by the known procedure,[17] and this method was also applied to the preparation of **3** and **16**. The nmr spectrum of **3** (see Experimental Section) establishes that the cyclization of *m*-methoxybenzylmercaptoacetic acid resulted in ring closure *para* to the methoxyl group to form **3** rather than *ortho* to the methoxyl group. The preparation of the necessary arylmethylmercaptoacetic acids is described in the Experimental Section. Isothiochroman-4-ones **8** and **9** were prepared by alkylation of the enolate anion of **2** with excess methyl iodide and were separated by column chromatography.

Compound **14** was prepared by cyclization of the sodium salt of S-2-methylallylmercaptoacetic acid[21] with excess oxalyl chloride followed by work-up with aqueous ammonia at 0°. The ketone was purified by distillation followed by column chromatography.

Structure Proof of Photochemical Products.—The structures of the products from irradiation of **1** were established by comparison of gas chromatographic retention times and ir spectra with those of authentic samples.

The structure of **5** from irradiation of **2** was established by synthesis of an authentic sample as outlined in Scheme I.

Thiosalicylic acid was alkylated in 92% yield with ethyl bromoacetate and 2 equiv of sodium ethoxide in ethanol to give **18** which was converted into the acid chloride in 82% yield with thionyl chloride. Reaction of the acid chloride in ether with excess diazomethane gave 95% crystalline diazo ketone **19**. A modified Wolff rearrangement of **19** in absolute ethanol with catalytic amounts of silver benzoate–triethylamine reagent[22] produced diester **20** in yields of 62–82%. The normal silver oxide catalyst was unsatisfactory. Dieckmann cyclization of **20** with excess sodium hydride in refluxing tetrahydrofuran afforded a mixture of crude β-keto ester **21** and **5** which could be hydrolyzed and decarboxylated to pure **5**. This material was identical in all respects with **5** obtained from irradiation of **2**. The thiaindan isolated from this irradiation was identical in all respects with an authentic sample.[23]

The structure of **6** from irradiation of **3** was identical in all respects with an authentic sample prepared as outlined in Scheme II.

(13) Rayonet Photochemical Reactor with sixteen 3500-Å General Electric "black phosphor" lamps.

(14) The triene should show an absorption maximum at ~303 mμ.

(15) G. S. Hammond and P. A. Leermakers, *J. Amer. Chem. Soc.*, **84**, 207 (1962).

(16) A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1909 (1951).

(17) C. C. Price, *et al.*, *J. Amer. Chem. Soc.*, **85**, 2278 (1963).

(18) J. von Braun and K. Weissbach, *Ber.*, **62**, 2416 (1929).

(19) P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 1998 (1959).

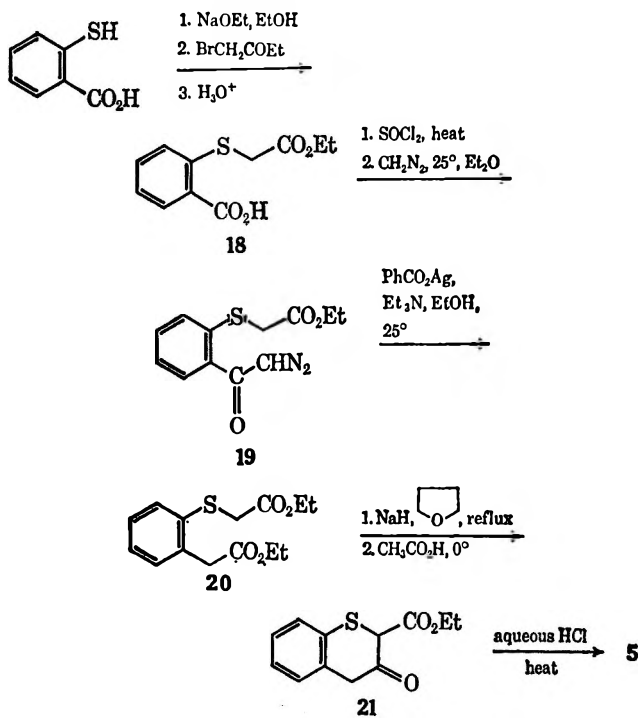
(20) P. Cagniant, G. Jecko and D. Cagniant, *ibid.*, 2225 (1961).

(21) Q. Soper, *et al.*, *J. Amer. Chem. Soc.*, **70**, 2849 (1948).

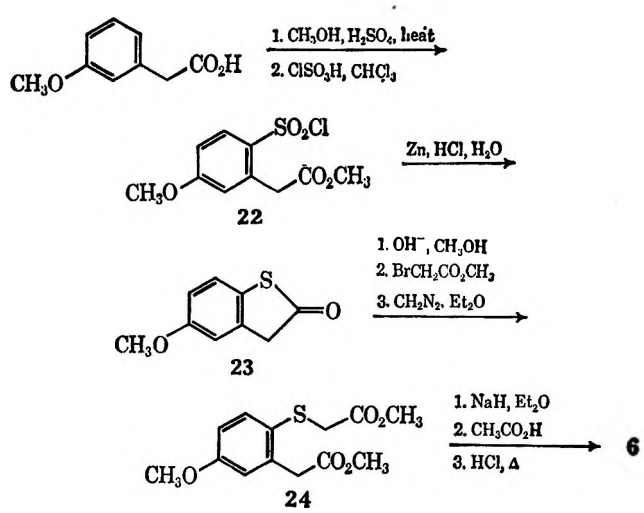
(22) M. S. Newman and P. F. Beal, III, *ibid.*, **72**, 5163 (1950).

(23) S. F. Birch, R. A. Dean, and E. V. Whitehead, *Inst. Petrol. J.*, **40**, 76 (1954).

SCHEME I



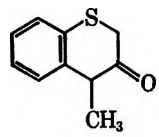
SCHEME II



Chlorosulfonation of methyl *m*-methoxyphenylacetate gave the crystalline sulfonyl chloride **22** in 6–11% yield; the low yield is probably due to an unfavorable equilibrium with the corresponding sulfonic acid.[24] Structure **22** was assigned by analogy to the chlorosulfonation of anisole[25] and on the basis of reductive cyclization to the thiolactone **23** with zinc and hydrochloric acid in 18% yield. Esterification of **23** followed by alkylation with methyl bromoacetate produced **24** in 93% yield. Dieckmann cyclization of **24** followed by hydrolysis and decarboxylation gave a 9% yield of **6**.

The structure of **7** from irradiation of **3** is assigned by analogy to the formation of **6**.

The structure of **10** is confirmed by the intense peaks at *m/e* 122 and 121 in the mass spectrum due to fragmentation of the elements of methylketene from the molecular ion (*m/e* 122) and subsequent loss of a hydrogen atom (*m/e* 121). This fragmentation is expected for **10** but is unreasonable for the alternative structure **25**, the molecular ion of which should lose the elements of ketene rather than methylketene.

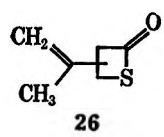


25

Loss of ketene and a methyl radical from the molecular ion of **25** is reasonable but this would lead to *m/e* 121 and no *m/e* 122. A similar argument confirms the structure of **11**.

The structure of the byproduct **12** from irradiation of **9** was assigned on the basis of its mass spectrum. The molecular ion at *m/e* 196 and the m + 1 and m + 2 peaks established the molecular formula as $C_{10}H_{12}S_2$. The principal fragment ions at *m/e* 181, 153, 122, and 121 show loss of CH_3, C_3H_6, C_3H_6S, and C_3H_7S, respectively, as a fragmentation pattern consistent with structure **12**.

The product from irradiation of **14** was established as **15** on the basis of the spectral data listed in the Experimental Section. These data rule out the alternative structures **26** as well as other isomeric structures.



26

Experimental Section[26]

2-*t*-Butylmercaptocyclohexanone (1).—This compound was prepared by a general procedure[27] from 2-chlorocyclohexanone (66.3 g, 0.50 mol) and a solution of *t*-butyl mercaptan (45.1 g, 0.50 mol) in ethanolic sodium ethoxide (from 11.5 g, 0.50 g-atom of sodium in 500 ml of absolute ethanol). There was obtained 12.0 g of a forerun, bp 25–68° (6 mm) and 59.4 g of colorless liquid, bp 68–116° (6–4.5 mm). The forerun contained a major component identified as ethyl cyclopentanecarboxylate by ir comparison. The higher boiling fraction was purified by distillation (spinning band) and gave 33.8 g (36%) of a colorless liquid: bp 123–124° (16 mm); $n^{20}D$ 1.4952; $\nu_{max}^{CHCl_3}$ 2950, 1700, 1459, 1368, 1336, 1313, 1283, and 916 cm^{-1}; λ_{max}^{EtOH} 245 mμ (ε 430) and 304 (294); nmr ($CDCl_3$) δ 3.43 (multiplet, 1 H), 3.03 (multiplet, 1 H), 1.94 (multiplet, 7 H), and 1.33 ppm (singlet, 9 H).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74; S, 17.21. Found: C, 64.30; H, 9.84; S, 16.75.

Photolysis of 1.—Irradiation[28] of **1** (5.00 g in 500 ml of cy-

(24) F. Muth, "Methoden Der Organischen Chemie" (Houben-Weyl), Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p 573.

(25) M. S. Morgan and L. H. Cretcher, *J. Amer. Chem. Soc.*, **70**, 375 (1948).

(26) All melting points are corrected and boiling points are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 237 or 337 recording spectrophotometer. The uv spectra were recorded on a Cary Model 14 spectrophotometer. The nmr spectra were recorded on a Varian A-60 nmr spectrometer, and chemical shift data are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard in CCl_4 or $CDCl_3$. Mass spectra were determined on a Consolidated Electrodynamics Model 21-130 or a Hitachi Perkin-Elmer Model RMU-6D (direct inlet) mass spectrometer with an ionizing potential of 68 V. The gas chromatographic analyses and isolations were made on an 8 ft × ¼ in. column with 20% SE-30 on neutral 60–80 mesh Chromosorb P (thermal conductivity detector) or a 12 ft × ¼ in. column of the same packing adapted to an Aerograph Hy-Fi Model 600 gas chromatograph with flame ionization detector. The drying agent in extraction procedures was $MgSO_4$ or Na_2SO_4, and solvents were removed at reduced pressure on a Büchi Rotovapor apparatus using a water bath at temperatures below 35° unless otherwise specified. Microanalyses were performed by Galbraith Laboratories, Inc., or S. M. Nagy and associate.

(27) C. K. Bradsher, F. C. Brown and R. J. Grantham, *ibid.*, **76**, 114 (1954).

(28) Hanovia Type L, 450-W, high pressure mercury lamp.

clohexane) with a Corex 9700 filter for 2 hr gave 4.06 g of a yellow oil after removal of the solvent. Distillation gave 1.10 g of material, bp ~65° (5 mm), and 0.65 g of higher boiling material, bp 120–125° (0.35 mm), which was not further examined. Analysis of the lower boiling fraction by vpc (10% SE-30 on Chromosorb P, 165°) showed the presence of three components in the ratio (area) 5.1:1.4:1, identified respectively as di-*t*-butyl disulfide, cyclohexenone, and cyclohexanone by peak enhancement and comparison of ir spectra with the spectra of authentic samples.

Isothiochroman-4-one (2).—Ketone **2** was prepared from S-benzylthioglycolic acid by a known procedure[17] in 24–26% yield, mp 59–60° (lit.[16] mp 59–60°).

7-Methoxyisothiochroman-4-one (3).—*m*-Methoxybenzyl chloride (prepared from *m*-methoxybenzyl alcohol by the method of Fuchs and Carlton[29]) was heated with an equivalent amount of thiourea in ethanol until the salt crystallized according to the procedure of Mndzhoyan and Aroyan.[30] Recrystallization from ethanol-ether gave the salt in 97% yield, mp 172.5–173.5°.

Anal. Calcd for $C_9H_{13}ClN_2OS$: C, 46.44; H, 5.63; Cl, 15.24; N, 12.04; S, 13.78. Found: C, 46.65; H, 5.70; Cl, 15.19; N, 11.93; S, 13.97.

Following the procedure of Mndzhoyan and Aroyan,[30] *m*-methoxybenzylmercaptoacetic acid was prepared by heating (80°) the isothiuronium salt (25.0 g, 0.107 mol) with chloracetic acid (15.1 g, 0.160 mol) in absolute ethanol (50 ml) under N_2 and treating the stirred mixture dropwise during 1 hr with a solution of NaOH (21.6 g, 0.54 mol) in ethanol (100 ml) and water (200 ml). The mixture was heated at 90–100° for 4 hr, the aqueous mixture was acidified with concentrated HCl (45 ml), and the oil which separated was extracted into ether. The ether layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated. Distillation of the crude oil gave 20.0 g (88%) of a colorless syrup: bp 159–167° (0.18 mm); $n^{21}D$ 1.5699; $\nu_{max}^{CHCl_3}$ 3500, 3400–2500, 1760, 1708, 1600, 1580, 1485, 1460, 1448, 1425, 1290, 1265, and 1150 cm^{-1}; λ_{max}^{EtOH} 275.5 mμ (ε 2230) and 282.5 (2010); nmr ($CDCl_3$) δ 11.1 (singlet, 1 H), 7.12 (multiplet, 4 H), 3.85 (singlet, 2 H), 3.82 (singlet, 3 H), and 3.12 ppm (singlet, 2 H).

Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.68; H, 5.70; S, 15.11. Found: C, 56.78; H, 5.91; S, 14.95.

Cyclization of this acid to **3** was effected by adding a mixture of phosphorus pentoxide (26.3 g, 0.185 mol) and "Hyflo-Super Cel" (15 g) to dry benzene (300 ml) containing absolute ethanol (1 ml) and heating this mixture under reflux for 1 hr during which time a solution of *m*-methoxybenzylmercaptoacetic acid (19.6 g, 0.0925 mol) in benzene (100 ml) was added. The mixture was refluxed for 1 hr longer, the hot benzene solution was decanted through a filter, and the dark residue was leached with boiling benzene. The combined benzene layers were washed with 1 *N* NaOH (two 100-ml portions), water, and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the benzene and crystallization of the residue from ether–hexane gave 4.16 g of **3**, mp 96–97°. Starting acid (11.0 g) could be recovered by acidification of the basic washings with 6 *N* HCl. The yield of **3** based on recovered acid was 53%: $\nu_{max}^{CCl_4}$ 3050–2825, 1680, 1600, 1275, 1112, 1045, and 1020 cm^{-1}; λ_{max}^{EtOH} 229 (ε 11,000) and 285 (12,300); nmr (CCl_4) δ 8.16 (doublet, J = 9 cps, 1 H), 6.94 (doublet of doublets, J = 9 and 2.5 cps, 1 H), 6.75 (doublet, J = 2.5 cps, 1 H), 3.90 (broad singlet, 5 H), and 3.53 ppm (singlet, 2 H).

8-Methylisothiochroman-4-one (4).—This material was prepared by the procedure described for the preparation of **3** except that the acid was cyclized by the procedure of Price, *et al.*[17]

o-Methylbenzylisothiuronium bromide was prepared from *o*-bromoxylene in 92% yield: mp 169–170° (ethanol–ether); ν_{max}^{KBr} 1640, 1545, 1262, 788, 745, 734, 700, 670, 483, and 463 cm^{-1}.

Anal. Calcd for $C_9H_{13}BrN_2S$: C, 41.38; H, 5.20; Br, 30.60; N, 10.73. Found: C, 41.59; H, 5.20; Br, 30.75; N, 10.61.

o-Methylbenzylmercaptoacetic acid was prepared from the isothiuronium salt in 84% yield: bp 150.5–152° (1 mm) [lit.[20] bp 159° (2.5 mm)]; $\nu_{max}^{CCl_4}$ 3500–2500, 1710, 1488, 1420, and 1290 cm^{-1}.

Cyclization of the acid gave **4** in 21% yield: bp 100–101° (0.15 mm) [lit.[20] bp 182° (14.8 mm)]. The distilled ketone crystallized on standing as colorless needles: mp 50–51° (recrystallized from ether–pentane); $\nu_{max}^{CCl_4}$ 3050, 2960, 1687, 1587, 1455, 1282, and 1068 cm^{-1}.

3-Methylisothiochroman-4-one (8) and 3,3-Dimethylisothiochroman-4-one (9).—To a cooled solution (0°) of sodium (6.90 g, 0.30 g-atom) in absolute ethanol (300 ml) under N_2 was added **2** (16.4 g, 0.100 mol) with stirring until a clear, orange solution formed. Methyl iodide (42.6 g, 0.300 mol) was added rapidly with stirring. The ice bath was removed and the mixture was stirred for 3 hr at room temperature, after which a deep red color had developed. The mixture was immediately poured into a slurry of ice and 6 *N* HCl (100 ml) and the mixture was extracted with four 100-ml portions of ether. The combined ether extracts were washed with water, saturated Na_2CO_3 solution, and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left 7.0 g of a dark red oil which was short path distilled to give a clear, deep red oil, 5.5 g, bp ~100° (0.2 mm). The nmr spectrum of this oil indicated ~45% dialkylated and ~55% monoalkylated ketone.

The mixture was separated by column chromatography (300 g of silicic acid, Merck reagent grade, 100–200 mesh). Elution with 10% ether–90% hexane gave 2.17 g (11%) of **9**; elution with 20% ether–80% *n*-hexane to pure ether gave 1.96 g (11%) of **8**. Recrystallization of **8** (ether–pentane) gave colorless needles, mp 52–53° (lit.[19] mp 51°). Distillation of **9** gave a colorless oil: bp 108° (1.5 mm); $n^{26}D$ 1.5841; $\nu_{max}^{CCl_4}$ 3050, 2980, 2930, 1685, 1603, 1480–1450, 1413, 1381, 1367, 1300, 1273, 1181, 1158, 1130, 1095, and 982 cm^{-1}.

Deuteration of 2.—A mixture of deuterium oxide (3.50 g, 0.175 mol), anhydrous Na_2CO_3 (35 mg), **2** (5.00 g, 0.0305 mol), and ethylene glycol dimethyl ether (21 ml, distilled from Na and then from $LiAlH_4$) was refluxed under N_2 for 17 hr. The mixture was cooled and diluted with ether and the ether solution was washed with five 50-ml portions of water and 50 ml of saturated NaCl solution and dried ($MgSO_4$). Evaporation on a steam bath gave 4 g of partially deuterated ketone, mp 58.5–59°. The mass spectrum showed the ketone to be 25% d_0, 24.5% d_1, 43.4% d_2, 6.9% d_3, and 0.2% d_4. The d_3 and d_4 species presumably arise from partial deuteration at C-1. That the deuteration is predominantly at C-3 was established by inspection of the fragment resulting from loss of thioformaldehyde from the molecular ion which indicated 10.1% monodeuteration at C-1.

1,2,3,4-Tetrahydro-1-keto-3-thiaphenanthrene (16).—This compound was prepared from 1-(chloromethyl)naphthalene by the same general procedure described for the preparation of **3**.

1-Naphthylisothiuronium chloride was prepared in 86–94% yield from 1-(chloromethyl)naphthalene and thiourea in hot ethanol: fuses at 227.5–228.5°, sealed tube (ethanol–ether); ν_{max}^{KBr} 1642, 1525, 1515, 1440, 795, and 770 cm^{-1}.

Anal. Calcd for $C_{17}H_{13}ClN_2S$: C, 57.02; H, 5.18; Cl, 14.03; S, 12.69. Found: C, 56.97; H, 5.34; Cl, 14.20; S, 12.43.

1-Naphthylmercaptoacetic acid was prepared in 80–93% yield from the thiuronium chloride: mp 110.5–111° (cyclohexane); ν_{max}^{KBr} 1703, 1595, 1510, 1425, 1395, 1307, 1218, 1160, 1133, 1017, 950, 800, and 775 cm^{-1}; λ_{max}^{EtOH} 224.5 mμ (ε 78,100) and 284 (8190); nmr ($CDCl_3$) δ11.7 (singlet, 1 H), 7.75 (multiplet, 7 H), 4.30 (singlet, 2 H), and 3.11 ppm (singlet, 2 H).

Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21; S, 13.81. Found: C, 67.10; H, 5.18; S, 13.61.

Cyclization of 1-naphthylmercaptoacetic acid (26.0 g, 0.112 mol) with phosphorus pentoxide (45.6 g, 0.321 mol) mixed with "Hyflo-Super Cel" (16 g) in 300 ml of refluxing benzene for 4 hr produced **16** which was purified by two sublimations [100° (0.1 mm)] and recrystallization from absolute ethanol to give 4.5 g (19%) of **16**: mp 125–126°; $\nu_{max}^{CHCl_3}$ 3050, 2860, 1685, 1342, 1275, and 1085 cm^{-1}; λ_{max}^{EtOH} 211.5 mμ (ε 30,100), 251 (39,700), 289 (8120) and 345 (2140); nmr ($CDCl_3$) δ 8.07 (doublet, J = 9 cps, 1 H), 7.66 (multiplet, 5 H), 4.21 (singlet, 2 H), and 3.50 ppm (singlet, 2 H).

Anal. Calcd for $C_{13}H_{10}O_5$: C, 72.86; H, 4.70; S, 14.97. Found: C, 72.97; H, 4.90; S, 14.89.

5-Methyl-2,3-dihydro-2H,6H-thiopyran-3-one (14).—S-(2-Methylallyl)mercaptoacetic acid[31] (60.0 g, 0.411 mol) and anhydrous $NaHCO_3$ (34.6 g, 0.411 mol) were heated (neat, 100°) in a nitrogen atmosphere until CO_2 was no longer evolved. Dry benzene (500 ml) was added and the mixture was refluxed

(29) R. Fuchs and D. M. Carlton, *J. Amer. Chem. Soc.*, **85**, 104 (1963).

(30) A. L. Mndzhoyan and A. Aroyan, *Izv. Akad. Nauk Arm. SSR Khim. Nauk*, **12**, 63 (1959); *Chem. Abstr.*, **54**, 6679 (1960).

(31) Q. Soper, *et al.*, *J. Amer. Chem. Soc.*, **70**, 2849 (1948).

16 hr. A Dean–Stark azeotrope trap was connected and reflux was continued until water no longer separated. The mixture was filtered; the filter cake was dried by suction and then in a steam-heated oven to yield 68.5 g (99%) of sodium salt.

A solution of oxalyl chloride (25 g, 0.20 mol) in dry benzene (50 ml) was cooled in an ice bath to 0–5°. The powdered sodium salt of S-(2-methylallyl)mercaptoacetic acid (16.8 g, 0.100 mol) was added in portions to the rapidly stirred oxalyl chloride by means of Gooch rubber addition tubing. The mixture was kept under a slight positive pressure of N_2, and the temperature was maintained at 10–20° during the addition. The mixture was then heated to reflux for 25 min, cooled, and filtered by suction. The dark red filtrate was shaken vigorously with a slurry of ice and concentrated ammonium hydroxide (20 ml). The organic layer was separated, washed with 1 *N* HCl (30 ml), saturated $NaHCO_3$ solution, water, and saturated NaCl solution, and dried ($MgSO_4$). Filtration and evaporation of the filtrate *in vacuo* left 6.0 g of a dark oil which was short path distilled to give a light yellow oil (3.8 g, 30%), bp 57–70° (0.15–0.40 mm).

The ir spectrum of this oil showed bands at 1680 and 1721 cm^{-1} for the conjugated and unconjugated isomers of 5-methyldihydropyran-3-one, respectively, with the former being the stronger band. Column chromatography of the crude material on silicic acid (Merck, reagent grade, 60 g), eluting first with benzene (225 ml) and then with 10% EtOAc–90% C_6H_6 gave, with the latter, mixed fractions (25 ml each) containing both isomers (0.26 g) and fractions containing 2.52 g of pure **14**. Distillation of the conjugated ketone gave a faintly yellow oil: bp 105–106° (6 mm); $n^{25}D$ 1.5579; $\nu_{max}^{CCl_4}$ 3035, 2986, 2882, 1675, 1438, 1409, 1390, 1380, 1335, 1275, 1177, 1129, 1026, and 892 cm^{-1}; $\lambda_{max}^{isooctane}$ 231.5 mμ (ε 9340), 270 (302), and 347 (97.8); nmr (CCl_4) δ 5.74 (quartet, J = 1.5 cps, 1 H), 3.17 (broad singlet, 2 H), 3.08 (singlet, 2 H), and 1.99 ppm (broad singlet, 3 H).

Anal. Calcd for C_6H_8OS: C, 56.21; H, 6.29; S, 25.02. Found: C, 56.07; H, 6.31; S, 24.82.

Photolysis of 2. Run 1.—Irradiation[28] of **2** (2.00 g, 0.0122 mol) in 500 ml of cyclohexane with a Pyrex 7740 filter was carried out for a total of 16 hr. Periodic cleaning of the immersion well was essential owing to the formation of a coating of polymer. The ir spectra (CCl_4) of residues from evaporation of aliquots taken during the irradiation showed gradual disappearance of the band at 1685 cm^{-1} for starting material and formation of a new intense band at 1725 cm^{-1}. The murky solution was filtered and the clear filtrate evaporated leaving 0.72 g of crude residue. Chromatography of the residue on Florisil, eluting with *n*-hexane containing 0, 2.5, 5.0, and 10% ether gave, with the latter, 303 mg (15%) of an orange oil characterized as **5** by comparison with an authentic sample after purification by short-path distillation.

Run 2.—A similar irradiation[28] for 14 hr with a Corex 9700 filter gave 264 mg (13%) of **5**.

Run 3.—Irradiation of 200 mg of **2** in 50 ml of cyclohexane for 57.5 hr with a 3500-Å source[13] gave a murky mixture which was filtered, evaporated, and distilled (short path) to give 39 mg of an orange oil. The ir spectrum ($CHCl_3$) of this oil showed only weak absorption at 1720 and 1685 and moderately strong absorption at 1770 cm^{-1}. No pure products could be isolated from this residue.

Run 4.—Irradiation[28] of **2** (1.00 g, 6.10 mmol) in 500 ml of cyclohexane for 5 hr with a Pyrex 7740 filter, followed by filtration, evaporation, chromatography of the residue on silicic acid (50 g, elution with 10% ether–90% *n*-hexane), and distillation gave 192 mg (19%) of **5** which was identified by comparison with an authentic sample.

Run 5.—Irradiation[28] of **2** (1.00 g, 6.10 mmol) in "Genetron 113" (500 ml) for 8.25 hr with a Pyrex 7740 filter gave, after short-path distillation of the crude photoproduct, 301 mg of an orange oil which contained a major and a minor product. The minor product (6% corrected vpc yield) was collected by vpc and identified as 1-thiaindan by comparison with an authentic sample prepared as previously reported.[23] The major component (21% corrected vpc yield) was identified as thiochroman-3-one, **5**, by comparison with an authentic sample: $\nu_{max}^{CCl_4}$ 3084, 1723, 1468, 1443, 1385, 1253, 1236, 951, 500, and 440 cm^{-1}; $\lambda_{max}^{isooctane}$ 254 mμ (ε 6900) and 357 (150); nmr (CCl_4) δ 7.93–7.04 (multiplet, 4 H), 3.55 singlet, 2 H), and 3.15 ppm (singlet, 2 H).

Anal. Calcd for C_9H_8OS: C, 65.82; H, 4.91; S, 19.53. Found: C, 65.99; H, 4.80; S, 19.25.

Photolysis of 3, 4, 8, 9, and Deuterated 2.—Irradiation[28] of these materials with a Pyrex 7740 filter was carried out analogously to run 4 for **2** with 1.00 g of ketone in 500 ml of cyclohexane.

7-Methoxyisothiochroman-4-one (**3**) was irradiated for 3 hr. 6-Methoxythiochroman-3-one was isolated in 40% yield: $\nu_{max}^{CCl_4}$ 3050–2825, 1725, 1600, 1572, 1480, 1467, 1310, 1250, 1160, 1070, and 1030 cm^{-1}; λ_{max}^{EtOH} 251.5 mμ (ε 10,200) and 291 (1860); nmr (CCl_4) δ 7.40 (doublet, apparent J = 9 cps, 1 H), 6.82 (quartet, apparent J = 3 cps, 1 H), 6.74 (singlet, 1 H), 3.80 (singlet, 3 H), 3.64 (singlet, 2 H), and 3.22 ppm (singlet, 2 H).

8-Methylisothiochroman-4-one (**4**) was irradiated for 5 hr. 5-Methylthiochroman-3-one was isolated by vpc (corrected vpc yield was 30%): $\nu_{max}^{CCl_4}$ 3060, 2970, 2905, 1723, 1455, 1380, and 1225 cm^{-1}; λ_{max}^{EtOH} 209 mμ (ε 16,200), 247.5 (6760), and 287 (sh) (891); nmr (CCl_4) δ 7.17 (multiplet, 3 H), 3.58 (singlet, 2 H), 3.20 (singlet, 2 H), and 2.28 ppm (singlet, 3 H).

3-Methylisothiochroman-4-one (**8**) was irradiated for 4 hr. 2-Methylthiochroman-3-one (**10**) was isolated by vpc (corrected vpc yield was 30%): $\nu_{max}^{CCl_4}$ 3050, 2960, 2923, 1725, 1473, 1443, 1390, 1200, and 1073 cm^{-1}; λ_{max}^{EtOH} 210 mμ (infl) (45,700) and 246.5 (7580); nmr (CCl_4) δ 7.30 (multiplet, 1 H), 7.09 (multiplet, 3 H), 3.62 (singlet, 2 H), 3.28 (quartet, J = 7 cps, 1 H), and 1.36 ppm (doublet, J = 7 cps, 3 H).

3,3-Dimethylisothiochroman-4-one (**9**) was irradiated for 1 hr. The chromatographic fractions contained three components identified as (1) unreacted **9** (5% corrected vpc yield; (2) 2,2-dimethylthiochroman-3-one (**11**) [37% corrected vpc yield; $\nu_{max}^{CCl_4}$ 3055, 2972, 2929, 2855, 1715, 1468, 1437, 1377, 1358, 1244, 1140, 1122, and 1096 cm^{-1}; λ_{max}^{EtOH} 248 mμ (ε 6610); nmr (CCl_4) δ 7.21 (multiplet, 4 H), 3.74 (singlet, 2 H), and 1.38 ppm (singlet, 6 H)]; (3) 2,2-dimethyl-1,3-dithiatetralin (**12**) (6% corrected vpc yield).

Deuterated 2 was irradiated for 6 hr to give 270 mg (27%) of deuterated **5** which was shown by mass spectrometry to be 34% d_0, 43% d_1, 20% d_2, and 3% d_4 species. The corrected intensities of the peaks at m/e 123 and 122 corresponded to 2.2 and 1.5% monodeuterated species at m/e 122 and 121, respectively, in the undeuterated sample.

Photolysis of 5-Methyl-2,3-dihydro-2H,6H-thiapyran-3-one (**14**).—Irradiation[28] of a solution of **14** (1.00 g, 7.82 mmol) in cyclohexane (500 ml) for 2 hr with a Pyrex 7740 filter gave a slightly cloudy solution which was filtered and concentrated by evaporation. The pale yellow residue (0.87 g) was distilled (Klagen tube, pot temperature 100–110° (0.1 mm)] to give a nearly colorless oil (282–350 mg, 28–35%) which rapidly discolored on standing. The product was identified as **15** from its analytical and spectral data: $n^{25}D$ 1.5193; $\nu_{max}^{CCl_4}$ 3082, 2978, 2918, 1780, 1641, 1448, 1397, 1374, 1168, 1127, and 910 cm^{-1}; λ_{max}^{EtOH} 245 mμ (ε 912) and 330 (166); nmr (CCl_4) δ 5.25 (multiplet, 1 H), 5.10 (multiplet, 1 H), 5.00 (doublet, J = 0.6 cps, 1 H), 4.14 (doublet–quartet, J = 14 and 0.6 cps, 2 H), and 1.85 ppm (finely split singlet, 3 H).

Anal. Calcd for C_6H_8OS: C, 56.21; H, 6.29; S, 25.02. Found: C, 56.51; H, 6.48; S, 24.78.

Photolysis of 1,2,3,4-Tetrahydro-1-keto-3-thiaphenanthrene (**16**). A.—Irradiation[28] of a solution of **16** (1.00 g, 4.68 mmol) in cyclohexane (500 ml) for 7 hr with a Pyrex 7740 filter gave a murky mixture which was filtered and the filtrate was evaporated. The solid residue was combined with the precipitate from the filtration (815 mg total) and sublimed [110° (0.15 mm)] to give 234 mg of pale yellow solid. Except for very weak bands at 1775 and 1720 cm^{-1}, the ir spectrum (CCl_4) of this material was identical with the spectrum of **16**.

B.—Irradiation[13] of a solution of **16** (501 mg, 2.34 mmol) in cyclohexane for 24 hr and evaporation of an aliquot gave a residue whose ir spectrum showed a strong band at 1685 for starting material and a moderately strong band at 1770 cm^{-1}. The reaction was not investigated further.

***o*-(Ethyl carboxymethylmercapto)benzoic Acid** (**18**).—To a stirred solution of Na metal (12.5 g, 0.542 g-atom) in absolute ethanol (750 ml) under N_2 was added thiosalicylic acid (41.7 g, 0.271 mol); a heavy, white precipitate formed immediately. The mixture was stirred for 30 min at room temperature and ethyl bromoacetate was added rapidly. A mildly exothermic reaction occurred with dissolution of the original precipitate and formation of a considerably less bulky precipitate. After refluxing for 1 hr, the mixture was cooled and treated with concentrated HCl (23 ml). Evaporation of the solvents left a rock

hard residue which was ground to a powder with mortar and pestle. The powdered material was leached with 500 ml of hot water and collected by filtration as a buff powder (59.8 g, 92%). Recrystallization from ethanol–water gave colorless needles: mp 125.5–126.5°; ν_{max}^{KBr} 3500–3000, 1731, 1695, 1589, 1562, 1470, 1416, 1319, 1284, 1196, 1164, 1070, 1053, 1032, 895, 745, 699, 652, and 556 cm^{-1}; λ_{max}^{EtOH} 222 mμ (ε 20,400), 256.5 (7510) and 314 (2980); nmr ($CDCl_3$) δ 11.64 (singlet, 1 H), 8.23 (doublet, J = 8 cps, 1 H), 7.67–7.17 (multiplet, 3 H), 4.25 (quartet, J = 7 cps, 2 H), 3.78 (singlet, 2 H), and 1.27 (triplet, J = 7 cps, 3 H).

Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.98; H, 5.04; S, 13.35. Found: C, 54.84; H, 5.01; S, 13.31.

o-(Ethyl carboxymethylmercapto)diazoacetophenone (19).—A mixture of **18** (49.3 g, 0.205 mol) and $SOCl_2$ (65 ml) was refluxed on a steam bath for 30 min. The resulting deep red solution was evacuated with a water aspirator to remove excess $SOCl_2$ and the residue was distilled to give 43.5 g (82%) of clear, yellow acid chloride: bp 164–166° (1.5 mm), 140–142.5° (0.1 mm); $n^{30}D$ 1.5868; $\nu_{max}^{CCl_4}$ 2980, 1766, 1735, 1587, 1455, 1272, 1200, 1131, 1031, 873, and 700 cm^{-1}; nmr (CCl_4) δ 8.33 (doublet, J = 7.5 cps, 1 H), 7.43 (multiplet, 3 H), 4.18 (quartet, J = 7 cps, 2 H), 3.67 (singlet, 2 H), and 1.25 (triplet, J = 7 cps, 3 H).

Anal. Calcd for $C_{11}H_{11}ClO_3S$: C, 51.06; H, 4.09; S, 12.40; Cl, 13.71. Found: C, 51.18; H, 4.17; S, 12.59; Cl, 13.74.

A solution of diazomethane[32] was prepared from 18.5 g of "EXR-101" and to this solution was added dropwise at 0° during 1 hr a solution of the acid chloride (6.45 g, 0.025 mol) in ether (50 ml). The solution was allowed to warm gradually to room temperature and stand for 38–40 hr. Removal of the ether at 30° left a bright yellow crystalline residue which was triturated with pentane and filtered to give 6.25 g (95%) of crude diazo ketone **19**, mp 67–70°. Recrystallization of a sample from ether–pentane gave tiny, yellow rhombs: mp 68–69°; ν_{max}^{KBr} 3107, 2978, 2957, 2103, 1739, 1727, 1605, 1583, 1460, 1353, 1292, 1167, 1019, 875, and 739 cm^{-1}; λ_{max}^{EtOH} 237 mμ (ε 16,900), 290 (10,900), and 326 (sh) (3260); nmr ($CDCl_3$) δ 7.63 (multiplet, 3 H), 7.39 (multiplet, 1 H), 6.00 (singlet, 1 H), 4.23 (quartet, J = 7.5 cps, 2 H), 3.75 (singlet, 2 H), and 1.23 (triplet, J = 7.5 cps, 3 H).

Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.37; H, 4.62; N, 10.80; S, 12.43.

Ethyl *o*-(Ethyl carboxymethylmercapto)phenyl Acetate (20).—A solution of $AgNO_3$ (5.90 g, 0.0298 mol) in water (100 ml) and a solution of sodium benzoate (5.00 g, 0.0298 mol) in water (100 ml) were mixed and the precipitate of silver benzoate was collected and washed with several portions of water on a suction funnel. The filter cake was broken up and dried *in vacuo* [75° (3 mm) for 24 hr and then 25° (0.1 mm) for 24 hr]. A solution of silver benzoate (2.00 g) in triethylamine (18.2 g, distilled from $LiAlH_4$) was prepared and stored in a vacuum-dried bottle fitted with a "no-air" stopper.

To a slurry of the diazo ketone **19** (2.00 g, 7.59 mmol) in 13 ml of absolute EtOH in a flask connected to a gas buret was added, dropwise with stirring at 25°, the silver benzoate–triethylamine reagent. Initially a few drops were added followed by portions necessary to maintain evolution of N_2. After addition of *ca.* 2.0 g of the reagent during 25 min, N_2 evolution had ceased and 160 ml of the gas (~90% of the theoretical) had been collected. The dark red mixture was refluxed with Norit for 5 min on a steam bath, cooled, diluted with an equal volume of EtOH, and filtered. Concentration of the filtrate *in vacuo* left a dark syrup which was dissolved in 100 ml of ether. The ether solution was washed with two 20-ml portions of saturated $NaHCO_3$ solution and 20 ml of saturated NaCl solution, dried, evaporated, and distilled to give 1.53 g (72%) of a clear, yellow liquid: bp 121–124° (0.15 mm); $n^{30}D$ 1.5281; $\nu_{max}^{CCl_4}$ 3055, 2989, 1743, 1275, 1162, and 1038 cm^{-1}; λ_{max}^{EtOH} 250 mμ (sh) (ε 3500); nmr (CCl_4) δ 7.55 (multiplet, 1 H), 7.27 (multiplet, 3 H), 4.13 (quartet, J = 7 cps, 2 H), 4.08 (quartet, J = 7 cps, 2 H), 3.83 (singlet, 2 H), 3.50 (singlet, 2 H), 1.24 (triplet, J = 7 cps, 3 H), and 1.18 ppm (triplet, J = 7 cps, 3 H).

Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.42; S, 11.36. Found: C, 59.71; H, 6.49; S, 11.52.

Ethyl Thiochroman-3-one-2-carboxylate (21).—Sodium hydride (2.30 g of an approximately 50% by weight dispersion in Nujol, *ca.* 0.048 mol) was washed with dry *n*-hexane by decantation under N_2 and suspended in tetrahydrofuran (100 ml, distilled from sodium hydride). To this slurry was added dropwise a solution of **20** (6.76 g, 0.024 mol) in 20 ml of dry tetrahydrofuran during 1 hr at 65–70°. The mixture was refluxed under N_2 for 7.5 hr and then cooled to room temperature. Absolute EtOH (2 ml) was added, the mixture was poured onto a slurry of ice (100 g) and glacial HOAc (7.5 ml), and the oily suspension was extracted with three 100-ml portions of ether. The combined ether layers were washed with water and with saturated NaCl solution, dried ($MgSO_4$), evaporated, and distilled to give two fractions, bp 119–132° (0.35–0.4 mm) and 132–137° (0.4–0.6 mm). Spectral data (ir and nmr) indicated that the lower boiling fraction (1.32 g) was a mixture (~1:1) of **21** and **5**, and the higher boiling fraction (2.71 g) was essentially pure β-keto ester **21** (combined yield 76%).

Evaporative distillation of the higher boiling fraction gave colorless product **21**: $\nu_{max}^{CHCl_3}$ 3500–2500, 3055, 2980, 1716, 1635, 1603, 1565, 1465, 1440, 1410, 1395, 1370, 1330, 1312, 1290, 1260, 1225, 1170, 1100, 1072, 1042, 1035, 950, 922, 890, 860, 650, and 578 cm^{-1}; λ_{max}^{EtOH} 229 mμ (ε 10,700), 261 (8900), and 299 (2610); nmr ($CDCl_3$) δ 7.5 (complex, 4 H), 4.45 and 4.42 (two quartets, J = 7.5 cps, 2 H), 1.38 (triplet, J = 7.5 cps, 3 H), and 3.85–3.42 and 12.6 ppm (multiplet and singlet, 3 H).

Anal. Calcd for $C_{12}H_{12}O_3S$: C, 60.99; H, 5.12; S, 13.57. Found: C, 61.09; H, 4.96; S, 13.76.

Thiochroman-3-one (5).—The mixture of β-keto ester **21** and ketone **5** obtained in the preparation of **21** was refluxed under N_2 with 50 ml of 20% HCl for 8.5 hr (bath temperature 140°). The mixture was cooled and extracted with ether. The ether extracts were washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a red oil (3.55 g) which was chromatographed on Florisil (40 g). Elution with *n*-hexane gave 0.97 g of recovered **21** and with 10% ether–90% *n*-hexane gave 1.53 g of desired ketone **5**. Distillation of the ketone gave 1.30 g (41% based on recovered **21**) of a nearly colorless product, bp 98–99° (1.6 mm).

The ir spectrum of this material indicated that it still contained a trace of **21** which was removed by a second chromatography on Florisil followed by short-path distillation. The spectral data and vpc data of this ketone were identical with those of **5** obtained from irradiation of **2**.

Methyl 2-Chlorosulfonyl-5-methoxyphenylacetate (22).—A solution of *m*-methoxyphenylacetic acid (16.6 g, 0.10 mol) in methanol (50 ml) containing concentrated H_2SO_4 (4.5 ml) was refluxed for 4 hr on a steam bath. Water (100 ml) was added, the mixture was extracted with ether, and the ether extracts were washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried, and evaporated. Distillation afforded 15.9 g (88%) of methyl *m*-methoxyphenylacetate: bp 107–108° (2 mm); $n^{28}D$ 1.5130; $\nu_{max}^{CCl_4}$ 3000, 2950, 2835, 1744, 1603, 1587, 1493, 1469, 1455, 1438, 1265, 1153, 1060, 1048, 1021, 735, and 692 cm^{-1}; nmr (CCl_4) δ 7.05 (triplet, apparent J = 8 cps, 1 H), 6.68 (multiplet, 3 H), 3.84 (singlet, 3 H), 3.57 (singlet, 3 H), and 3.44 ppm (singlet, 2 H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.37; H, 6.66.

To a solution of methyl *m*-methoxyphenylacetate (29.0 g, 0.161 mol) in $CHCl_3$ (80 ml) under N_2 and cooled to −8° was added dropwise, with vigorous stirring, freshly distilled chlorosulfonic acid (38.5 g, 0.329 mol) while the temperature was maintained below 0°. The ice bath was removed and the mixture was stirred under N_2 for 1.25 hr while it was warmed to room temperature. The mixture was poured onto a slurry of ice and $CHCl_3$, the layers were separated, and the $CHCl_3$ layer was washed with two 75-ml portions of ice-water and dried (Na_2SO_4). Evaporation of the solvent left an oil which gave 5.0 g (11%) of white, crystalline **22** after trituration with pentane, mp 82–83°. The nearly pure product could be recrystallized from cyclohexane containing a little ether: mp 83–84°; $\nu_{max}^{CHCl_3}$ 3006, 2938, 2835, 1742, 1597, 1569, 1480, 1460, 1430, 1374, 1339, 1320, 1252, 1170, 1055, and 1000 cm^{-1}; nmr ($CDCl_3$) δ 8.03–6.97 (multiplet, 3 H), 4.13 (singlet, 2 H), 3.90 (singlet, 3 H), and 3.72 ppm (singlet, 3 H).

Anal. Calcd for $C_{10}H_{11}ClO_5S$: C, 43.09; H, 3.98; Cl, 12.72; S, 11.51. Found: C, 43.12; H, 4.11; Cl, 12.90; S, 11.45.

5-Methoxy-1-thiaindan-2-one (23).—The sulfonyl chloride **22** (4.91 g, 17.6 mmol) was added in portions to a vigorously stirred suspension of zinc dust (6.0 g) in water (16 ml) during 1 hr. Water (6 ml) was added and the stirred mixture was

(32) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

heated to 60–80° (bath temperature) for 1 hr under N_2. During the heating period an additional 0.8 g of zinc dust was added in small portions. The mixture was cooled to 0–10° and a solution of 40 ml of concentrated HCl in 10 ml of water was added in small portions. After the mixture was stirred vigorously for 18 hr at 20°, a flocculent, gray precipitate had formed. An additional 4.0 g of zinc dust was added and the mixture was heated to gentle reflux under N_2 for 1 hr. The mixture was cooled, filtered through glass wool, and extracted with ether. The acidic aqueous layer was saturated with NaCl and extracted with ether. The combined ether extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a semisolid residue. Trituration with pentane gave solid **23** (0.56 g, 18%), mp 110–116°, which was purified by sublimation: mp 122–123°; $\nu_{max}^{CHCl_3}$ 3010, 2945, 2905, 2830, 1712, 1601, 1578, 1469, 1429, 1304, 1225, 1150, 1080, 1033, and 1012 cm^{-1}; λ_{max}^{EtOH} 216 mμ (ε 11,100) 234.5 (11,100), 270.5 (5750), and 298 (934); nmr ($CDCl_3$) δ 7.19–6.81 (multiplet, 3 H), 3.89 (singlet, 2 H), and 3.79 (singlet, 3 H).

Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 59.94; H, 4.48; S, 17.88.

Methyl 2-(Methyl carboxymethyl)-4-methoxyphenylmercaptoacetate (24).—To a slurry of thiolactone **23** (226 mg, 1.26 mmol) in 5 ml of 80% methanol–water under N_2 was added solid KOH (160 mg, 2.85 mmol). The solution was stirred for 15 min at room temperature and methyl bromoacetate (301 mg, 1.97 mmol) was added. The mixture was stirred for 15 min at room temperature and then heated under reflux for 1 hr. Water (10 ml) and 6 *N* HCl (0.5 ml) were added and 5 ml of distillate was collected. The mixture was cooled and extracted with three 30-ml portions of ether. The combined ether extracts were washed with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a yellow oil. The oil was dissolved in 10 ml of ether; the solution was cooled to 0° and treated with a solution of diazomethane in ether (prepared from 715 mg N′-nitro-N-methyl-N-nitrosoguanidine and a mixture of 3 ml of 50% aqueous KOH and 18 ml of ether)[33] until a yellow color persisted. After the mixture was stirred for 10 min while it warmed to room temperature, the yellow color was carefully discharged with a few drops of glacial HOAc. The ether solution was diluted to 100 ml (ether), dried ($MgSO_4$), and evaporated to give 332 mg (93%) of **24**. A sample of this material was purified by short-path distillation [Klagen tube, bath temperature 210° (0.1 mm)] to give a nearly colorless oil: $\nu_{max}^{CCl_4}$ 3003, 2954, 2838, 1742, 1596, 1569, 1480, 1467, 1433, 1335, 1300–1230, 1156, 1068, 1028, and 1008 cm^{-1}; nmr (CCl_4) δ 7.44 (doublet of doublets, J = 7 and 2 cps, 1 H), 6.74 (doublet, J = 2 cps, 1 H), 6.70 (doublet of doublets, J = 7 and 2 cps, 1 H), 3.81 (singlet, 2 H), 3.69 (singlet, 3 H), 3.60 (singlet, 3 H), 3.55 (singlet, 3 H), and 3.35 (singlet, 2 H).

(33) A. F. McKay, *J. Amer. Chem. Soc.*, **70**, 1974 (1948).

Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.91; H, 5.67; S, 11.28. Found: C, 55.04; H, 5.77; S, 11.14.

6-Methoxythiochroman-3-one (6).—Sodium hydride (*ca.* 50% Nujol dispersion, 115 mg, *ca.* 2.4 mmol) was washed free of Nujol with three 5-ml portions of *n*-hexane under N_2 and 5 ml of ether was added. The vigorously stirred slurry was treated dropwise during 45 min with a solution of **24** (339 mg, 1.2 mmol) in ether (10 ml) containing 3 microdrops of methanol. A mildly exothermic evolution of H_2 took place after a short while with development of a light yellow color and formation of a copius gray to tan precipitate. Stirring at room temperature was continued for 0.5 hr longer and the mixture was heated under reflux for 1 hr (bath temperature 45°). The mixture was cooled and poured into a slurry of ice–water (20 g) and glacial HOAc (0.3 g). The layers were separated and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether extracts were washed with water (20 ml), a mixture of saturated $NaHCO_3$ solution (2 ml) and water (8 ml), and saturated NaCl solution, dried (Na_2SO_4), and evaporated to give 285 mg (94%) of crude β-keto ester as an amber, partially crystallized oil (keto/enol forms, *ca.* 3:1).

The crude β-keto ester was heated under reflux with 1 ml of 6 *N* HCl (oil bath, 130–140°) under N_2 for 45 min. The mixture was cooled and poured into a solution of Na_2CO_3 (0.50 g) in water (9 ml). The mixture was shaken, the layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 2 *N* NaOH (10 ml), water, and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a dark residue which was distilled (Klagen tube, *ca.* 0.6 mm) to give 17.1 mg of a light yellow oil. The major component was collected by vpc and was identical in all respects with the sample of **6** from irradiation of **3**.

Registry No.—**1**, 18926-31-3; **2**, 4426-76-0; **3**, 16994-31-3; **4**, 16994-30-2; **5**, 16895-58-2; **6**, 18926-35-7; **9**, 16994-33-5; **10**, 18926-36-8; **11**, 18926-37-9; **14**, 16994-29-9; **15**, 18926-39-1; **16**, 5254-94-4; **18**, 18926-41-5; **18** (acid chloride), 18926-42-6; **19**, 18926-43-7; **20**, 18926-44-8; **21**, 18926-45-9; **22**, 18944-99-5; **23**, 18926-46-0; **24**, 18945-00-1; *m*-methoxybenzylmercaptoacetic acid, 18926-47-1; *o*-methylbenzylisothiuronium bromide, 18926-48-2; *o*-methylbenzylmercaptoacetic acid, 18926-49-3; 1-napthylisothiuronium chloride, 18945-01-2; 1-napthylmercaptoacetic acid, 10404-24-7; 6-methoxythiochroman-3-one, 18926-35-7; 5-methylthiochroman-3-one, 18927-04-3; methyl *m*-methoxyphenylacetate, 18927-05-4.

Synthesis of New Indole Alkaloid Types

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A new series of compounds related to tubulosine has been synthesized. The designation "methylenebis type" is proposed for this general structural class. The compounds were prepared by condensing various esters represented by **5a** with homoveratrylamine or tryptamine; the resulting amides (*e.g.*, **6a**) were cyclized with phosphoryl chloride. Reduction of **7a** with sodium borohydride gave mixtures of the corresponding epimeric pair **8a**. This mixture was separated, and the major epimer was N-methylated *via* lithium aluminum hydride reduction of its N-formamide. The mass spectra of the compounds described showed fragmentation patterns analogous to those arising from emetine and tubulosine, thereby confirming the structures expected on the basis of the synthetic sequence.

For many years, the ipecacuanha alkaloids,[1] as represented by the pharmacologically important compound emetine[2] (**1a**), were the only compounds of the "methylenebis"[3] alkaloid type known to occur naturally. Members of this series possess benzoisoquinolizidine and isoquinoline moieties, connected by a methylene bridge.

(1) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p 370.

(2) The Merck Index, 7th ed, Merck and Co. Inc., Rahway, N. J., 1960, p 401.

(3) We propose the general designation "methylenebis type" for this class of alkaloids and related substances containing two discrete basic moieties connected by a methylene bridge.

TABLE I
ANALYTICAL DATA

Compd	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6a	273–275	82	$C_{29}H_{37}N_3O_3$	73.26	7.84	8.84	72.98	8.08	8.66
6b	155–157	63	$C_{30}H_{39}N_3O_4$	71.26	7.77	8.31	71.13	7.79	8.28
7a	260–262 dec	64	$C_{29}H_{37}Cl_2N_3O_2 \cdot 2H_2O$[a]	61.47	7.29	7.42	61.55	7.14	7.50
7b	234–237 dec	68	$C_{30}H_{39}Cl_2N_3O_3 \cdot 1.5H_2O$[a]	61.32	7.20	7.15	61.22	7.28	6.94
8a	305–307 dec	7	$C_{29}H_{39}Cl_2N_3O_3 \cdot 0.5H_2O$[a]	64.32	7.44	7.75	64.54	7.59	7.80
	266–268 dec	63	$C_{29}H_{39}Cl_2N_3O_2 \cdot 2H_2O$[a]	61.26	7.61	7.39	61.56	7.64	7.26
8b	265–267 dec	66	$C_{30}H_{41}Cl_2N_3O_3 \cdot H_2O$[a]	62.06	7.47	7.24	62.20	7.52	7.05
9a	295	71	$C_{30}H_{41}Cl_2N_3O_2 \cdot 0.5H_2O$[a]	64.85	7.62	7.56	65.01	7.82	7.47
9b	231–233	47	$C_{31}H_{43}Cl_2N_3O_3 \cdot H_2O$[a]	62.62	7.63	7.08	62.82	7.76	6.88
10a	188–189	57	$C_{29}H_{34}N_4O$	76.62	7.54	12.33	76.31	7.67	12.10
10b	187–189	47	$C_{30}H_{36}N_4O_2$	74.35	7.49	11.56	74.05	7.48	11.52
11a	301–303 dec	70	$C_{29}H_{34}Cl_2N_4 \cdot 0.5H_2O$[a]	61.47	7.29	7.42	61.55	7.14	7.50
11b	263–265 dec	53	$C_{30}H_{36}Cl_2N_4O \cdot 1.5H_2O$[a]	63.59	6.93	9.89	63.30	7.14	9.69

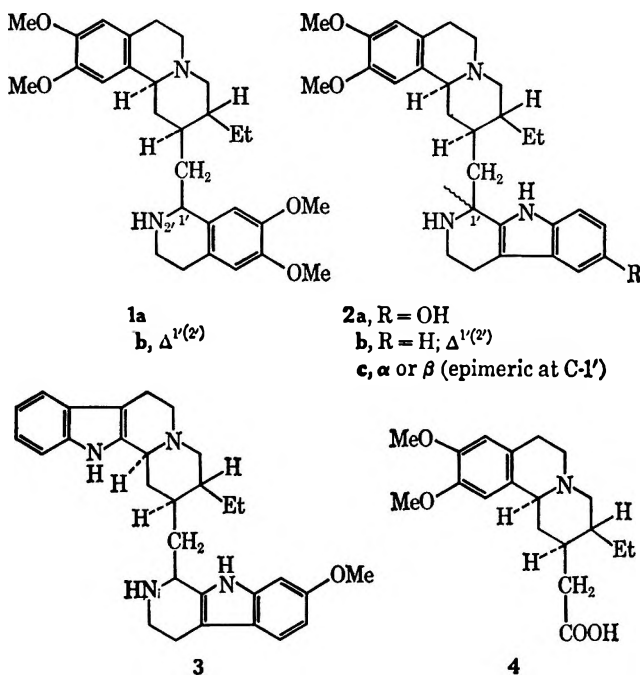
[a] Analyzed as the dihydrochloride.

Recently, a new series of "methylenebis" type alkaloids containing β-carboline residues similarily linked to benzoquinolizidine residues has been isolated. Examples of this group are the first known member, tubulosine[4] (**2a**), desoxytubulosine,[5,6] isotubulosine,[7] and alangimarckine.[8] Structural assignments for these alkaloids were based primarily on the interpretation of their mass spectra, using as a standard the fragmentation pattern obtained from a synthetic specimen of *dl*-deoxytubulosine prepared[9] several years before for another study. More recently, the skeletal structure of tubulosine and deoxytubulosine was confirmed, and their absolute configurations established by total synthesis.[5,10]

Two additional types of "methylenebis" compounds are biogenetically plausible, based on the theory of Robinson[11] as elaborated by Battersby and Harper[12] and Brauchli, *et al.*[4] They are exemplified by **7a** and **11a**. Although they have not yet been found in nature, it is interesting that, during a structural study, Potier, *et al.*,[13] synthesized a crude specimen of **3** in order to examine it as a possible structure (negative result) for the alkaloid cinchophyllamine.

As it is anticipated that these compounds exist as natural products, and because of a pharmacological interest in compounds of these classes, synthesis of several compounds, including **7a** and **11a**, was initiated.

Several approaches to the preparation of this type of substance are on record. Potier, *et al.*,[13] prepared crude **3** by condensing dihydrocorynantheal with 6-methoxytryptamine. Battersby, *et al.*,[9] prepared the base **2b** by condensing the mixed anhydride of ethyl hydrogen carbonate and the amino acid **4** with tryptamine, and cyclizing the resultant amide with phosphoryl chloride.



Catalytic hydrogenation or sodium borohydride reduction of the base **2b** gave the mixture **2c**. A modification of these procedures established a pattern for preparation of the bases listed in Table I. Esters of formula **5**[14] were heated with homoveratrylamine or tryptamine to give amides **6** and **10** (Scheme I). Cyclization of the amides with phosphorus oxychloride gave bases **7** and **11**. Sodium borohydride reduction of **7a** gave a separable mixture of disastereoisomers **8a** (stereochemistry undetermined), **7** and 63%, respectively.

Methylation was achieved by converting the more abundant isomer into its formyl derivative, and reducing this to the corresponding N-methyl compound (**9a**) with lithium aluminum hydride.

The mass spectra of the ipecacuanha alkaloids, as well as of tubulosine, have been interpreted.[4,15,16]

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(5) A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar, *Chem. Commun.*, 315 (1965).
(6) H. Monteiro, H. Budzikiewicz, C. Djerassi, R. R. Arndt, and W. H. Baarschers, *ibid.*, 317 (1965).
(7) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, 5077 (1966).
(8) A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *ibid.*, 4965 (1966).
(9) A. R. Battersby, G. C. Davidson, and J. C. Turner, *J. Chem. Soc.*, 3899 (1961).
(10) H. T. Openshaw and N. Whittaker, *Chem. Commun.*, 131 (1966).
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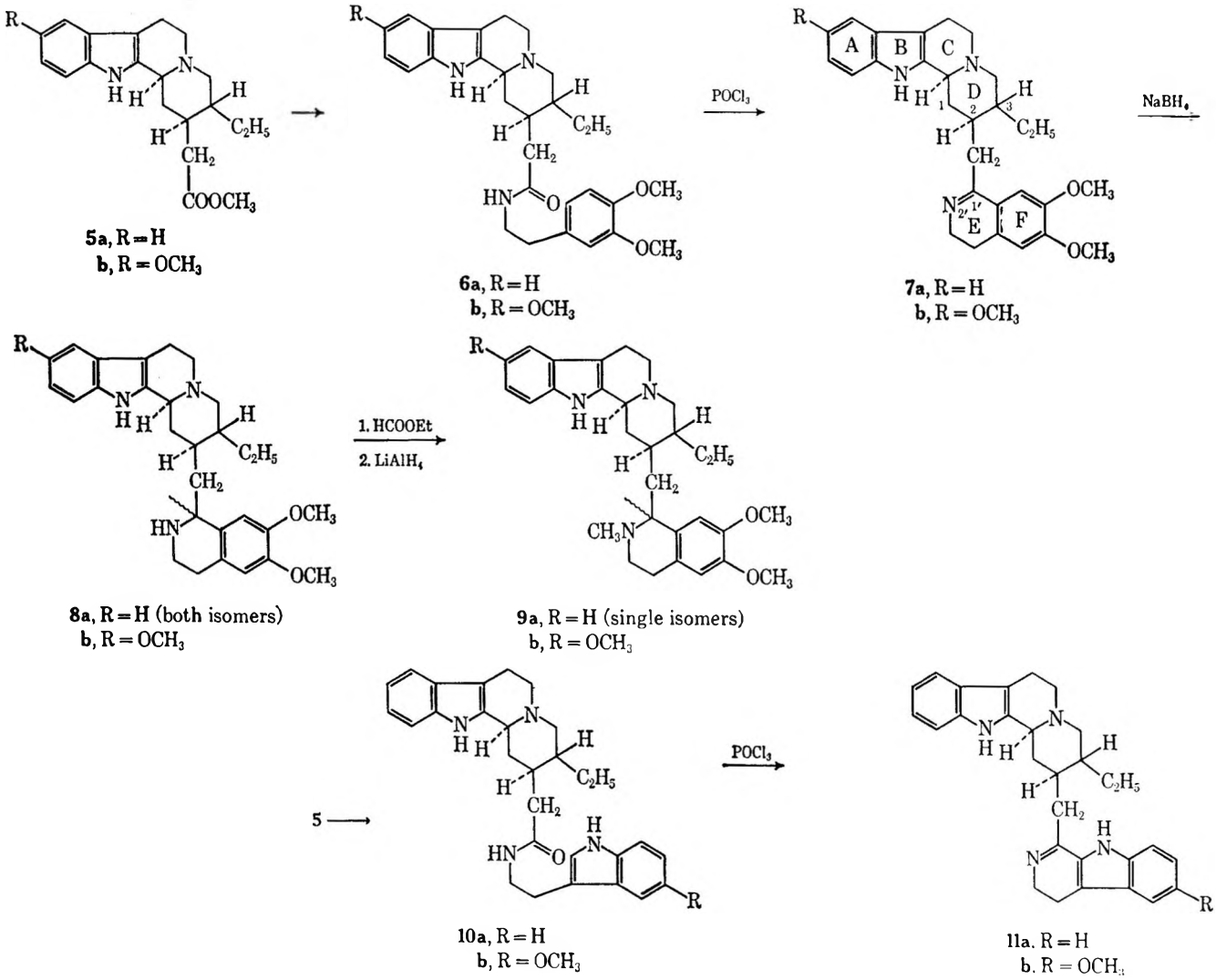
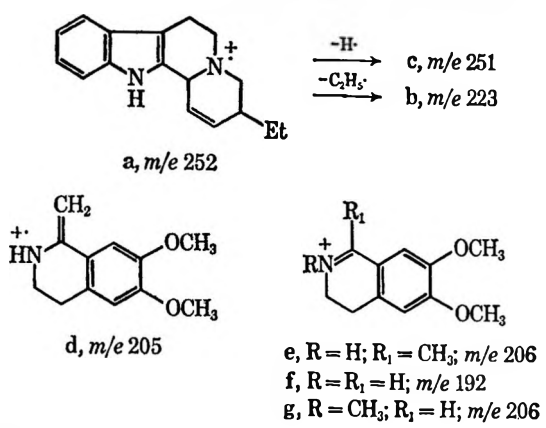
(12) A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1748 (1959).
(13) P. Potier, C. Kan, J. LeMen, M. M. Janot, H. Budzikiewicz, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 2309 (1966).
(14) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Lett.*, 3457 (1965).
(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry, Vol. I: Alkaloids," Holden-Day, Inc., London, 1964, p 184.
(16) H. Budzikiewicz, S. C. Pakrashi, and H. Vorbrüggen, *Tetrahedron*, **20**, 399 (1964).

SCHEME I



Similar patterns were exhibited by compounds **7a**, **8a**, and **9a**, and the structures of the latter compounds were thereby confirmed. Thus, the molecular ion peak of **7a**, which is characterized by a 1′, 2′ double bond in ring E, is at *m/e* 457. Its base peak, which occurs at *m/e* 252, may be assigned to the ion radical a. The peaks at *m/e* 251 (b) and 223 (c) correspond to fragments arising from the ion radical a through the loss of hydrogen and of the allylic ethyl groups. The fragments corresponding to 156, 169, 170, and 184 characteristically occur in tetrahydro-β-carbolines.[17] The peaks at *m/e* 205 and 206 correspond to d and e, while 190 and 192 are characteristic of isoquinoline ions; they are also found in the spectrum of psychotrine methyl ester (**1b**).



The molecular peak of **8a** is at *m/e* 459. In **8a**, which possesses a tetrahydroisoquinoline system, the intensity of the fragments found on the spectrum of **7a** is reduced. Benzylic activation of the 1′-methylene bridge gives a high-intensity peak at *m/e* 192 (fragment f) as in emetine (**1a**). The mass spectrum of **9a** is similar to that of **8a**. The ion peak appears at *m/e* 473, with a base peak at *m/e* 206 (fragment g); the mass shift is due to the methyl group present in **9a**.

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Microanalyses were performed in the Analytical Department of Smith Kline and French Laboratories. Infrared spectra were determined on a Perkin-Elmer Model 137B spectrophotometer. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E instrument.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-N-(3′,4′-dimethoxyphenethyl)indolo[2,3-*a*]quinolizine-2-acetamide (6a).—A mixture of ester (2.3 g, 0.0074 mol) and homoveratrylamine (3 g, 0.0165 mol) was heated under nitrogen at 190–210° for *ca.* 2 hr, or until ester carbonyl absorption at 5.75 μ disappeared. The mixture was cooled, and the resulting viscous oil was dissolved in methylene chloride. When it was diluted with ether, 1.9 g of the amide **6a** crystallized, mp 165–168°. An additional 0.5 g of the same melting point material (total yield 71%) was obtained when the mother liquor was chromatographed on Florisil (eluted with

(17) Reference 15, p 81.

chloroform–methanol, 99:1). An analytical sample of **6a** melted at 171–173°; uv, λ_{max}^{EtOH} 227 mμ (ε 45,100), 279 (10,400). *Anal.* Calcd for $C_{29}H_{37}N_3O_3$: C, 73.26; H, 7.84; N, 8.84. Found: C, 72.98; H, 8.08; N, 8.66.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(3′,4′-dihydro-6′,7′-dimethoxyl-1-isoquinolinyl)methylindolo[2,3-*a*]quinolizine Dihydrochloride (7a).—The amide **6a** (5 g, 0.001 mol) in 100 ml of 1,2-dichloroethane was refluxed for 3.5 hr with 10 ml of phosphorus oxychloride, then cooled to 4°. The excess phosphorus oxychloride was decomposed with water, and 10% dilute ammonium hydroxide solution was added until the solution was basic. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The residue in chloroform was chromatographed on Florisil. Fractions eluted with chloroform–methanol (99:1) crystallized from methylene chloride–ether. The product **7a** (3.1 g, 64% yield) melted at 180–183°. A perfect analysis for the base could not be obtained. It was converted into the hydrochloride on treatment with methanolic HCl and the product was recrystallized from methanol–ethyl acetate. The analytical sample melted at 260–262°; uv, λ_{max}^{EtOH} 220 mμ (ε 44,600), 248 (15,200), 273 (9600), 282 (10,300), 290 (10,200), 306 (8500), 360 (7400). *Anal.* Calcd for $C_{29}H_{35}N_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 61.47; H, 7.29; N, 7.42; mol wt (free base), 457.6. Found: C, 61.55; H, 7.14; N, 7.56; mol wt (mass spectrum), 457.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(1′,2′,3′,4′-tetrahydro-6′,7′-dimethoxy-1-isoquinolinyl)methylindolo[2,3-*a*]quinolizine Dihydrochloride (8a).—The base **7a** (3 g, 0.0066 mol) in 120 ml of methanol and 5.0 ml of water was reduced with 0.6 g of sodium borohydride for 0.5 hr at reflux and 1 hr at 25°. Excess hydride was destroyed with acetic acid, the methanol was evaporated, and the residue was made basic with 10% ammonium hydroxide solution. The chloroform extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The amorphous residue was converted into the hydrochloride by treatment with methanolic HCl, and recrystallized from methanol to yield 0.25 g of one isomer of **8a** (7%). Further recrystallization from methanol–ethyl acetate gave an analytical sample with mp 305–307°. *Anal.* Calcd for $C_{29}H_{37}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 64.32; H, 7.44; N, 7.75; mol wt (free base), 459.6. Found: C, 64.54; H, 7.59; N, 7.80; mol wt (mass spectrum), 459.

Another isomer (2.35 g, 62.5% yield) was obtained when the mother liquors were crystallized from methanol–ethyl acetate. The analytical sample melted at 266–268°; uv, λ_{max}^{EtOH} 223 mμ (ε 44,600), 281 (11,400), 288 (sh) (9300). *Anal.* Calcd for $C_{29}H_{37}N_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 61.26; H, 7.61; N, 7.39. Found: C, 61.56; H, 7.61; N, 7.26.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(1′,2′,3′,4′-tetrahydro 6′,7′-dimethoxy-2′-methyl-1-isoquinolinyl)methylindolo[2,3-*a*]-quinolizine Dihydrochloride (9a).—The major isomer **8a** (1.97 g) was liberated from its hydrochloride with dilute ammonium hydroxide and extracted into chloroform. The solution was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated. The residue in 30 ml of ethyl formate was heated for 16 hr on a steam bath under 40 psi pressure. The mixture was cooled, the solution was evaporated, and the residue was partitioned between chloroform and 10% ammonium hydroxide solution. The chloroform layer was washed with saturated sodium chloride solution and dried over sodium sulfate. On concentration to dryness, 1.86 g of amorphous formyl compound was obtained.

A solution of the formyl compound (1.7 g) in 30 ml of tetrahydrofuran was added to a solution of 1 g (0.03 mol) of lithium aluminum hydride in 100 ml of tetrahydrofuran, and heated at reflux for 6 hr. The mixture was cooled, excess hydride was destroyed with water, and the mixture was filtered. The filtrate was acidified with 10% sulfuric acid, washed with ether, made basic with 10% ammonium hydroxide solution, and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was converted into the dihydrochloride of **9a**, which was crystallized from methanol–ethyl acetate. It melted above 295°; uv, λ_{max}^{EtOH} 220 mμ (ε 54,200), 273 (sh) (12,600), 279 (12,900), 288 (11,900). *Anal.* Calcd for $C_{30}H_{39}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 64.85; H, 7.62; N, 7.56; mol wt (free base), 473.6. Found: C, 65.01; H, 7.82; N, 7.47; mol wt (mass spectrum), 473.

Registry No.—**6a**, 19202-96-1; **6b**, 19203-01-1; **7a**, 19202-97-2; **7b**, 19203-02-2; **8a** (α), 19202-98-3; **8a** (β), 19203-03-3; **8b**, 19203-04-4; **9a**, 19202-99-4; **9b**, 19233-86-4; **10a**, 19203-05-5; **10b**, 19203-06-6; **11a**, 19203-07-7; **11b**, 19203-08-8.

Structure Elucidation and Chemistry of *Catharanthus* Alkaloids. IV.[1,2] Structures of Horhammericine and Horhammerinine

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Several α-methyleneindoline bases have been reported isolated and characterized from *Catharanthus*, as well as from other species of plants. None of the monomeric α-methyleneindoline alkaloids from *Catharanthus* species have been shown to elicit antitumor activity; however, we have shown that lochnerinine exhibits significant cytotoxicity in cell culture against Eagle's 9 KB carcinoma of the nasopharynx.[3]

The purpose of this report is to present our evidence for the structures of two new α-methyleneindoline bases which we have recently isolated and characterized from the apocynaceous plant *Catharanthus lanceus*, namely, horhammericine (**1**) and horhammerinine (**2**).[4,5]

Both **1** and **2** could be analyzed in comparison with three other alkaloids of known structure, *i.e.*, lochnericine (**3**),[6–9] lochnerinine (**4**),[6–9] and minovincinine (**5**).[10,11]

The mass spectral fragmentations of **3** and **4** are presented in Scheme I.[6,9] It can readily be seen that

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(2) For the previous paper in this series, see D. J. Abraham and N. R. Farnsworth, *J. Pharm. Sci.*, in press. Inquiries should be directed to D. J. Abraham.

(3) N. R. Farnsworth, R. N. Blomster, and J. P. Buckley, *ibid.*, **56**, 23 (1967).

(4) R. N. Blomster, N. R. Farsnworth, and D. J. Abraham, *Naturwissenschaften*, **55**, 298 (1968).

(5) N. R. Farnsworth, W. D. Loub, R. N. Blomster, and D. J. Abraham, *Z. Naturforsch.*, **23b**, 1061 (1968).

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(7) C. P. N. Nair and P. P. Pillay, *Tetrahedron Lett.*, 89 (1959).

(8) G. H. Svoboda, N. Neuss, and M. Gorman, *J. Amer. Pharm. Assoc., Sci. Educ.*, **48**, 659 (1959).

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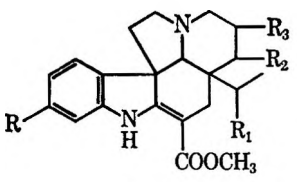
(10) M. Plat, J. LeMen, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 2237 (1962).

(11) M. Plat, E. Fellion, J. LeMen, and M.-M. Janot, *Ann. Pharm. Franc.*, **20**, 899 (1962).

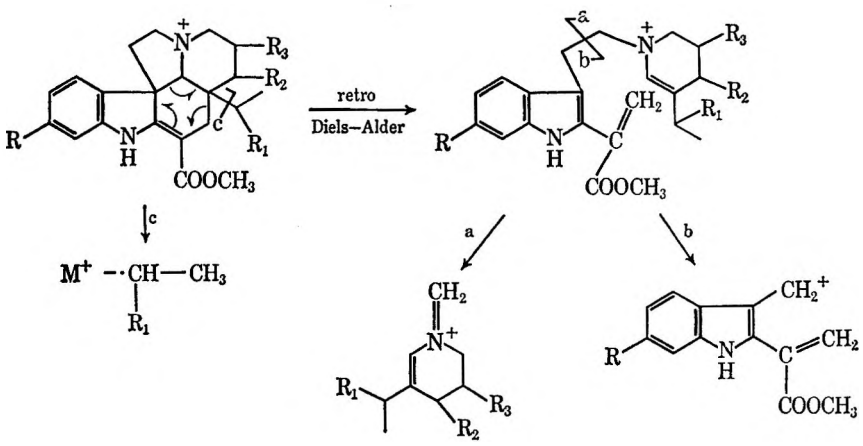


Alkaloid	R	R_1	R_2	R_3
Horhammericine (1)	H	OH	-O-	
Horhammerinine (2)	CH_3O	OH	-O-	
Lochnericine (3)	H	H	-O-	
Lochnerinine (4)	CH_3O	H	-O-	
Minovincinine (5)	H	OH	H	H

gave a peak at *m/e* 336 ($M^+ - 18$). The other analytical techniques such as nmr and ir also verified the presented structures of **3**, **4**, and **5**.[6-11]

The ultraviolet spectra of **1**[5] and **2**,[4] as well as **3**,[6-9] are compared in Table I. Lochnericine (**3**) and horhammericine (**1**) are comparable, as are lochnerinine (**4**) and horhammerinine (**2**), all being of the α-methyleneindoline type. The main mass spectral fragmentation peaks of horhammericine and horhammerinine are also summarized in Table I. It can readily be seen from Scheme I that the combination of a hydroxy side chain

SCHEME I



the typical primary fragmentation of the α-methyleneindolines is a retro-Diels–Alder reaction giving fragments according to pathway a or b. Fragmentation a shows the presence of the epoxy moiety in both **3** and **4** at *m/e* 138, whereas fragmentation b indicates that **4** has a methoxyl group on the aromatic nucleus, which raises the *m/e* value by 30 (*m/e* 244) over that obtained in **3** at *m/e* 214.

Loss of the ethyl side chain is indicated (pathway c) by the $M^+ - 29$ peak at *m/e* 323 in compound **3**, and at *m/e* 353 in compound **4**.

A look at the mass spectral fragmentation pattern of **5** (Scheme I) shows the same type of degradation as seen in **3** and **4**.[10] Fragmentation pathway a gives *m/e* 140, consistent with the structure given, and pathway b shows the ion *m/e* 214 as observed in **3**. Loss of the hydroxy ethyl side chain gave a peak at *m/e* 309 ($M^+ - 45$), and loss of the hydroxy group as water

TABLE I

UV AND MASS SPECTRAL COMPARISONS

R	Alkaloid	Uv
H	Lochnericine	226, 297, 327
OCH_3	Lochnerinine	247, 326
H	Horhammericine	228, 299, 327
OCH_3	Horhammerinine	245, 325

Horhammericine ($C_{21}H_{24}N_2O_4$) M^+	Horhammerinine ($C_{22}H_{26}N_2O_5$) M^+
368	398
350 ($-H_2O$)	380 ($-H_2O$)
323 ($M^+ - 45$)	353 ($M^+ - 45$)
214	244
154	154

of **5** with the presence of the epoxide group of **3** and **4** would lead to the proposed structures **1** and **2**. Both **1** and **2** lose water ($M^+ - 18$) and the hydroxy side chain ($M^+ - 45$) by pathway c. The basic aromatic fragments at *m/e* 214 and 244, pathway b, are the same as those exhibited in the spectra for **3**[6,9] and **4**.[6,9] The ion at *m/e* 154 can then be accounted for as shown by pathway a, both containing the epoxide and hydroxy side chain.

The nmr spectra of the aromatic regions of **1** and **3** were comparable, as were the aromatic regions of **2** and **4**. The methyl signal of the hydroxy side chain in both **1** and **2** was split into a doublet at σ 1.0, as would be expected. The ir spectra of **1** and **2** contained the hydroxyl absorption at *ca.* 3.0 μ.

Deuterium oxide was injected into the mass spectrometer with compound **2**, which resulted in a shift of the molecular ion peak to *m/e* 399. The deuterated analog showed a large $M^+ - 19$ peak which indicated that the hydroxyl group of the side chain did indeed exchange deuterium for hydrogen as expected. A comparison of the peak at *m/e* 155 in both charts also shows that the deuterium-enriched sample exchanged deuterium for hydrogen of the hydroxyl group. The fact that there was an increase in intensity of the *m/e* 245 and 259 peaks in the deuterated sample also indicate some NH to ND exchange. The rest of the deuterated spectrum compared very closely with that obtained prior to deuterium introduction.

Registry No.—Horhammericine, 19459-04-2; horhammerinine, 19459-05-3; lochnericine, 2447-58-7; lochnerinine, 2579-65-9.

Alkaloids from *Solanum congestiflorum*[1]

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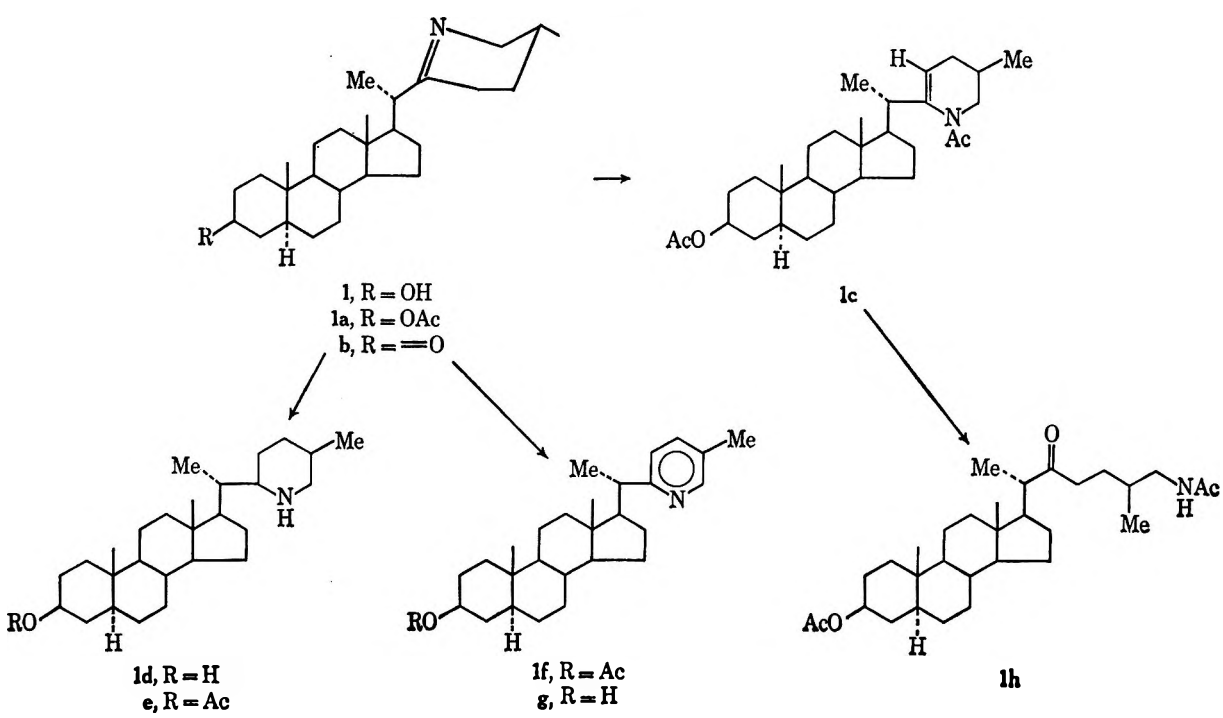
Four steroidal alkaloids, namely, solacongestidine, solafloridine, and 23-oxo- and 24-oxosolacongestidine, were isolated from *Solanum congestiflorum* Dun. DC. Solacongestidine is (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol and solafloridine is the 3β,16α-diol of the same basic moiety.

Solanum congestiflorum Dun. DC., commonly known as Natri, and collected in the environs of Santiago, Chile, afforded after acidic hydrolysis and extensive chromatography four new steroidal alkaloids which we named solacongestidine (**1**), solafloridine (**2**), and 23-oxo- (**3**) and 24-oxosolacongestidine (**4**).

Solacongestidine (**1**) (Scheme I) possesses the formulation $C_{27}H_{45}NO$ with two tertiary and two secondary methyls in the nmr spectrum, a pattern typical of the solanum-type steroidal alkaloids. In the infrared spectrum, absorption bands at 2.78, 3.00 and 6.05 μ are observed. The first two bands are due to the hydroxyl group as shown by its ready conversion into O-monoacetate **1a** ($\lambda_{max}^{CHCl_3}$ 5.78 μ), prepared by shaking **1** in a mixture of acetic and hydrochloric acid. This hydroxyl is easily oxidized with chromic acid to a ketone, **1b**, which causes a larger paramagnetic shift (0.20 ppm) on the 19-methyl signal than on the 18-methyl (0.03 ppm), an observation indicative of a 3-ketone function in the steroid moiety. The infrared absorption at 6.05 μ is ascribed to a C=N moiety[3] which can be converted into an acetylenamine functionality (**1c**) by acetylation in the conventional manner with acetic anhydride–pyridine. This is also supported by the appearance of an olefinic proton in the nmr spectrum of **1c**. In addition, the 18-, 21- and 27-methyl signals in **1** are subjected to paramagnetic shifts of 0.03–0.19 ppm while the 19-methyl resonance appears unperturbed (*cf.* cholestanol).[4] This perturbation can be attributed to the effect of the C=N chromophore being in close proximity to these methyl functions.

Either catalytic hydrogenation or lithium aluminum hydride reduction of **1** adds 1 mol of hydrogen to the alkamine to afford the secondary amine, dihydrosolacongestidine (**1d**) along with its stereoisomers. The melting points of **1d** and its O-monoacetate, **1e**, are in agreement with those described in the literature.[5] In addition, dehydrogenation of monoacetate **1a**, with palladium–charcoal produces the β-picolyl derivative, **1f**, possibly contaminated by its C-20 stereoisomer. The mass spectra of **1** and its dihydro derivative, **1d**, afford further evidence that the site of unsaturation is located in a piperidine side chain, for the spectrum of

Scheme I



(1) Portions of the paper were presented at the XIth Pacific Science Congress, Tokyo, Japan, Aug 21–30, 1966.

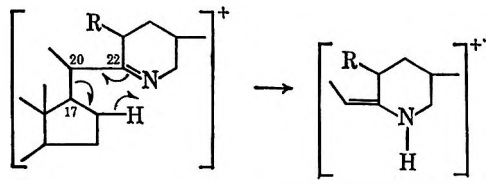
(2) Visiting scientists: Y. Sato (1964-1966), H. Kaneko (1963–1964), E. Bianchi (1963–1964), and H. Kataoka (1966–1968).

(3) E. Bianchi, C. Djerassi, H. Budzikiewicz, and Y. Sato, *J. Org. Chem.*, **30**, 754 (1965).

(4) Nmr of cholestanol in $CDCl_3$ δ 0.87 (21-, 26-, 27-*sec*-CH_3), 0.80 (19-CH_3), 0.65 (18-CH_3), 3.55 ppm (3α-H).

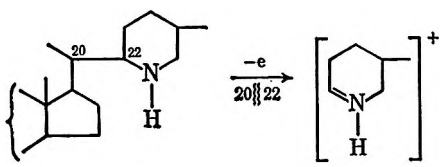
(5) K. Schreiber and G. Adam, *Tetrahedron*, **20**, 1707 (1964).

1, aside from the molecular ion peak (*m/e* 399), shows two prominent peaks at *m/e* 111 (111.1049, $C_7H_{13}N$) and 125, the latter of which can be ascribed the structure A arising from the rupture of the C_{17}–C_{20} bond.[3]



A ($C_8H_{16}N$, *m/e* 125), R = H
C ($C_8H_{13}NO$, *m/e* 139), R = =O

The spectra of dihydrosolacongestidine (**1d**) on the other hand yields a prominent fragment at *m/e* 98 (structure B) ascribable to the fragmentation scheme as shown.[3]



B ($C_6H_{12}N$, *m/e* 98)

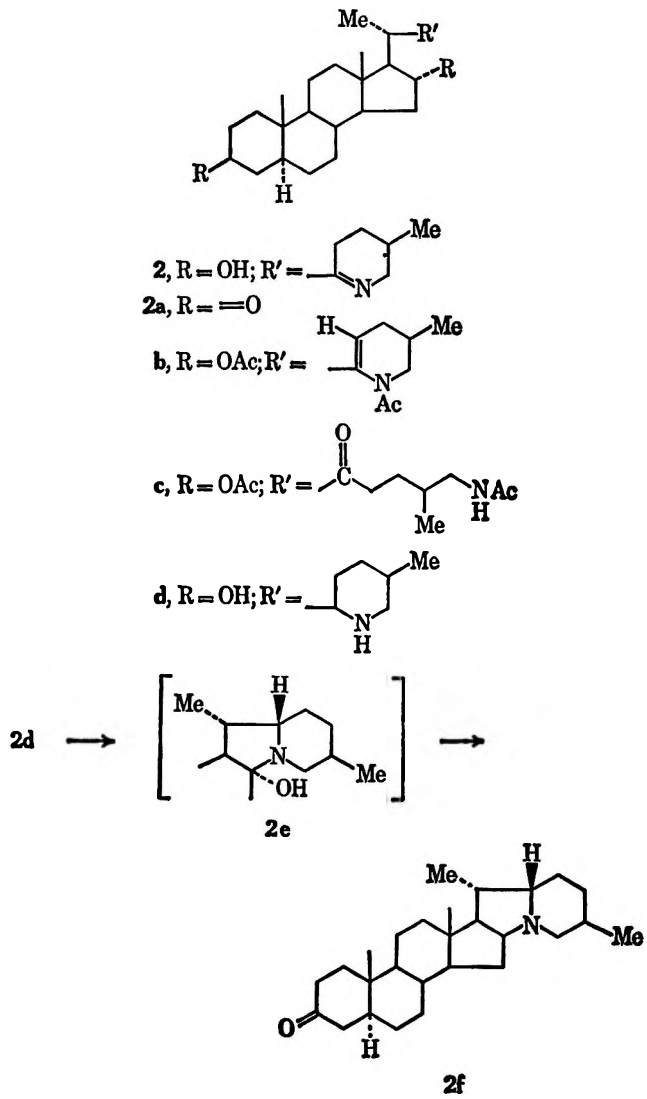
That the site of unsaturation is, indeed, located in the piperidine ring was affirmed by hydrolysis of the O,N-diacetate, **1c**, with hydrochloric acid in acetic acid which lead to the opening of the side-chain ring to yield an acetylamino ketone, **1h**, characteristic of a Δ^2-tetrahydropyridine function.[6]

The fragmentation pattern of 1, its physical data, and the spectral and chemical behavior thus gleaned, were reminiscent of 5,6-dihydrodeoxotomatillidine obtained from the Wolff–Kishner reduction of dihydrotomatillidine, a steroidal alkaloid obtained from *Solanum tomatillo*[3] indigenous to Chile. This was, indeed, found to be the case when the products derived from the two species were compared. In confirmation, it was also found that solacongestidine agreed in properties with a synthetic specimen of (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol[5] prepared in an unambiguous manner.

It is of some interest to note that recently the Δ^5 C-25 epimer (25*S*) of **1** named Verazine have been isolated from a subspecies of Veratrum album.[7] These steroidal alkaloids with a piperideine side chain ($\Delta^{22(N)}$) are of considerable interest since they can be viewed as potential intermediates in the biosynthesis of a number of steroidal alkaloids of the solasodine, solanidine, jerveratrum and ceveratrum type.[8]

Solafloridine (**2**) (Scheme II), the minor component in the plant, analyzes for the formulation $C_{27}H_{45}NO_2$ and possesses an ultraviolet spectrum similar to that of solacongestidine (**1**). Its infrared and nmr spectra indicate the presence of an extra hydroxyl group. Oxidation of **2** with chromic acid afforded a diketone, **2a**, one of which indicated a six-membered-ring and the other a five-membered-ring carbonyl as judged from the infrared data. The alkamine formed by acetylation an amorphous O,O,N-triacetyl derivative (**2b**) which displayed an enamine acetate functionality in the ultraviolet and infrared spectra as well as in the nmr spectrum. It was hydrolyzed, like solacongestidine O,N-diacetate (**1c**), by hydrochloric acid in acetic acid to yield an amorphous ω-acetylamino ketone (**2c**).

SCHEME II



The mass spectrum of the alkamine showed the characteristic ion peak at *m/e* 125 for fragment A while dihydro derivative **2d** had an *m/e* 98 peak for methylpiperidine ion B, as in dihydrosolacongestidine (**1d**). These results indicate that the extra hydroxyl function is very probably located on the steroidal portion of the molecule since a hydroxyl moiety on the piperidine side chain has been shown to afford a fragment of *m/e* 114, an increment of 16 over the methylpiperidine peak of *m/e* 98, corresponding to a hydroxyl group.

The location of the hydroxyl function on the steroid ring in solafloridine (**2**) was shown to be at C-16 by its conversion into (22*S*:25*R*)-solanidan-3-one (**2** → **2d** → **2e** → **2f**), a known isomeric solanidanone.[9] The α orientation is assigned to the hydroxylic function

(6) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **25**, 786 (1960), and papers cited therein.

(7) G. Adam, K. Schreiber, J. Tomko, and A. Vassova, *Tetrahedron*, **23**, 167 (1967).

(8) K. Schreiber "The Alkaloids," Vol. X, Academic Press, New York, N. Y., 1968, pp 115–125.

(9) E. Höhne, K. Schreiber, H. Ripperger, and H.-H. Worch, *Tetrahedron*, **22**, 673 (1966), and papers cited therein.

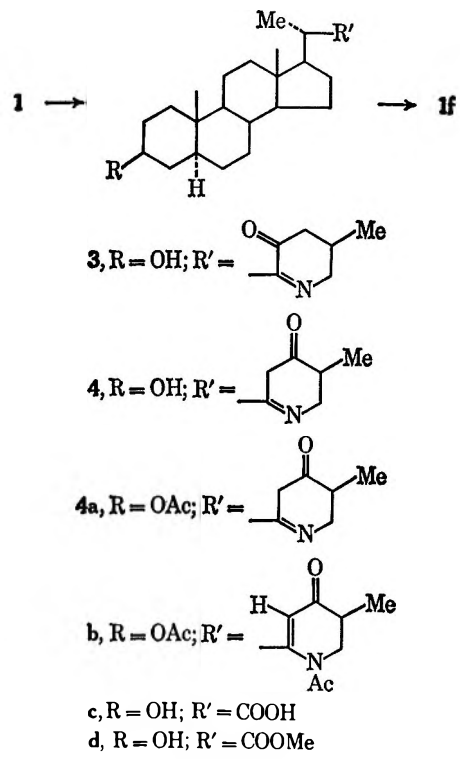
at C-16 in **2** since dihydrosolafloridine (**2d**) does not possess physical constants in agreement with the known isomeric tetrahydrosolasodine[10] having a 16β-hydroxyl moiety. Solafloridine also failed to cyclize to the spiroamino ketal base (dihydrosolasodine) when submitted to refluxing in alcoholic base. This is consistent with the observations of Schreiber and Adam,[11] who have also found that a 16α-hydroxy- in contrast to 16β-hydroxy-$\Delta^{22(N)}$-22,26-imino-5α-cholestene does not cyclize. Finally, the infrared spectra of our alkamine (**2**) and the dihydro derivative (**2d**) were found to be in agreement with the synthetic specimens.[12]

The 23- and 24-oxosolacongestidines are two oxygenated alkaloids which occur in minor amounts and persistently accompany solacongestidine during its isolation. Although it probably exists in the plant *per se*, there appears to be some augmentation during the work-up of solacongestidine.

The structure of 23-oxosolacongestidine (**3**) (Scheme III) was deduced principally from spectral data. It displays in the infrared spectrum characteristic absorption bands at 5.86 and 6.13 μ, and a series of ultraviolet absorption maxima at *ca.* 210 mμ (log ε 3.72), 267 (2.52), 277 (2.45) and 405 (1.83).[13] The mass spectrum shows a fairly strong peak at *m/e* 139 representing a fragment $C_8H_{13}NO$ (C) which is an increment of 14 over the corresponding peak, *m/e* 125 (A), in solacongestidine (**1**). Wolff–Kishner reduction of compound **3** affords **1** which can be oxidized with manganese dioxide or selenium dioxide to a mixture of the 23- and 24-oxo compounds (**3**, **4**). An interesting feature of the 23-oxo compound (**3**) is that it readily suffers aromatization into 3β-acetoxy-20-[2-(5-methylpyridyl)]-5α-pregnane (**1f**) by refluxing briefly in acetic anhydride. Although the aromatization is unique in the case of a Δ^1-piperidone-3, an analogy can be found in the conversion of 1,2,3,4-tetrahydro-1-oxoquinolizium bromide into a quinolizium salt by boiling acetic anhydride.[14]

24-Oxosolacongestidine (**4**) (Scheme III) possesses infrared absorption bands at 5.92 and 6.19 μ. In the ultraviolet spectrum (ethanol) it absorbs at *ca.* 211 and 270 mμ (log ε 3.66 and 2.32). The nmr spectrum reveals no olefinic proton. Upon acetylation (acetic anhydride–pyridine) for 3 hr at room temperature, the predominant product proved to be the 3β-acetate (**4a**) of **4** whereas prolongation of the acetylation period for 14 hr or boiling in acetic anhydride for 1 hr afforded principally the O,N-diacetate (**4b**). The latter displayed infrared spectrum bands for an enamine acetate system conjugated to a carbonyl function [5.81 (OAc), 5.94, 6.04, 6.30 μ (AcNC=CC=O)] and an appropriate ultraviolet absorption spectrum [222 and 275 mμ (log ε 3.75 and 3.60)]. The nmr spectrum also indicated the presence of an olefinic proton at 5.97 ppm (doublet, J = 3 cps).

SCHEME III



c, R = OH; R' = COOH
d, R = OH; R' = COOMe

The oxygenated enamine system of **4** appears to be very unstable to alkaline condition. Its ultraviolet absorption changes significantly in 3% potassium hydroxide–methanol solution at room temperature within 1 day.[15] During 4 hr of heating in 1% potassium hydroxide–methanol at 130° (bath temperature), **4** is completely changed, and an acidic product identified as 3β-hydroxybisnorallocholanic acid (**4c**) was isolated. Although the spectra of the acid and its methyl ester (**4d**) were identical with authentic samples, the melting points were somewhat lower. We believe this is due to slight contamination by the C-20 isomer. The alkaline and neutral products are still unidentified. The degradation can be visualized as the alkali-catalyzed fission of a β-diketone formed by hydrolysis of the Schiff base type of bond in the piperideine side chain.

Experimental Section[16]

Hydrolysis of the Glycosides.[17]—A solution of 10 g of the crude glycosides in 120 ml of 90% aqueous MeOH and 6 ml of concentrated HCl was refluxed for 2 hr, concentrated to a small

(10) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1469 (1957).

(11) K. Schreiber and G. Adam, *Ann. Chem.* **166**, 176 (1963).

(12) We are grateful to Professor K. Schreiber of the Deutsche Akademie der Wissenschaften zu Berlin, Institut für Biochemie der Pflanzen, D. D. R., for providing us the spectra of these compounds. Schreiber and Adam[11] have reported mp 168–170°, $[\alpha]^{26}D$ +114.8°, for their product (**2**).

(13) K. Schreiber and H. Ripperger [*Chem. Ber.*, **96**, 3094 (1963)] report for (25*R*)-3β,16β-diacetoxy-22,26-imino-5α-cholest-22(N)-en-23-one the following spectral data: ir 5.75 (OAc), 5.87 (ketone), 6.11 μ (C=N); λ_{max} 228 (3.30), 397 mμ (1.97).

(14) E. E. Glover and G. Jones, *J. Chem. Soc.*, 3021 (1958).

(15) The same phenomenon is observed in the case of dihydrotomatillidine[3] which is provisionally regarded as a C-25 stereoisomer of 24-oxosolacongestidine.

(16) Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this laboratory. Infrared spectra were obtained with a Model 421 Perkin-Elmer spectrophotometer. Optical rotations were obtained in a 1-dm tube with a Mode. 141 Perkin-Elmer polarimeter. Nmr spectra were determined on the Model A-60 Varian Associates spectrometer, using $CDCl_3$ as solvent with tetramethylsilane as internal standard, and described in δ values (TMS = 0.0 ppm). Ultraviolet spectra were recorded with Model 15 Cary spectrophotometer and the absorption data in shortwave regions are uncertain. The mass spectra in these experiments have been measured with an AEI MS-9 spectrometer. Tlc plates were precoated with silica gel G and purchased from Analtech, Inc., Wilmington, Del.

(17) The isolation and characterization of the glycosides will appear in a forthcoming publication.

volume in the rotatory evaporator until a heavy residue was obtained. The residue was triturated with NH_4OH and extracted with $CHCl_3$ to yield 4.5 g of the crude free base. Two major [R_f 0.55 (I), 0.28 (II)] and three minor fractions [R_f 0.73 (III), 0.8 (IV), 0.4] were separated on tlc (CH_2Cl_2–AcOEt–MeOH, 2:2:1). Each component could be crudely separated on a larger scale by using columns of 100 parts of silica gel (0.05–0.2 mm) with the solvent system of benzene–AcOEt–MeOH (12:12:5). More chromatography and recrystallization were required for further refinement.

Solacongestidine (I).—The fraction of R_f 0.55 was recrystallized quickly from either Me_2CO, EtOAc, Et_2O or aqueous MeOH, preferably in an oxygen-free atmosphere, to yield rods melting at 169–174°: $[\alpha]^{20}D$ +35.6° (*c* 1.6, $CHCl_3$); mass spectrum 399 (M^+, $C_{27}H_{45}NO$), 384, 164, 151, 125 (strong, $C_8H_{16}N$), 111 (strong, $C_7H_{13}N$); mass spectrum of the trimethylsilyl ether 471 (M^+) 456, 151, 125, 121, 111; $\lambda_{max}^{CHCl_3}$ 2.78, 3.00 (OH), 6.05 (C=N), 6.25, 9.75 μ (C–O); λ_{max}^{EtOH} 239 mμ (ε 360), end absorption $\lambda^{EtOH-HCl}$ 222 mμ (ε 1560); nmr 0.69 (18-CH_3), 0.81 (19-CH_3), 0.90 (d, *J* = 6 cps, 3 H), 1.06 (d, *J* = 7 cps, 3 H), 2.14 (OH), 2.95 (26α-H), 3–4 ppm (26β-H and 3α-H), no olefinic proton; ORD (*c* 0.047, EtOH) $[\alpha]_{300}$ +233°, $[\alpha]_{250}$ +891° (peak), $[\alpha]_{228.5}$ +222° (trough), $[\alpha]_{210}$ +947°.

Anal. Calcd for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N, 3.51. Found: C, 81.08; H, 11.17; N, 3.40. (The specimen for analysis was dried at 110° for 20 hr.) The compound was identical (mixture melting point and ir) with a specimen derived from dihydrotomatillidine, and with a synthetic specimen of (25*R*)-22,26-imino-5α-cholest-22(N)-en-3β-ol.

Chromic Acid Oxidation of Solacongestidine.—To a solution of 120 mg of **1** in 25 ml of Me_2CO was added 0.8 ml of Kiliani's reagent[18] at 5–10°. After the reaction mixture was allowed to stand *ca.* 0.5 hr at room temperature, 2 ml of *i*-PrOH was added to destroy the excess oxidant. The reaction mixture was brought to dryness at room temperature *in vacuo*, and dissolved in a slight amount of water. The aqueous solution was made alkaline with K_2CO_3, and extracted with Et_2O. The crystalline residue which amounted to about 110 mg was subjected to tlc (benzene–AcOEt–MeOH, 3:3:1). A band at R_f 0.5 was extracted with MeOH–AcOEt to yield 45 mg of pale yellow flakes melting at 134–142° (**1b**). Recrystallization from AcOEt gave a product of mp 139–142°; $[\alpha]^{20}D$ +51° (*c* 0.19, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.87 (C=O), 6.06 μ (C=N), no OH band; nmr 0.72 (18-CH_3), 0.91 (d, *J* = 6 cps, *sec*-CH_3), 1.01 (19-CH_3), 1.08 ppm (d, *J* = 7 cps, *sec*-CH_3), no olefinic proton; mass spectrum 397 (M^+, $C_{27}H_{43}NO$), 382, 125, 111.

Acetylation of Solacongestidine with Acetic Anhydride–Pyridine.—A mixture of 306 mg of **1**, 3 ml of anhydrous pyridine and 3 ml of Ac_2O was allowed to stand at room temperature (22–23°) for 19 hr. It was poured into ice–water to afford a white powder (348 mg), which when twice crystallized from MeOH gave crystals melting at 156–158° (**1c**, 171 mg): $\lambda_{max}^{CHCl_3}$ 5.78 (ester C=O), 5.99 and 6.09 μ (–C=CNAc); nmr 0.67 (18-CH_3), 0.82 (19-CH_3), 0.93 (d, *J* = 6 cps, *sec*-CH_3), 1.12 (d, *J* = 7 cps, *sec*-CH_3), 2.02 (OAc), 2.15 (NAc), 3.38 (26-H), 4.7 (m, 3α-H), 5.2 (olefinic proton); mass spectrum 483 (M^+, $C_{31}H_{49}NO_3$), 468, 441, 440, 426, 423 ($M^+ - 60$) 185, 167, 166, 152, 143, 125, 111; λ_{max}^{EtOH} 235 mμ (log ε 3.90).

3β-Acetoxy-26-acetylamino-5α-cholestan-22-one (1h).—A solution of 130 mg of **1c**, 0.6 ml of 4 *N* HCl in 3 ml of acetic acid was allowed to stand for 1 hr at room temperature. After addition of water and neutralization with $NaHCO_3$, it was extracted with $CHCl_3$. The organic layer yielded 149 mg of solid, which was purified by tlc and recrystallized from MeOH to afford rods (**1h**) melting at 138–140°: nmr 0.67 (18-CH_3), 0.82 (19-CH_3), 0.88 (d, *J* = *ca.* 6 cps, *sec*-CH_3) 1.07 (d, *J* = 7 cps, *sec*-CH_3), 1.97 and 1.99 (2Ac), 3.06 (t, *J* = 5.5 cps, C_{26}-H_2).

Acetylation of Solacongestidine with Acetic–Hydrochloric Acid Mixture.—A solution of 64 mg of **1**, 20 ml of AcOH and 0.4 ml of concentrated HCl was shaken at room temperature for 25 hr, poured into ice–water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The organic layer yielded 65 mg of solid, which was submitted for purification by tlc (*n*-heptane–AcOEt, 13:7). The main band at R_f 0.24 on the tlc plate was extracted with mixture of MeOH and $CHCl_3$ to afford 47 mg of the monoacetate. Two recrystallizations from Me_2CO gave needles (**1a**): mp 185–195°; mass spectrum 441 (M^+, $C_{29}H_{47}NO_2$), 426 ($M^+ - 15$), 164, 151, 125, 111 (strong); nmr 0.68 (18-CH_3), 0.82 (19-CH_3), 0.92 (d, *J* = 6 cps, *sec*-CH_3), 1.07 (d, *J* = 7 cps, *sec*-CH_3), 2.01 (OAc), 4.7 (m, 3α-H); $\lambda_{max}^{CHCl_3}$ 5.78 (OAc), 6.05 μ (C=N).

Dehydrogenation of Solacongestidine O-Monoacetate.—A mixture of 250 mg of **1a** and 250 mg of 5% Pd–C in 10 ml of isoquinoline was heated at 240–250° for 4 hr under a nitrogen atmosphere. The reaction mixture was concentrated to a small volume, and extraction of the residue with $CHCl_3$ afforded 347 mg of a brownish oily mass. The separation of the product with the solvent system, cyclohexane–AcOEt (3:1), on tlc provided 0.17 g of oil (R_f 0.75), which still consisted of two components. Further chromatography on alumina[19] and elution with benzene–petroleum ether (bp 30–60°) (1:1) afforded a crystalline mass which crystallized from acetone as needles of mp 164–166° (**1f**); mass spectrum 437 (M^+), 422, 121, 120; λ_{max}^{KBr} 5.79 (OAc), 6.27, 6.39, 6.74, 8.05, 9.77, 12.07 μ (pyridine ring); nmr 0.78 (18-CH_3), 0.83 (19-CH_3), 1.28 (d, *J* = 7 cps, *sec*-CH_3), 2.01 (OAc), 2.29 ($C_{5'}$-CH_3), 4.67 (3α-H), 6.98 (d, $J_{3',4'}$ = 8 cps, $C_{3'}$-H), 7.40 (q, $J_{3',4'}$ = 8 cps, $J_{4',6'}$ = 2 cps, $C_{4'}$-H), 8.33 ($C_{6'}$-H).

Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.58; H, 9.90; N, 3.20. Found: C, 79.51; H, 9.68; N, 3.47.

Hydrolysis of the Dehydrogenation Product.—A mixture of 36 mg of the dehydrogenation product (**1f**), 3 ml of saturated $KHCO_3$–MeOH and 1 drop of water was refluxed for 2 hr under N_2. The solvent was removed. The white precipitate which formed on dilution of the residue in ice–water was collected, washed with water and twice recrystallized from acetone. It gave 12 mg of hexagonal plates (**1g**): mp 261–262°; λ_{max}^{KBr} 2.92 (OH), 6.26, 6.39, 6.74, 9.71 μ.

Anal. Calcd for $C_{27}H_{41}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.87; H, 10.20; N, 3.43.

This product was identical with the compound of mp 254–256° (**1g**) derived from 23-oxosolacongestidine (**3**) by Ac_2O treatment and hydrolysis. There was no melting point depression on admixture and the ir spectra were in good agreement.

Manganese Dioxide Oxidation of Solacongestidine.—A solution of 82 mg of **1** in 8 ml of $CHCl_3$ was stirred with 0.8 g of active MnO_2[20] at room temperature for 4 hr until the starting material was no longer detectable on tlc (benzene–AcOEt, 1:1). The inorganic material was filtered off and washed with $CHCl_3$. The combined $CHCl_3$ solution yielded 87 mg of solid, which was absorbed on 1 g of Al_2O_3 and placed on a column of 5 g of Al_2O_3 (grade 1). Elution with 1% MeOH–Et_2O furnished 75 mg of crude crystals. Recrystallization from MeOH–Me_2CO gave pale yellow needles (**3**), mp 198–208°, which were identical with 23-oxosolacongestidine (**3**) in every respect (mixture melting point, uv, ir, nmr, mass spectrum). Tlc revealed the presence of a small amount of 24-oxosolacongestidine (**4**) in the mother liquor.

Selenious Acid Oxidation of Solacongestidine.—**1** (200 mg) was added to a mixture of 55 mg of freshly sublimated SeO_2, 10 ml of *p*-dioxane and 5 drops of water. The mixture was warmed at 70° for 3 hr, cooled, filtered, and evaporated to dryness. The residue was chromatographed on 10 g of Al_2O_3 (grade I) into three fractions: 1 (1% MeOH–Et_2O), 16 mg of nearly pure compound, mp 135–155°, proved to be identical with **4**; **2** (the same solvent), 72 mg of mixture of **3** and **4**, mp 130–198°; 3 (2% MeOH–Et_2O), 14 mg of crystals, mp 180–194°. Recrystallization from MeOH–Me_2CO gave pale yellow needles, mp 190–205°, identical with alkamine **3**.

Hydrogenation of Solacongestidine.—Alkamine **1** (100 mg) was dissolved in 6 ml of AcOH and hydrogenated over 72 mg of PtO_2 catalyst under atmospheric pressure. After about 25 min, the absorption ceased with the uptake of 1 mol equiv of H_2 (22.1 ml, 21°). The catalyst was removed and the AcOH solution evaporated to dryness *in vacuo*. The residue was made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract provided 110 mg of white powder, which was separated

(18) A solution of 53 g of chromium trioxide and 80 g of sulfuric acid in 400 g of water (118 mg of CrO_3/ml).

(19) The other component, which emerged first from the glpc column, could not be crystallized. However, it appeared to be a C-20 isomer having a similar nmr pattern: 0.67 (18-CH_3) 0.73 (19-CH_3), 1.19 (d, *J* = 7 cps, *sec*-CH_3), 2.01 (OAc), 2.29 ($C_{5'}$-CH_3), 4.67 (3α-H), 7.0 (d, *J* = 8 cps, $C_{3'}$-H), 7.40 (q, $C_{4'}$-H), 8.30 ($C_{6'}$-H).

(20) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

on tlc (CH_2Cl_2–AcOEt–MeOH, 3:3:1). A band at R_f 0.5 was extracted with MeOH–$CHCl_3$ and recrystallized from MeOH to yield 11 mg of needles (**1d**): mp 233–236°; mass spectrum 401 (M^+, $C_{27}H_{47}NO$), 400, 386, 165, 164, 125, 111, 98 (very strong, $C_6H_{12}N$).

The reduction of 50.5 mg of **1** with 62 mg of $LiAlH_4$ in Et_2O for 7 hr gave 44 mg of the crude product. It showed four spots on tlc and looked almost the same as in the catalytic hydrogenation of **1**.

The combined crude reaction mixture (187 mg) of several reductions was partially acetylated by stirring in 40 ml of AcOH with 1 ml of concentrated HCl at 23° for 1 day. The product (154 mg) was separated by tlc (CH_2Cl_2–AcOEt–MeOH, 45:45:11). A zone at R_f 0.3–0.5 gave 67 mg of dihydrosolacongestidine O-monoacetate (**1e**): mp 215–217° (Et_2O); $\lambda_{max}^{CHCl_3}$ 5.80 μ (OAc); nmr 0.66 (18-CH_3), 0.82 (19-CH_3), 2.02 (OAc); HCl salt, mp 323–326° (MeOH).

Solafloridine (2).—A crude fraction (R_f 0.28) contaminated with small amounts of R_f 0.73 material was obtained from the silica gel column and converted into its hydrochloride in MeOH. An analytical specimen of solafloridine hydrochloride monohydrate (mp 280–288°) was prepared from aqueous MeOH and dried over P_2O_5 at 80° for 5 hr *in vacuo*.

Anal. Calcd for $C_{27}H_{45}NO_2HCl$: C, 71.72; H, 10.25. Found: C, 71.83; H, 10.05.

Liberation of the free base with K_2CO_3 and rapid crystallization from Me_2CO yielded needles of mp 162–165°.[12] On the other hand, if the compound is allowed to crystallize slowly from a dilute solution, prisms of mp 172–175° were recovered. Their ir spectra ($CHCl_3$) were identical.

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.01; H, 10.91; N, 3.38. Found: C, 78.23; H, 10.77; N, 3.51.

Data follow: $\lambda_{max}^{CHCl_3}$ 2.74, 3.03 (OH), 6.03 μ (C=N); λ_{max}^{EtOH} 240 mμ (ϵ 260); nmr 0.71 (18-CH_3), 0.80 (19-CH_3), 0.92 (d, J = 7 cps, *sec*-CH_3), 1.03 (d, J = 6.5 cps, *sec*-CH_3), 4.7 ppm (OH), no olefinic proton; mass spectra 415 (M^+, $C_{27}H_{45}NO_2$), 398, 162, 138, 125, 98; $[\alpha]^{20}D$ +122.7° (*c* 1.15, $CHCl_3$).

Acetylation of Solafloridine with Acetic Anhydride–Pyridine.—A solution of 170 mg of **2**, 10 ml of anhydrous pyridine and 7 ml of Ac_2O was kept standing at room temperature (*ca.* 23°) for 46 hr. Work-up in the usual manner gave 203 mg of amorphous material. The product was submitted to tlc (benzene–AcOEt, 2:1) to yield solafloridine triacetate (**2b**, R_f 0.45) but it failed to crystallize: $\lambda_{max}^{CHCl_3}$ 5.79 (strong OAc), 5.99, 6.08 μ (C=CNAc); λ_{max}^{EtOH} 238 mμ (log ϵ 3.60); nmr 0.7 (18-CH_3), 0.82 (19-CH_3), 0.92 (d, J = 6.5 cps, *sec*-CH_3), 1.07 (d, J = 6 cps, *sec*-CH_3), 1.97 ($C_{16\alpha}$-OAc), 2.02 ($C_{3\beta}$-OAc), 2.15 (NAc), 3.2–3.4 (C_{26}-H), 5.13 (olefinic proton).

Hydrolysis of Solafloridine Triacetate. A.—A solution of 18 mg of **2b**, obtained above, in 5 ml of 10% KOH–MeOH was refluxed for 7 hr, diluted with water, and extracted with $CHCl_3$ to yield 15 mg of oil, which solidified later and possessed the same R_f value as **2** on tlc. In the nmr all methyl signals associated with acetyl groups and the signals of the olefinic proton disappeared.

B.—A mixture of 110 mg of **2b**, 3 ml of AcOH and 0.6 ml of 4 *N* HCl was allowed to stand for 1 hr at room temperature, and then neutralized with excess aqueous $NaHCO_3$. The $CHCl_3$ extract gave 110 mg of oil, which was purified by tlc (AcOEt–MeOH, 15:1). The resulting product **2c**, R_f 0.6, did not crystallize: nmr 0.74 (18-CH_3), 0.82 (19-CH_3), 0.88 (d, J = 7 cps, *sec*-CH_3), 1.10 (d, J = 7 cps, *sec*-CH_3), 1.99, 2.01 and 2.04 ppm (three Ac).

Chromic Acid Oxidation of Solafloridine.—A mixture of 0.1 g of **2**, 100 ml of Me_2CO, and 0.6 ml of Kiliani's reagent was allowed to stand at room temperature and worked up in the same way as in the oxidation of alkamine **1** to produce 113 mg of amorphous substance. It was submitted to tlc (benzene–AcOEt, 11:3), and the band at R_f 0.5 (**2a**) was isolated. The compound possessed ir bands at $\lambda_{max}^{CHCl_3}$ 5.80 (five-membered-ring ketone) and 5.90 μ (six-membered-ring ketone).

Hydrogenation of Solafloridine.—A solution of 772 mg of **2** in 80 ml of EtOH was hydrogenated with 0.5 g of PtO_2 catalyst under 770-mm pressure at 21°. It consumed 1 mol equiv of H_2 in 3 hr. Crystallization of the product from MeOH gave 339 mg of crystals (**2d**) melting at 280–285°. Upon recrystallization its melting point rose to 282–285°: $[\alpha]^{20}D$ +25.9° (*c* 0.424, $CHCl_3$). Ir (Nujol) showed good agreement with the synthetic specimen of (22*S*:25*R*)-22,26-imino-5α-cholestane-3β,16α-diol [lit.[11] mp 285–287°, $[\alpha]^{26}D$ +23.9° (*c* 0.481, $CHCl_3$)]: mass spectrum 417 (M^+, $C_{27}H_{47}NO_2$), 416, 402, 204, 150, 140, 98 (strong).

Conversion of Dihydrosolafloridine (2d) into (25*R*)-Isosolanidan-3-one (2f).—To a suspension of 0.2 g of **2d** in 65 ml of Me_2CO and 3 ml of AcOH was added 2.0 ml of Kiliani's solution dropwise in 10 min and stirred for 0.5 hr at room temperature. About 0.5 ml of 10% NaOH was added to the reaction mixture and the greenish precipitate was removed by filtration. The filtrate was diluted with 200 ml of water and made alkaline with aqueous NaOH. The resulting precipitate was collected and thoroughly washed with water. The crude semicrystalline mass (138 mg) which was dried *in vacuo* at room temperature crystallized from MeOH and melted at *ca.* 125°. The carbinolamine possessed the same R_f value as an authentic specimen on tlc (R_f 0.75, AcOEt–CH_2Cl_2–NEt_3, 14:14:3). The oxidation product was hydrogenated with 0.1 g of 10% Pd–C in 12 ml of EtOH under atmospheric pressure. After consuming 1 mol equiv of H_2 in 195 min, the product was worked up in the usual manner to give 138 mg of a mixture. The main component (**2f**) was isolated by tlc (AcOEt–CH_2Cl_2–MeOH, 9:9:2, R_f 0.33), and crystallized from aqueous Me_2CO. Flakes with mp 137–144° were obtained. It showed no depression on admixture with an authentic specimen (mp 146–147°),[10] λ_{max} 5.84 μ (C=O). The spectral pattern was identical with that of an authentic sample.

23-Oxosolacongestidine (3).—A crude fraction from the column chromatography, which was eluted just after 24-oxosolacongestidine (**4**), was further purified on tlc. The band at R_f 0.73 was extracted with $CHCl_3$ and recrystallized from MeOH–Me_2CO to afford pale, yellow needles (**3**) melting unsharply at 213–223° and above 300° with some decomposition.

Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.39; H, 10.55; N, 3.48.

Data follow: λ_{max}^{EtOH} 267, 277, 405 mμ (log ϵ 2.52, 2.45, 1.83) and *ca.* 210 (3.72); $\lambda_{max}^{CHCl_3}$ 2.73, 2.9 (OH), 5.86, 6.13 (COC=N–); $[\alpha]^{20}D$ +33.0° (*c* 1.1, $CHCl_3$); nmr 0.72 (18-CH_3), 0.80 (19-CH_3), 1.02 (d, J = 5.5 cps, *sec*-CH_3), 1.04 (d, J = 7 cps, *sec*-CH_3); mass spectrum 413 (M^+), 395, 161, 139, 121, 111.

Acetic Anhydride Treatment of 23-Oxosolacongestidine.—A solution of 72 mg of **3** in 8 ml of Ac_2O was refluxed over N_2 for 45 min, diluted with water, made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract yielded 89 mg of an amorphous residue, which was chromatographed on tlc (cyclohexane–AcOEt, 13:7). A band at R_f 0.8 was extracted with $CHCl_3$–MeOH, and the extract crystallized from acetone to furnish 10 mg of needles, mp 159–164°. This was in every respect identical with 3β-acetoxy-20-[2-(5-methylpyridyl)] 5α-pregnane (**1f**) derived from **1a** by Pd–C dehydrogenation: ORD (*c* 0.058, $[\alpha]_{290}$ 0°, $[\alpha]_{282}$ +37.9°, $[\alpha]_{265}$ −145°, $[\alpha]_{255}$ −465°; λ_{max}^{EtOH} 269 mμ (log 3.58), 276 (3.46), end absorption [*ca.* 212 mμ, (log ϵ = 3.92)].

Hydrolysis of this compound by refluxing in MeOH half-saturated with $KHCO_3$ for 2 hr, and crystallizing from Me_2CO gave needles melting at 254–256° (1 g): $\lambda_{max}^{CHCl_3}$ 2.73 (OH), 6.22 and 6.37 μ (C=N, C=C); λ_{max}^{MeOH} 269 and 276 mμ (log ϵ 3.51, 3.37); $\lambda_{max}^{0.1\,N\,HCl\text{-}MeOH}$ 272 mμ (log ϵ 3.85); end absorption [*ca.* 200 mμ (log ϵ 3.92)].

Wolff–Kishner Reduction of 23-Oxosolacongestidine.—A mixture of 80 mg of **3** in 2 ml of EtOH, 2 ml of diethylene glycol and 0.36 ml of 85% NH_2NH_2–H_2O under N_2 atmosphere was refluxed for 25 min. After addition of 0.2 g of KOH, the mixture was heated for another 35 min until the temperature rose to 190°. The mixture was poured into ice–water and the precipitate was crystallized from Me_2CO to give needles with melting point of 166–170°. The ir spectrum of the compound was superposable with that of solacongestidine (**1**) or dihydrodeoxotomatillidine and the mixture melting point was undepressed.

24-Oxosolacongestidine (4).—The first crystalline fraction eluted from the silica gel column was recrystallized from MeOH. The lusterous, pale yellow plates contained 1 mol of the solvent (MeOH), which was removed at 110° *in vacuo*.

Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.45; H, 10.68; N, 3.27.

Data follow: mp 158–162°; $[\alpha]^{23}D$ +40.9° (*c* 0.8, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.8 (OH), 5.92 (C=O), 6.20 μ (C=N); λ_{max}^{EtOH} 270 mμ (ϵ 149), 345 (37); end absorption [*ca.* 211 mμ (ϵ 5540)]; nmr 0.72 (18-CH_3), 0.79 (19-CH_3), 1.01 (d, J = 6.5 cps, *sec*-CH_3), 111 (d, J = 7 cps, *sec*-CH_3); mass spectrum 413 (M^+) 398, 385, 166, 140 (strong), 139, 111; ORD (MeOH) $[\alpha]_{600}$ +56°,

$[\alpha]_{600}$ +77°, $[\alpha]_{375}$ +220° (peak), $[\alpha]_{320}$ +10° (trough), $[\alpha]_{260}$ +505°.

24-Oxosolacongestidine O-Acetate (4a).—A solution of 14 mg of **4**, 0.6 ml of anhydrous pyridine, and 0.45 ml of Ac_2O was allowed to stand at room temperature for 3 hr. To the reaction mixture was added ice–water to decompose excess Ac_2O, and the product was extracted with $CHCl_3$. The $CHCl_3$ extract gave 19 mg of amorphous mixture, which was chromatographed on tlc plates (benzene–AcOEt, 2:1). The substance eluted from the R_f 0.85 band (10 mg) was recrystallized from acetone to give prisms (**4a**): mp 200–203°; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.92 (C=O); mass spectrum 455 (M^+, $C_{29}H_{45}NO_3$), 440, 427, 140, 139, 395, 111; the mass spectrum pattern was almost the same as that of alkamine **4**.

The other component (R_f 0.3) was identified as 24-oxosolacongestidine O,N-diacetate (**4b**). When the reaction time was prolonged for 14 hr, diacetate **4b** was formed predominantly.

24-Oxosolacongestidine O,N-Diacetate (4b).—**4** (90 mg) in 5 ml of Ac_2O was refluxed under N_2 for 1 hr. The reaction mixture, worked up in the conventional way, yielded 0.1 g of powder, which crystallized from Me_2CO to afford 22 mg of prisms (**4b**) of mp 184–187°; λ_{max}^{EtOH} 275 (log ϵ 3.60); end absorption [222 mμ (log ϵ 3.75)]; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.94, 6.04, 6.30 (AcNC=CCO), 9.83 μ (CO).

Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52. Found: C, 74.50; H, 9.43.

Data follow: nmr 0.65 (18-CH_3), 0.79 (19-CH_3), 1.13 (d, J = 6.5 cps, *sec*-CH_3), 1.17 (d, J = 7 cps, *sec*-CH_3), 1.98 (OAc), 2.02 (NAc), 5.97 (d, J = 3 cps, C_{23}-H); mass spectrum 497 (M^+), 455, 454, 152, 140, 124.

Alkali Treatment of 24-Oxosolacongestidine.—A solution of 80 mg of **4** in 5 ml of 1% KOH–MeOH was refluxed at 130° (bath temperature) for 4 hr under N_2. After removal of the solvent, and addition of water, the $CHCl_3$ extract gave about 60 mg of amorphous powder[21] (mainly basic and neutral substances). Extraction of the aqueous layer with $CHCl_3$ after acidification with dilute H_2SO_4 yielded about 28 mg of brown powder (acid part). The acidic fraction was purified by tlc (benzene–AcOEt–MeOH, 15:15:4) to afford crystals (**4c**) of mp 255–265°. Treatment of the acid with CH_2N_2 in MeOH–Et_2O overnight afforded methyl ester[22] **4d**: mp 130–145°; $\lambda_{max}^{CHCl_3}$ 2.79, 2.95 (OH), 5.78 (OAc), 8.66, 9.78, 11.72 μ; mass spectrum 362 (M^+), 347, 329, 233, 215, 165, 147. The acid and the ester proved to be 3β-hydroxybisnorallocholanic acid and its methyl ester by comparison with an authentic sample (tlc, ir, glpc, and mass spectrum).

Registry No.—**1**, 984-82-7; **1a**, 19374-52-8; **1b**, 19374-53-9; **1c**, 19398-17-5; **1d**, 19398-18-6; **1e**, 19374-54-0; **1f**, 19374-55-1; **1g**, 19374-56-2; **1h**, 19374-57-3; **2**, 19374-58-4; **2** HCl, 19374-59-5; **3**, 19374-60-8; **4**, 19374-61-9; **4a**, 19398-19-7; **4b**, 19374-62-0.

(21) From the amorphous fraction, about 5 mg of unidentified crystals were obtained by tlc (benzene–AcOEt–MeOH, 15:15:2, R_f 0.6). Crystallization from MeOH–$CHCl_3$ yielded fine needles of mp 275–280°; mass spectra 411 (M^+, strong), 396, 139, 108; nmr 0.77 (18- and 19-CH_3), 2.05 3.55, 4.30, 6.79 ppm; λ_{max}^{MeOH} 254 mμ (ϵ 990), 299 (2520); λ_{max}^{Nujol} 6.12 (sharp, medium), 7.24, 8.03, 8.68, 10.30 μ.

(22) W. Bergman, D. H. Gould, and E. M. Low, *J. Org. Chem.*, **10**, 570 (1945): 3β-hydroxybisnorallocholanic acid, mp 274–276°; methyl ester, mp 151–152.5°. The same alkali treatment of an authentic specimen lowered its melting point to 240–255° (acid) and 125–140° (methyl ester).

Synthesis of Dihydrothiazines Related to Deacetylcephalosporin Lactones. An Alternate Total Synthesis of Deacetylcephalosporin Lactones

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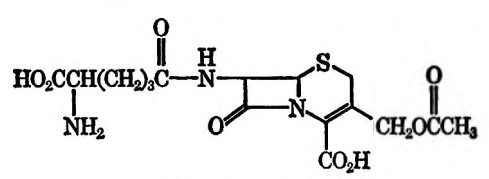
A unique synthesis of dihydrothiazines related to the cephalosporins is based upon the reaction of 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone I with aldehydes to form an imine, followed by acid-catalyzed cyclization with the simultaneous loss of the trityl group. The synthesis has been used to produce a compound [XI, R = $C(CH_3)_3$] which is a known intermediate for the synthesis of deacetylcephalosporin lactones.

The cephalosporin antibiotics are widely recognized as interesting and useful broad spectrum antimicrobial agents. Cephalosporin C was discovered by Abraham



cephalosporin C

and Newton[1] as a result of their studies on the antibiotic components produced by a species of *Cephalosporium* isolated by Brotzu.[2] Classical degradative studies[3] culminated in a tentative structure assignment which received confirmation by X-ray crystallographic studies.[4] Cephalosporin C, the subject of these pioneering studies, was therefore unambiguously assigned its now accepted structure. A recent review[5] has cataloged with clarity and thoroughness the major points of interest in the developing area of cephalosporin antibiotics.

The Squibb Institute has been responsive to the challenge involved in the synthesis of the cephalosporins for some time.[6a] At the present date several approaches of various degrees of success have been described.[6] In common to all of these propositions is the construction of a 1,3-[6H]-dihydrothiazine system. The formation of model 1,3-dihydrothiazines structurally related to cephalosporins has been studied by a number of groups.[6,7]

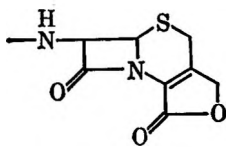
An approach to cephalosporin synthesis which depended upon the preparation of a deacetylcephalosporin lactone, a type represented by the following

(1) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **58**, 266 (1954).
(2) G. Brotzu, *Lav. Ist. Igiene Cagliari*, 1948.
(3) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961).
(4) D. Hodgkin and E. N. Maslen, *ibid.*, **79**, 393 (1901).
(5) E. P. Abraham, *Quart. Rev.* (London), **21**, 231 (1967).

(6) (a) E. Galantay, H. Engel, A. Szabo, and J. Fried, *J. Org. Chem.*, **29**, 3560 (1964); (b) R. Heymés, G. Amiard, and G. Nominé, *C. R. Acad. Sci., Paris*, **263**, 170 (1966); (c) G. Stork and H. T. Cheung, *J. Amer. Chem. Soc.*, **87**, 3783 (1965); (d) R. B. Woodward, K. Heusler, J. Gosteli, P. Nalgeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *ibid.*, **88**, 852 (1966).

(7) See, *inter alia*, G. C. Barrett, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 783 (1964); D. M. Greene, A. G. Long, P. J. May, and A. F. Turner, *ibid.*, 766 (1964); A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966); J. C. Sheehan and J. A. Schneider, *ibid.*, **31**, 1635 (1966).

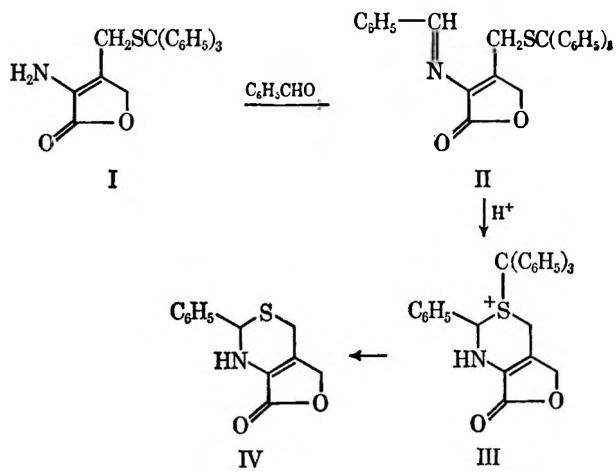
partial structure, had been suggested previously by Squibb scientists.[6a] It was anticipated that opening of



the lactone ring would lead to the formation of the 3-acetoxymethyl and 4-carboxy functions of the natural antibiotic. In a continuation of the earlier work we decided to study the possibilities of using 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone (I) as a precursor of dihydrothiazine lactones.

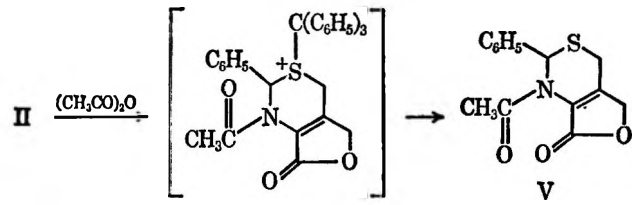
The nucleophilicity of the amino group of aminobutenolide I is low and salt formation with mineral acids does not occur under normal circumstances. However, reaction with aldehydes does occur and the corresponding imines can be obtained in generally high yield by refluxing a benzene solution of the reactants with concomitant removal of water. For example, reaction of amino lactone I with benzaldehyde produces an 88% yield of imine II (Scheme I). It was anticipated that imine II might be utilized directly in an acid-catalyzed reaction to produce dihydrothiazine lactone IV, with the intermediacy of cyclic sulfonium ion III. Indeed, when imine II was subjected to boiling with alcoholic hydrogen chloride the process of cyclization–detritylation occurred readily and the product dihydrothiazine IV crystallized from the solution in 60% yield. The material, mp 180–181°, analyzed correctly for $C_{12}H_{11}NO_2S$ and showed a characteristic lactone carbonyl absorption at 5.70 μ in the infrared spectrum. The ultraviolet spectrum revealed a maximum at 269 mμ (ϵ 4220). The pmr spectrum exhibited a quartet (J = 17.5 Hz) at τ 6.45 (CH_2S), singlet at 5.18 (CH_2O), doublet (J = 4.5 Hz) at 4.56 (benzylic H) and a broad absorption at 5.52 (NH) with a broad aromatic absorption at 2.6. The integrated ratios were in accord with the structure.

SCHEME I



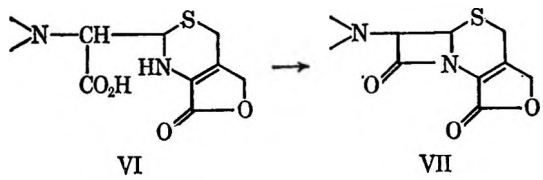
During our work a publication of Stork and Cheung[6c] appeared describing a clever synthesis of the N-acetyl derivative (V) of dihydrothiazine IV. We were able to effect a direct synthesis in 72% yield of the compound by heating imine II with acetic anhydride at 100°, the reaction presumably occurring by Scheme II.

SCHEME II



Our product (V) exhibited spectral values essentially identical with those published by Stork and Cheung. Having developed a reliable and convenient method of synthesis for dihydrothiazines related to the antibiotic, we turned our attention to the more complicated structures which might serve as intermediates in cephalosporin synthesis.

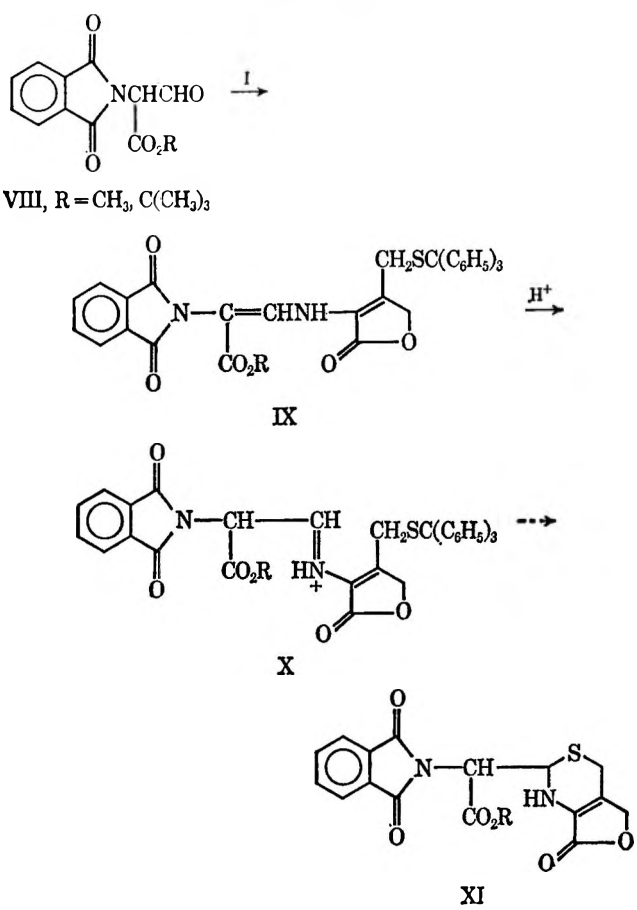
Consistent with the earlier design of the over-all synthetic plan[6a] was the preparation of an acid (VI)



which could logically serve as a precursor for β-lactam VII; there are numerous published methods for cyclizing β-amino acids (and their esters) to β-lactams.

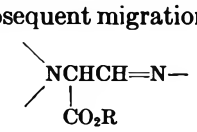
The reaction of α-phthalimidomalonaldehydic esters VIII with amino lactone I gave, as expected, an enamine type of product (IX) (Scheme III). The methyl

SCHEME III



ester (IX, R = CH_3) is readily obtained as *either* the *cis* or *trans*[8] forms depending upon the reaction conditions. In methanol containing a trace of acid, the reaction of methyl α-phthalimidomalonaldehydate (VIII, R = CH_3) with amino lactone I produces a precipitate of the predominantly *trans* form of amino ester IX in 84% yield. The pure material, mp 239–241°, exhibits a pmr spectrum (dimethyl sulfoxide solvent) in which the amino proton absorbs at τ 1.70 and the vinyl proton at 0.90 (J = 13.5 Hz). In contrast, reaction of the substrates in refluxing benzene containing *p*-toluenesulfonic acid produces mainly the *cis* isomer, mp 215–217°. The pmr spectrum absorption of the amino proton appears at τ 0.17 and the vinyl proton at 2.20 (J = 14 Hz). The assignment of the amino protons in both cases was confirmed by deuterium exchange. The downfield shift of the amino proton in the *cis* isomer is consistent with an internally hydrogen bonded structure and is used for the geometric assignment. This method of assignment has been neatly applied by Huisgen[9a] in similar situations. The position of the vinyl hydrogen absorption at a higher relative field in the *cis* isomer (in which this proton is *trans* to the carboxyl group) is consistent with independent correlations in other aminoacrylic esters.[9] The mobility of the *cis* ester possessing an internally hydrogen-bonded structure is greater than the *trans* on thin layer chromatography, an observation circumstantially in accord with the geometric assignments.

The clear stereochemical discrimination is difficult to rationalize on the basis of the formation of an initial aldimine structure (XII), since there is no compelling reason why the subsequent migration of the double bond

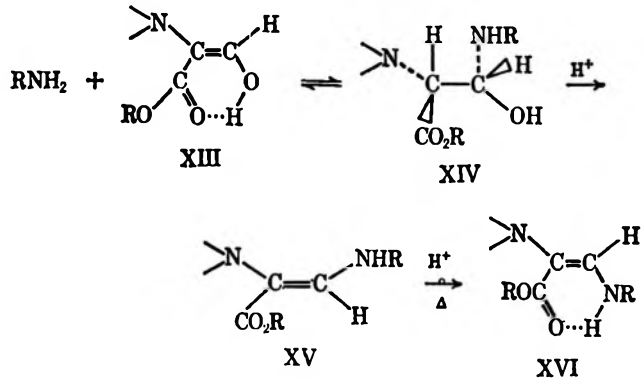


XII

should favor the exclusive formation of the *trans* form in acidic methanol. However, it would seem more appropriate to consider the reaction paths possible on the enol form of the malonaldehydic ester rather than the carbonyl form since pmr measurements in deuteriochloroform or dimethyl sulfoxide-d_6 show a 4:1 ratio favoring the enol. A concerted Michael addition to the hydrogen-bonded enol (XIII) would lead to an *erythro* intermediate (XIV) which upon concerted loss of water would be expected to produce *trans* isomer XV. In light of earlier findings[9a,10] with regard to the stability of β-aminocrotonic esters, it is to be expected that the kinetically produced *trans* isomer XV would be thermodynamically less stable than the *cis* isomer, which tends to be stabilized by hydrogen bonding. It is reasonable then that more energetic reaction conditions (refluxing benzene with *p*-toluenesulfonic acid) would facilitate the accumulation of the more stable *cis* isomer (XVI)[11] (Scheme IV).

The conversion of either the geometric isomers (IX,

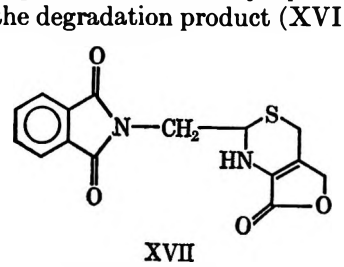
SCHEME IV



XIII XIV XV XVI

R = CH_3) into dihydrothiazines proceeded readily in nitromethane containing hydrogen chloride, a mixture of diastereomers (XI, R = CH_3) being obtained. From the mixtures a crystalline isomer, mp 211–215°, was easily separated. The structure of the material was determined to be of the *erythro* configuration by X-ray crystallographic analysis.[12] The *threo* racemate, corresponding to the natural cephalosporin configuration, remained a glass. However, both of the corresponding carboxylic acids were obtained as pure solids as a result of experiments with the *t*-butyl esters.

Reaction of *t*-butyl α-phthalimidomalonaldehydate [VIII, R = $C(CH_3)_3$] with amino lactone I gave the intermediate [IX, R = $C(CH_3)_3$] as an amorphous solid which does convert easily into the dihydrothiazine system. However, the ring formation may be attended by loss of the *t*-butyl group as well as the carboxyl group and the nature of the isolated product is very much a function of the conditions of reaction, particularly the temperature. A nearly quantitative conversion into the degradation product (XVII) is effected



XVII

by hydrogen chloride in nitromethane at room temperature. Conducting the same reaction at 0° permits only a trace of compound XVII to form, while a 65% yield of diastereomeric acids (XI, R = H) is obtained which can be quite readily separated owing to their differing solubilities and crystallization rates in chloroform. The isomeric acids decarboxylate on heating to 167–175 and 202–208°, respectively, with the final melting point coinciding with that of the decarboxylated compound XVII at 255° in both cases. The process of decarboxylation, crystal reorientation and final melting transitions are best followed and confirmed by differential thermal analysis.[13]

Esterification of the more stable acid (202–208°, $-CO_2$) with diazomethane gave a compound, mp 214–218°, identical (mixture melting point, infrared

(8) *cis* and *trans* here denote the relationship of the ester and β-amino groups.

(9) (a) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Ber.*, **99**, 2526 (1966); (b) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(10) K. Herbig, R. Huisgen, and H. Huber, *Ber.*, **99**, 2546 (1966); W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

(11) Thin layer chromatographic analysis of a warm (50°) benzene solution of the *trans* isomer with *p*-toluenesulfonic acid does show an accumulation of a preponderance of the *cis* isomer.

(12) We gratefully acknowledge the skillful cooperation of Professor J. Zanos Gougoutas and his collaborators of Harvard University who performed the structure determinations.

(13) These observations were made using a Du Pont 900 differential thermal analyzer through the courtesy and collaboration of Dr. Harold Jacobson of the Squibb Institute.

spectrum) with the ester previous discussed. The configuration of the less stable acid corresponds to the *threo* compound related to the natural cephalosporins.

When the temperature of the hydrogen chloride–nitromethane cyclization of the *t*-butyl ester [IX, R = $C(CH_3)_3$] is lowered to −20 to −25°, good yields of the *t*-butyl products (XI) may be obtained. Since the conversion of these materials into a racemate of cephalosporin lactones has been reported by French workers,[6b] an alternate total synthesis for the cephalosporin lactones is thus provided.

Experimental Section

All melting points are corrected. Proton magnetic resonance spectra were obtained on a Varian A-60 instrument by Dr. A. I. Cohen and values are reported in τ units using internal tetramethylsilane standard. Microanalytical data were obtained by Mr. J. Alicino and his staff.

2-(Benzylidenamino)-4-hydroxy-3-(tritylthiomethyl)crotonic Acid Lactone (II).—A solution of 1.00 g (2.58 mmol) of 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone[6a] (I) and 550 mg (5.2 mmol) of redistilled benzaldehyde in 25 ml benzene was heated at reflux with a Dean–Stark water separator for 1 hr after which the (cooled) solution was evaporated at reduced pressure. The oily residue was triturated with 7 ml of isopropyl alcohol to induce crystallization and then allowed to stand overnight in the cold room. The crystalline mass was separated by filtration and washed with hexane. In this way 1.07 g (88%) of product, mp 136–143°, was obtained. A recrystallization from isopropyl alcohol gave 840 mg (68%), mp 143–145°. (In earlier experiments a lower melting, less stable polymorph, mp 119–120°, was obtained which proved to be convertible into the higher melting form by crystallizing from a seeded isopropyl alcohol solution.)

Anal. Calcd for $C_{31}H_{25}O_2NS$: C, 78.35; H, 5.30; N, 2.95; S, 6.75. Found: C, 78.85; H, 5.90; N, 2.75; S, 6.93.

3,6-Dihydro-5-(hydroxymethyl)-2-phenyl-2H-1,3-thiazine-4-carboxylic Acid Lactone (IV).—A solution of 100 mg (0.210 mmol) of benzylidene compound II in 5 ml of isopropyl alcohol was obtained by gentle heating and was then acidified to Congo red paper with methanolic hydrogen chloride. The solution was heated to boiling on a steam bath for 30 sec, then allowed to cool. A crystalline mass formed and was subsequently filtered off. The product was obtained as 30 mg (61%) of pure white crystals, mp 180–181°. The pmr spectrum ($CDCl_3$) showed a quartet (J = 17.7 Hz) at τ 6.45; a singlet at 5.18; a doublet (J = 4 Hz) at 4.56; a broad absorption at 5.52. Spin decoupling of the 5.52 absorption resulted in the coalescence of the doublet at 5.18 to a singlet. The ultraviolet spectrum shows $\lambda_{max}^{ethanol}$ 269 mμ (ϵ 4220); the infrared spectrum showed λ_{max}^{KBr} 3.03, 5.80, 5.97 μ.

Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.85; H, 4.75. Found: C, 62.15; H, 5.04.

3-Acetyl-3,6-dihydro-5-(hydroxymethyl)-2-phenyl-2H-1,3-thiazine-4-carboxylic Acid Lactone (V).—A solution of 100 mg (0.210 mmol) of benzylidene compound II in 4 ml of acetic anhydride was heated on steam bath under nitrogen for 15 hr. The acetic anhydride was evaporated at reduced pressure leaving a pale yellow gum. The gum was dissolved in benzene and chromatographed on 5 g of Florisil (60–100 mesh). Elution with 50 ml of benzene removed triphenylcarbinol, identified by comparison of its infrared spectrum with that of an authentic sample; elution with chloroform then removed the product as 53 mg (93%) of pale yellow oil, $\lambda_{max}^{CHCl_3}$ 5.63, 5.91, 6.02 μ, values identical with those reported by Stork and Cheung[6c] for the material. Also in agreement was the pmr spectrum ($CDCl_3$) singlet at τ 6.03, quartet at 5.43 (J = 17.5 Hz), singlet at 2.98 and 7.01, aromatic hydrogens as broad singlet at 2.6. The material crystallized from hexane–carbon tetrachloride as 52 mg (72%) of colorless plates, mp 77–79° (lit.[6c] mp 77–78°).

3,6-Dihydro-5-(hydroxymethyl)-2-(phthalimidomethyl)-2H-1,3-thiazine-4-carboxylic Acid Lactone (XVII).—The starting material for this reaction was obtained by heating a solution of 289 mg (1 mmol) of *t*-butyl α-phthalimidomalonaldehydate and 387 mg (1 mmol) of aminobutenolide (I) in 25 ml of benzene under reflux for 4 hr, the water of reaction being removed by a Dean–Stark trap filled with Drierite. The solvent was then evaporated at reduced pressure; the residual gum formed a pale yellow amorphous solid upon trituration with hexane.

The crude intermediate was not purified further but was taken up in 50 ml of nitromethane and treated with a rapid stream of gaseous hydrogen chloride for 15 min at room temperature. Upon concentration of the reaction mixture at reduced pressure, 148 mg (47%) of the product, mp 251–254° dec, was obtained by allowing the residue to crystallize from acetonitrile. The ultraviolet absorption showed λ_{max}^{EtOH} 272 (ϵ 4490) as 218, 230, 239, 290 mμ. The pmr spectrum (CF_3CO_2H solvent) showed a quartet at τ 6.25 (J = 18 Hz), singlet at 4.88, doublet at 5.84, triplet at 4.93, in a ratio of 2:2:1:2:1; the NH absorption is masked owing to solvent exchange.

Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.90; H, 3.82; S, 10.12. Found: C, 56.80; H, 3.89; S, 10.08.

α-{[(2,5-Dihydro-2-oxo-4-(tritylthiomethyl)-3-furyl)amino]-methylene}-1,3-dioxo-2-isoindolineacetic acid *t*-butyl ester [IX, R = $C(CH_3)_3$] was prepared as described in a previous experiment, but the mixture of *cis–trans* isomers could not be purified well. The infrared red spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9–3.0, broad, weak; 5.68, 5.81, 5.97 μ. The material was used in further experiments without purification.

α-{[(2,5-Dihydro-2-oxo-4-(tritylthiomethyl)-3-furyl)amino]-methylene}-1,3-dioxo-2-isoindolineacetic Acid Methyl Ester (IX, R = CH_3), *trans* Isomer.—A solution of 247 mg (1 mmol) of methyl α-phthalimidomalonaldehydate[14] and 387 mg (1 mmol) of amino lactone I in 15 ml of methanol and 5 ml of chloroform was acidified to Congo red with methanolic hydrogen chloride and stirred at room temperature; a precipitate gradually formed. After 1 hr, filtration gave 274 mg (44.5%) of white solid, mp 225–226°. A second crop, mp 214–221°, 238 mg (38.6%), was obtained from mother liquors by evaporating at reduced pressure and trituration with 5 ml of cold methanol. A purified sample (mp 236–238°) could be obtained by crystallization from acetonitrile. The material showed a major spot, R_f 0.33, and a very minor spot, R_f 0.57, on tlc ($CHCl_3$–SiO_2).

Anal. Calcd for $C_{36}H_{28}N_2O_6S$: C, 70.12; H, 4.58; N, 4.55; S, 5.20. Found: C, 69.86; H, 4.76; N, 4.53; S, 5.36.

***cis* Isomer.**—A solution of equimillimolar amounts of the reactants, used in part A, in 30 ml of benzene containing 30 mg of *p*-toluenesulfonic acid hydrate was heated to reflux for 1 hr using a Dean–Stark water separator and then evaporated at reduced pressure. The resulting pale yellow foam solidified upon trituration with 5 ml of cold acetonitrile giving 440 mg (72%) of product, mp 212–213°. A recrystallization of a small sample from acetonitrile gave pure material, mp 214–217°. The mother liquors (from the previous trituration) gave an additional 160 mg (20%), mp 211–215°. A total of 600 mg (97%) of product was obtained. The total material recrystallized from methanol as 485 mg (79%), mp 213–217°. This material on thin layer chromatography showed a major spot, R_f 0.57, and a minor spot, R_f 0.33.

Anal. Calcd for $C_{36}H_{28}N_2O_6S$: C, 70.12; H, 4.58; N, 4.55; S, 5.20. Found: C, 70.23; H, 4.56; N, 4.66; S, 5.33.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazineacetic Acid Methyl Ester (XI, R = CH_3).—A suspension of 1.90 g (3.08 mmol) of *trans* isomer unsaturated ester (IX) in 250 ml of nitromethane was saturated with a rapid stream of hydrogen chloride for 15 min, a yellow solution being obtained. The reaction was stirred for a total of 1.5 hr at room temperature, then evaporated at reduced pressure. The residue was taken up in 10 ml of hot methanol. Cooling gave a small amount of product. Chromatography of the mother liquors on 60 g of Florisil gave, with chloroform, additional product. The combined product fractions crystallized from chloroform–methanol affording 532 mg (46%) of rhombic crystals, mp 211–215°.

Anal. Calcd for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77; S, 8.56. Found: C, 54.77; H, 3.95; S, 8.54.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazine Acetic Acid *t*-Butyl Ester [XI, R = $C(CH_3)_3$].—Under a nitrogen atmosphere, a solution of 20.0 g (51.6 mmol) of amino lactone I and 14.8 g (51.6 mmol) of *t*-butyl α-phthalimidomalonaldehydate[14] in 1.0 l. of benzene was refluxed for 4 hr, a Dean–Stark trap separating the water of reaction. The solution was evaporated at reduced pressure to provide the intermediate as a gum, which was then taken up in 600 ml of nitromethane and cooled to −20° by a Dry Ice–acetone bath. A

(14) J. C. Sheehan and D. A. Johnson, *J. Amer. Chem. Soc.*, **76**, 158 (1954).

rapid stream of gaseous hydrogen chloride was passed through the solution for 45 min, the temperature being maintained at or below −20° at all times. After this time a stream of nitrogen was passed through the reaction mixture to flush out the bulk of the hydrogen chloride. The solution was then diluted with 2 l. of chloroform, precooled to −20°, and evaporated at reduced pressure. The residue was taken up in 300 ml of benzene, washed with 250 ml of aqueous 10% sodium carbonate, dried over sodium sulfate, filtered and evaporated. This neutral material was chromatographed on 500 g of Florisil (60/100 mesh). Elution with 1:1 benzene–chloroform gave 9.7 g (52%) of diastereoisomeric product, which crystallized from chloroform–ether as needles, mp 189–190°. While careful chromatography on alumina or silica gel did not separate the isomers, repeated crystallization from chloroform–hexane gave a single racemate: mp 193°; uv max (C_2H_5OH) 268 mμ (ε 4700), 216 (41,700); ir ($CHCl_3$) 2.90 (NH), 5.70 (lactone C=O), 5.85 μ (ester C=O); pmr (pyridine-d_5) τ 1.9–2.6 (m, 4, aromatic), 3.83 (q, 1, J = 6, 10 Hz, CHS), 4.72 (d, 1, J = 10 Hz, CH—CO, 5.0 (m, 1, NH), 5.31 (s, 2, —OCH_2C=), 6.43 [q, 2, J = 18 Hz, SCH_2C(=C)—], 8.60 [s, 9, $OC(CH_3)_3$].

Anal. Calcd for $C_{20}H_{20}N_2O_6S$: C, 57.69; H, 4.80. Found: C, 57.44; H, 5.05.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazine Acetic Acid (XI, R = H).—The crude intermediate, obtained by allowing 1.16 g (4 mmol) of aldehyde [VIII, R = $C(CH_3)_3$] and 1.55 g (4 mmol) of amino lactone I to react in refluxing benzene for 3 hr, was dissolved in 80 ml of nitromethane and cooled to −15°; hydrogen chloride was passed through the solution for 15 min at this temperature; the solution was immediately diluted with 400 ml of ice-cold chloroform and the resulting solution evaporated at reduced pressure below 25°. The residue was taken up in 200 ml of benzene, and extracted with two 60-ml portions of 10% aqueous sodium bicarbonate. The extracts were cooled to 0° and acidified with dilute hydrochloric acid to pH 3 in the presence of 80 ml of chloroform. The aqueous layer was extracted with two additional (80-ml portions of chloroform. The combined chloroform solutions were dried (Na_2SO_4), filtered, and evaporated at reduced pressure below 25°. The resulting crude acid mixture weighed 661 mg (46%) and was immediately dissolved in 10 ml of chloroform and placed in the cold room overnight, producing 239 mg (16.5%) of acid isomer A, mp 162–164° (−CO_2), 248–250° dec. A differential thermal analysis indicated rapid loss of gas (CO_2) with concomitant melting at 167°, resolidification at 175° and finally remelting at 258°, with subsequent decomposition.

Anal. Calcd for $C_{16}H_{12}N_2SO_6$: C, 53.30; H, 3.36; N, 7.78. Found: C, 53.51; H, 3.87; N, 7.66.

The mother liquor on standing deposited 158 mg (11%) of acid isomer B, mp 192–193° (−CO_2) and 245–247° dec. Differential thermal analysis showed major loss of CO_2 and melting at 202° with resolidification at 208° and final melting at 255° with subsequent decomposition. A small depression in the curve at 168° showed the presence of a minor amount of isomer A.

Anal. Calcd for $C_{16}H_{12}N_2SO_6$: C, 53.30; H, 3.36; N, 7.78. Found: C, 53.50; H, 3.32; N, 7.39.

Isomer B was converted in 90% yield by ethereal diazomethane into material of mp 195–212°; recrystallization from acetonitrile gave 70% of pure product, mp 214–218°, identical (mixture melting point, infrared) with the methyl ester previously obtained by direct cyclization.

Registry No.—II, 19289-43-1; IV, 19289-44-2; V, 4019-12-9; IX, R = Me (*trans*), 19289-54-4; IX, R = Me (*cis*), 19289-55-5; XI, R = Me, 19289-46-4; XI, R = *t*-Bu, 17493-47-9; XI, R = H, 17833-99-7; XVII, 19289-57-7.

Polychlorinated Ketones. I. Synthesis and Fragmentation of β,β-Bis(trichloromethyl)-β-propiolactone

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Received August 6, 1968

The uncatalyzed cycloaddition of ketene to hexachloroacetone at 190–200° has given β,β-bis(trichloromethyl)-β-propiolactone (I) in 85% yield. In the presence of catalytic amounts of anhydrous ferric chloride, I underwent facile fragmentation when heated above its melting point to give 1,1,4,4,4-pentachloro-1-buten-3-one (XI), carbon monoxide, and hydrogen chloride. Addition of chlorine to the double bond of XI afforded 1,1,1,3,4,4,4-heptachlorobutan-2-one (XVI) which was readily dehydrochlorinated in the presence of triethylamine to give 1,1,2,4,4,4-hexachloro-1-buten-3-one (XXIV). The structure of lactone I and ketones XI, XVI, and XXIV is supported by physical and chemical investigations.

In connection with our work concerning the polymerization of lactones,[3] we were interested in studying the influence of electronegative groups in the β position of β-lactones on their polymerizability. One of the most widely used methods for the preparation of β-lactones is the reaction of a ketene with a carbonyl compound which requires catalysts in most cases. This reaction and the chemistry of β-lactones have been studied and reviewed in some detail.[4,5] More recently, the cycloaddition of ketene to hexafluoroacetone (ether, −78°, P_2O_5) has been found to give β,β-bis(trifluoromethyl)-β-propiolactone.[6] Similarly, β-trichloromethyl-β-propiolactone (II) was obtained from ketene and chloral at −80° [inert solvents, $BF_3 \cdot O(C_2H_5)_2$].[7] It has also been found that II can be prepared more conveniently from ketene and chloral at room temperature in the absence of solvents and catalysts.[8]

We have now found that when ketene was allowed to react with hexachloroacetone in the absence of catalysts and solvents at 190–200° β,β-bis(trichloromethyl)-β-propiolactone (I) was isolated in 85% yield. Catalysis of the cycloaddition reaction proved unsuccessful. Lewis acids in the presence or absence of a solvent

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(2) Farbenfabriken Bayer, Werk Dormagen, Germany.

(3) H. Ohse and H. Cherdron, *Makromol. Chem.*, **86**, 312 (1965).

(4) H. E. Zaugg, *Org. Reactions*, **8**, 305 (1954).

(5) H. Kröper in Houben-Weyl's "Methoden der organischen Chemie," Vol. 6, Georg Thieme Verlag, Stuttgart, 1963, p 511.

(6) I. L. Knunyants and Yn. A. Cheburkov, *Bull. Acad. Sci., USSR, Div. Chem. Sci.* (Engl. Transl.), 640 (1960).

(7) K. Schimmelschmidt and E. Mundlos, German Patent 1,136,323 (1962); *Chem. Abstr.*, **58**, 3321 (1963).

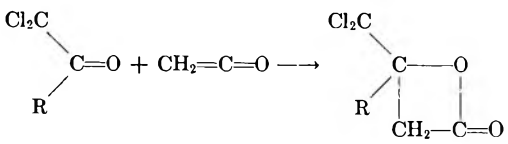
(8) H. Ohse, R. Palm, and H. Cherdron, *Monatsh. Chem.*, **98**, 2138 (1967).

TABLE I

A SUMMARY OF THE EFFECT OF CATALYST AND TEMPERATURE ON THE FORMATION OF β,β-BIS(TRICHLOROMETHYL)-β-PROPIOLACTONE (I)

Run	Solvent	Temp, °C	Catalyst	I, % yield
1	CH_2Cl_2	−25	$(CF_3CO_2)_2Zn$	
2	CH_2Cl_2	−25	$BF_3 \cdot O(C_2H_5)_2$	
3		+70	$(CF_3CO_2)_2Zn$	
4		+25		Traces
5		+130		68
6		+150		74
7		+195		85

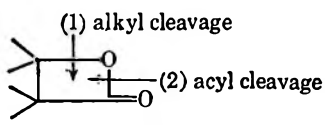
appear to have no influence on the formation of I at lower temperatures. The products isolated from these runs were hexachloroacetone and diketene. However,



I, R = CCl_3
II, R = H

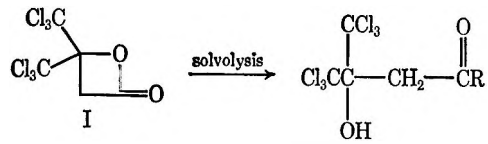
the rate of formation of I is largely dependent on the reaction temperature and proceeds with a measurable rate above 100°. As the temperature increases, the yield of I increases, and maximum yields of product are obtained at temperatures between 190 and 200°. The results are listed in Table I.

Compound I is obtained as white crystalline solid with a pleasant odor by distillation under vacuum [bp 103–105° (0.03 mm), mp 52° (from pentane)]. Elemental analysis and spectroscopic data are consistent with the β-lactone structure. Infrared absorption at $\nu_{C=O}$ 1860 and 1895 cm^{-1} confirms the expectation that two electron-withdrawing substituents in the β position in addition to an increased ring strain will result in a further shift toward higher frequencies as compared with γ-lactones.[9a] β-Lactones have properties determined by their ring-opening reactions which may take two different courses: (1) rupture of the bond between oxygen and carbon (alkyl cleavage), and (2) rupture of the bond between oxygen and the carbonyl group (acyl cleavage). Unlike II which reacts with water at 100° to give 4,4,4-trichloro-3-hydroxybutyric acid,[8] I is stable under these conditions.

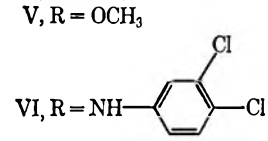


However, more drastic conditions, *i.e.*, prolonged heating in refluxing 30% sulfuric acid, brings about hydrolysis to 4,4,4-trichloro-3-trichloromethyl-3-hydroxybutyric acid (III). Methanol, ammonia and amines react analogously to give the products of an acyl cleavage of I.

These findings led us to the investigation of a series of catalysts and solvents for the polymerization of I. Initially, the action of anhydrous ferric chloride was



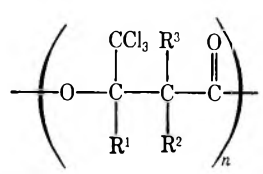
III, R = OH
IV, R = NH_2
V, R = OCH_3



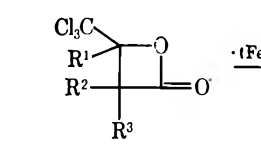
VI, R = NH–

studied, since this reagent had successfully effected the polymerization of II and α,α-dimethyl-β-trichloromethyl-β-propiolactone (VII) to give polyesters of general structure VIII and IX, respectively.[10] However, treatment of I with approximately 1×10^{-2} mol equiv of anhydrous ferric chloride gave no polyester X. Instead, lactone I decomposed when heated above its melting point to give carbon monoxide and hydrogen chloride (molar ratio 1:1) and 1,1,4,4,4-pentachloro-1-buten-3-one (XI) by a series of logical reactions (see below). After a cursory examination of other possible polymerization initiators,[10] it was found that only anhydrous ferric chloride furnished ketone XI (Scheme I).

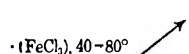
SCHEME I

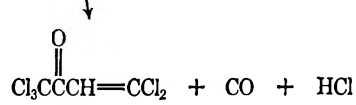


VIII, $R^1 = R^2 = R^3 = H$
IX, $R^1 = H$; $R^2 = R^3 = CH_3$
X, $R^1 = CCl_3$; $R^2 = R^3 = H$



I, $R^1 = CCl_3$; $R^2 = R^3 = H$
II, $R^1 = R^2 = R^3 = H$
VII, $R^1 = H$; $R^2 = R^3 = CH_3$





XI

A mechanism that accounts for these observations presumably involves formation of an intermediary complex of I with ferric chloride. In the presumed transition state (XII), it is probable that formation of a relatively stable O–Fe bond is necessary before the electronic shifts involving migration of a trichloromethyl anion from the β-carbon atom into the α position can occur. A logical precursor of XI would be the saturated ketone XIII which easily eliminates hydrogen chloride under the reaction conditions[11] to give XI (Scheme II).

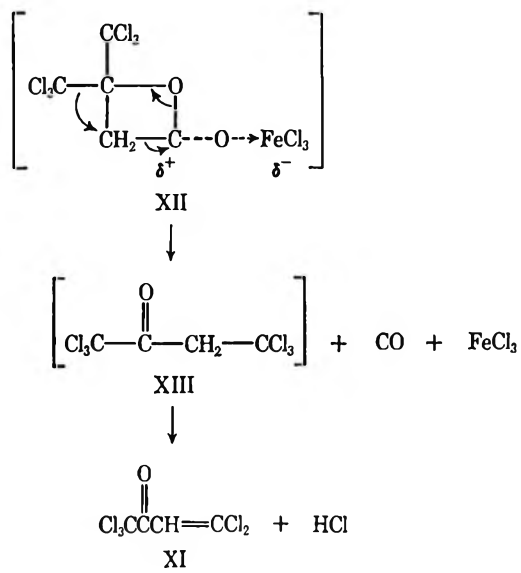
Compound XI is a colorless liquid which has the

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1965: (a) p 152; (b) p 115; (c) p 31; (d) p 117.

(10) H. Ohse and H. Cherdron, *Makromol. Chem.*, **108**, 193 (1967).

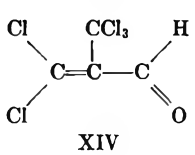
(11) β,β-Dichloroethyl ketones have been isolated and characterized in some cases, but normally they spontaneously eliminate hydrogen chloride on standing: V. Klimko, V. Michalev, and A. Skoldinov, *J. Gen. Chem. USSR*, **27**, 370 (1957); *Chem. Abstr.*, **51**, 15449 (1957).

SCHEME II



empirical formula C_4HCl_5O as calculated from its elemental analysis and its mass spectrum which shows the m/e peak at 242 corresponding to the parent peak (M). No evidence for either higher or lower molecular weight impurities was observed in the mass spectrum and by gas chromatographic analyses.

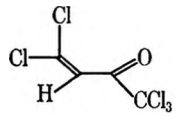
The infrared spectrum of XI shows very clearly the characteristic double-bond absorption at 1562 cm^{-1}, a split carbonyl peak at 1730 and 1705 cm^{-1} and the =CH stretching vibration at 3068 cm^{-1}. It should be noted that similar double-bond absorptions were observed by several authors in infrared spectra of α,β-unsaturated ketones.[12,13] The CH stretching frequency of an aldehyde, *i.e.*, perchloromethacrolein, C_4HCl_5O (XIV), which could also be considered to result from I by



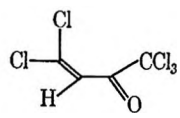
XIV

fragmentation, would be expected near 2900–2700 cm^{-1}.[9b] A splitting of the carbonyl band in the infrared spectra of α,β-unsaturated ketones has been attributed to various factors such as Fermi resonance,[14] rotational isomerism[12b] and to an equilibrium between the *S-cis* and *s-trans* configurations.[15–17] The latter effect does not seem likely for when unstrained coplanar configurations are possible one of these is preferred to the exclusion of the other.[16–18] The minor peak of the split carbonyl band in the infrared spectrum of methyl β,β-dichlorovinyl ketone has been attributed to the first overtone of the very strong C—Cl stretching fundamental.[13]

A Briegleb molecular model of XI shows considerable strain to attainment of coplanarity in the *s-trans* conformation. However, the coplanar *s-cis* structure is achieved without strain. A van der Waals overlap diagram reveals little or no steric hindrance in the *s-cis* configuration, but prohibitive overlap in the *s-trans* conformation.



XI, *s-cis*



s-trans

In the ultraviolet spectrum of XI, maximum absorption is observed at 259 mμ (ϵ 10,492), again indicating a coplanar and highly conjugated system. Methyl vinyl ketone,[18] methyl β-chlorovinyl ketone[18] and methyl β,β-dichlorovinyl ketone[13] absorb at 210 mμ (ϵ 7000), 228 (10,000), and 241 (11,900), respectively. Thus replacement of the methyl group by a trichloromethyl group in methyl β,β-dichlorovinyl ketone had caused a bathochromic shift of 18 mμ.

The nmr spectrum of XI shows one singlet at 7.26 ppm (calcd[19] δ 7.29 ppm); the chemical shift in XIV would be expected to be greater than 9.5 ppm. In summary, we infer from these data that XI exists in the *S-cis* conformation.

Additional evidence for the structure of XI has been obtained by a number of reactions (Scheme III). For example, with phenylhydrazine and XI, pyrazole XV is formed in an exothermic reaction. The initial product, the hydrazone, could not be isolated. Ketone XI does not decolorize bromine in carbon tetrachloride solution, although chlorine is added readily at 0° under irradiation with ultraviolet light to give 1,1,1,3,4,4,4-heptachlorobutan-2-one (XVI). As was to be expected, XI underwent the haloform cleavage fairly easily to give chloroform and β,β-dichloroacrylic acid (XVII). This reaction appears to be the most convenient method of preparation for XVII which is difficult to obtain otherwise.[20] The carbonyl group can be selectively reduced with sodium borohydride forming 1,1,4,4,4-pentachloro-1-buten-3-ol (XVIII). Replacement of the hydroxyl group in XVIII by chlorine with thionyl chloride proceeded smoothly; however, the corresponding chloro compound, XIX, is not obtained. The rearranged material, *trans*-1,1,1,4,4,4-hexachloro-2-butene (XXI), is isolated instead.[21] This reaction presumably involves the cyclic transition state shown in XX. The structure assignment of XXI is based on its infrared spectrum and dipole measurements. For example, the =CH stretching vibration is found at 3085 cm^{-1}; the out-of-plane =CH deformation frequency which is characteristic of a *trans*-olefinic structure[9c] is observed at 945 cm^{-1}. XXI has no dipole moment (measured in benzene) which is consistent with its *trans*-olefinic structure. Chlorination of XXI affords 1,1,1,2,3,4,4,4-octachlorobutane (XXII), whereas treatment with sulfuric acid followed by reaction with ethanol gives diethyl fumarate (XXIII).

(12) (a) W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **29**, 385 (1964); (b) J. Dabrowski and J. Terpinski, *ibid.*, **31**, 2159 (1966).

(13) S. Searles, Jr., R. A. Sanches, R. L. Sonlen, and D. G. Kundiger, *ibid.*, **32**, 2655 (1967).

(14) K. Noack, *Spectrochim. Acta.*, **18**, 697 (1962).

(15) R. Mecke and K. Noack, *Ber.* **93**, 210 (1960).

(16) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(17) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

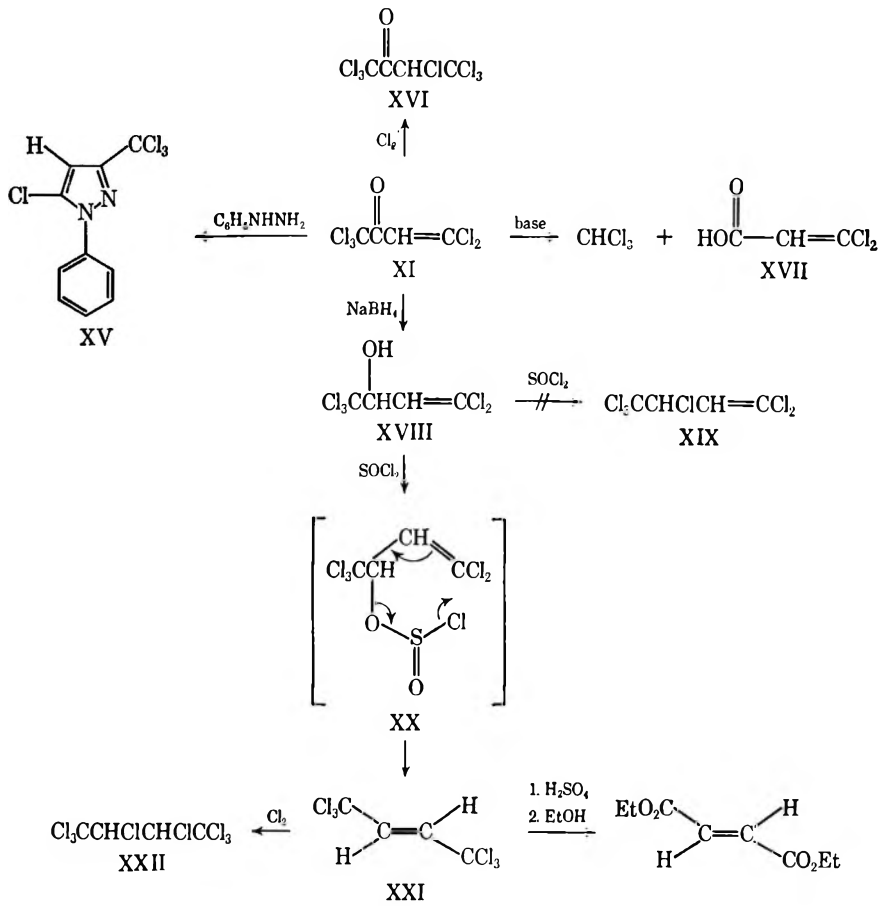
(18) M. Julia, *Ann. Chim.* (Paris), (12) **5**, 595 (1950).

(19) H. Primas, R. Arndt, and R. Ernst, International Meeting of Molecular Spectroscopy, Bologna, 1959.

(20) F. Straus, L. Kollek, and W. Heyn, *Ber.*, **63**, 1877 (1930).

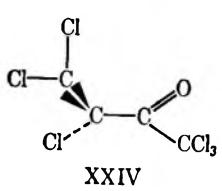
(21) Similar results were obtained by J. Meisenheimer and J. Link, *Ann.*, **479**, 258 (1930), on reaction of thionyl chloride with 1-penten-3-ol and 2-penten-1-ol, respectively.

SCHEME III



Ketone XVI can be readily dehydrochlorinated in the presence of triethylamine at room temperature to give 1,1,2,4,4,4-hexachloro-1-buten-3-one (XXIV) which is identical with the product obtained by dechlorination of octachlorobutanone with triphenylphosphine or a trialkyl phosphite.[22]

The ultraviolet spectrum of ketone XXIV shows maximum absorption at 205 mμ (ε 7139) and 245 (7430). The extinction coefficient is significantly low and presumably due to strain in the coplanar system,[23] or to noncoplanarity. A Briegleb molecular model of XXIV shows considerable steric hindrance to coplanarity in the *s-trans* conformation. A van der Waals overlap diagram shows overlap in both the *S-cis* and *s-trans* conformations. The carbonyl (1745 cm^{-1}) and double-bond (1575 cm^{-1}) absorption bands in the infrared spectrum of XXIV are observed at higher



XXIV

frequencies compared with that of XI indicative of decreased conjugation.[9d] Thus the available evidence indicates a noncoplanar configuration for XXIV induced by the α-chlorine atom.

The reactions which were carried out with XXIV are summarized in Scheme IV; the results are similar to those obtained with XI (see Scheme III).

Experimental Section[24]

β,β-Bis(trichloromethyl)-β-propiolactone (I).—In a 1000-ml, four-necked flask fitted with stirrer, thermometer, gas-inlet tube, and reflux condenser protected by a calcium chloride drying tube was placed 503 g (1.9 mol) of hexachloroacetone. The temperature of the condenser was adjusted at −80°, and hexachloroacetone was heated to 190°. Ketene, 84 g (2.0 mol), which was obtained by pyrolysis of diketene, and which had been twice distilled, was introduced through the gas-inlet tube with vigorous stirring. At the beginning, ketene was absorbed rapidly, but later on the consumption of ketene slackened. Stirring was continued for an additional 2 hr at 190° after the addition of ketene was completed. Distillation under vacuum afforded 497 g (85%) of I: bp 103–105° (0.03 mm); mp 52° (from pentane); ir main bands at 1860 and 1895 cm^{-1}.

Anal. Calcd for $C_5H_2Cl_6O_2$: C, 19.6; H, 0.7; Cl, 69.5. Found: C, 19.6; H, 0.8; Cl, 69.9.

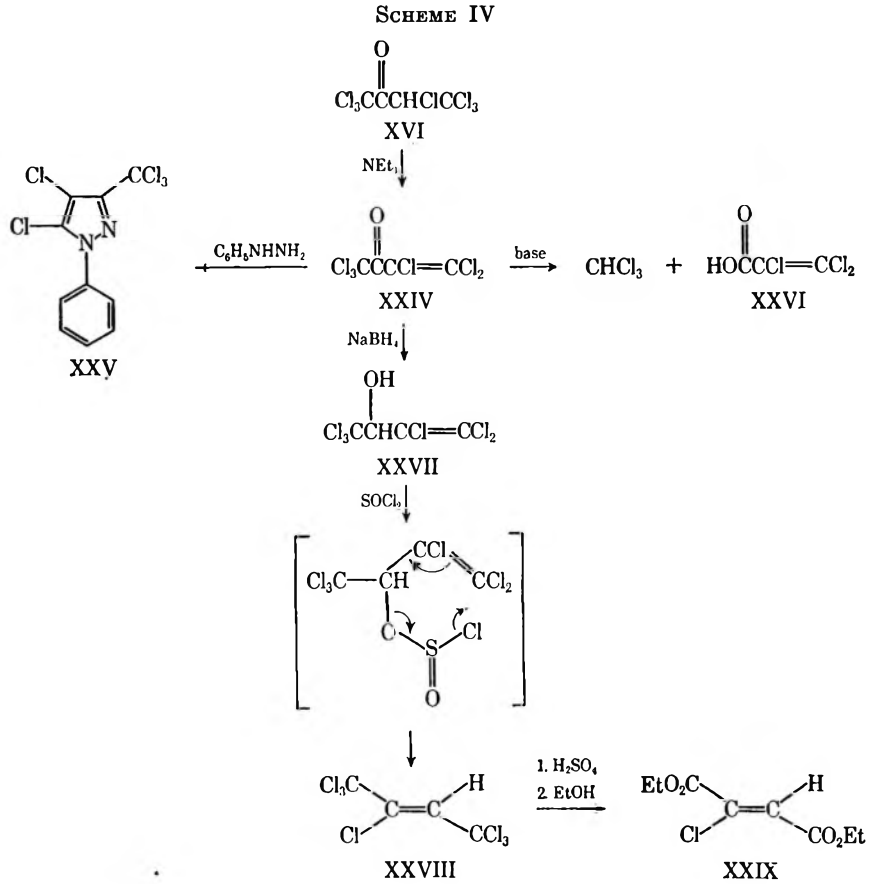
4,4,4-Trichloro-3-trichloromethyl-3-hydroxybutyric Acid (III).—A mixture of 50 g (0.163 mol) of I and 1500 ml of 30% sulfuric acid was heated at reflux for 14 hr and cooled. The solid product was suction filtered, washed well with water, dried, and recrys-

(22) K. Pilgram and H. Ohse, *Angew. Chem. Intern. Ed. Engl.*, **5**, 837 (1966). Attempts by A. Roedig and H. J. Becker [*Ber.*, **89**, 906 (1956)] to prepare XXIV by dechlorination of octachlorobutanone with aluminum filings were unsuccessful.

(23) R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.*, **73**, 1403 (1951).

(24) Ultraviolet spectra were recorded with a Cary 14 and Cary 15 recording spectrometers in the region 200–350 and 200–550 mμ, respectively, using methanol as solvent. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were obtained with a KIS-2 90-Mc spectrometer, using tetramethylsilane as internal standard; chemical shifts (parts per million) are expressed as δ values and coupling constants are given in cycles per second (cps). Melting and boiling points are uncorrected.

SCHEME IV



tallized from hexane to give III: yield 35 g (66.4%); mp 159–160°.

Anal. Calcd for $C_5H_4Cl_6O_3$: C, 18.5; H, 1.2; Cl, 65.6. Found: C, 18.9; H, 1.5; Cl, 65.0.

4,4,4-Trichloro-3-trichloromethyl-3-hydroxybutyramide (IV).—Dry ammonia was bubbled through a solution of I, 3.07 g (0.01 mol), in 50 ml of ether. The mixture was allowed to stand overnight, after which time a white solid had precipitated. Filtration yielded 3.2 g (98.3%) of IV, mp 227–228° (from tetrahydrofuran).

Anal. Calcd for $C_5H_5Cl_6NO_2$: C, 18.6; H, 1.5; Cl, 65.7; N, 4.3. Found: C, 18.8; H, 1.7; Cl, 65.1; N, 4.4.

Methyl 4,4,4-Trichloro-3-trichloromethyl-3-hydroxybutyrate (V).—A solution of 30.7 g (0.1 mol) of I and about 500 mg of *p*-toluenesulfonic acid in 250 ml of methanol was heated to reflux for 6 hr. Most of the excess methanol was removed under vacuum, and the residue was poured into water and extracted several times with ether. The combined ether extractions were dried ($MgSO_4$) and evaporated to dryness. The crystalline residue was recrystallized from petroleum ether to give 25.7 g (76%) of V, mp 55–56°.

Anal. Calcd for $C_6H_6Cl_6O_3$: C, 21.2; H, 1.8; Cl, 62.8. Found: C, 21.2; H, 1.9; Cl, 62.9.

3′,4,4,4,4′-Pentachloro-3-hydroxy-3-(trichloromethyl)butyranilide (VI).—A mixture of 61.4 g (0.2 mol) of I and 32.4 g of 3,4-dichloroaniline (0.2 mol), was heated with stirring at 130–140° over a 1-hr period. Benzene (150 ml) was added. After cooling, 400 ml of pentane was added and white crystalline VI, 42 g (44.8%), mp 212–215°, was collected.

Anal. Calcd for $C_{11}H_7Cl_8NO_2$: Cl, 60.6; N, 3.8. Found: Cl, 60.6; N, 3.2.

1,1,4,4,4-Pentachloro-1-buten-3-one (XI).—In a 500-ml, three-necked flask fitted with stirrer, thermometer, and reflux condenser protected by a calcium chloride drying tube was placed 102.3 g (0.33 mol) of I and 0.5 g of anhydrous ferric chloride. The mixture was heated with stirring in an oil bath at 52–70° until evolution of gas[25] had ceased (*ca.* 7 hr at 70°). The dark reaction mixture was purified by distillation to give 79.2 g (98.3%) of XI: bp 95–96° (13 mm); $n^{20}D$ 1.5423; d^{20}_4 1.6493; colorless liquid; ir (film) (cm^{-1}) main bands at 3068, 1730, 1705, 1562, 1092, 959, 870, 835, 770, 728 cm^{-1}; uv λ_{max} 259 mμ (ε 10,492); nmr (CCl_4) δ 7.26 (s, =CH).

Anal. Calcd for C_4HCl_5O: C, 19.8; H, 0.4; Cl, 73.2. Found: C, 19.7; H, 0.5; Cl, 73.4.

1-Phenyl-5-chloro-3-(trichloromethyl)pyrazole (XV).—To a solution of 24.25 g (0.1 mol) of XI in dry ether, 200 ml, was added dropwise with stirring a solution of 21.6 g (0.2 mol) of phenylhydrazine in 50 ml of dry ether. After the exothermic reaction was completed, 200 ml of water was added to the reaction mixture. The organic layer was washed with water and dried ($CaCl_2$). Ether was removed from the dark red solution to give crude XV which was purified by distillation: bp 112° (0.005 mm); 15.1 g (51%) of XV; $n^{20}D$ 1.5995; uv max 400 mμ (ε 91), 311 (132), 239 (11,953); nmr (hexadeuterioacetone) δ 6.66 (pyrazole H) and *ca.* 7.35 (phenyl H).

Anal. Calcd for $C_{10}H_5Cl_4N_2$: C, 40.5; H, 2.0; Cl, 47.9; N, 9.5. Found: C, 40.7; H, 1.8; Cl, 47.9; N, 9.1.

1,1,1,3,4,4,4-Heptachlorobutan-2-one (XVI).—Chlorine, 120 g, was introduced into 400 g (1.65 mol) of XI at 0°. After 3 hr, excess chlorine was removed under vacuum to give 505 g (97.5%) of crude XVI with an estimated purity of 99% (glpc). Distillation under vacuum furnished 485 g (93.7%) of XVI as colorless liquid: bp 110° (9 mm); mp 16°; $n^{20}D$ 1.5271; d^{20}_4 1.7561; nmr (CCl_4) δ 5.31 (s); ir (film) main bands at 2975, 1752, 1300, 1200, 1065, and 770–850 cm^{-1}.

Anal. Calcd for C_4HCl_7O: Cl, 15.3; H, 0.3; Cl, 79.2. Found: C, 15.6; H, 0.4; Cl, 79.1.

β,β-Dichloroacrylic Acid (XVII).—Ketone XI, 2.42 g (0.01 mol), was added dropwise with stirring to 15 ml of 1 *N* sodium hydroxide solution at room temperature. The reaction was exothermic. After 2 hr, chloroform was evaporated and identified by glpc. The aqueous phase was extracted with ether. Acidification of the aqueous solution with concentrated hydrochloric acid gave colorless crystals of crude XVII. Recrystallization from pentane gave 1.03 g (73%) of pure XVII, mp 75–76° (lit.[20] mp 76–77°).

1,1,4,4,4-Pentachloro-1-buten-3-ol (XVIII).—To a solution of 5 g (0.132 mol equiv) of sodium borohydride in 400 ml of water

(25) The water-soluble fraction of the gas was identified as hydrogen chloride (determined as AgCl). The water-insoluble fraction consisted of carbon monoxide which was identified by mass spectrometry: *m/e* 28 (M).

and 200 ml of ethanol was added dropwise with stirring 121.3 g (0.5 mol) of XI. The temperature was maintained at 10–15° by external cooling with ice water. After the reaction was completed, 400 ml of water was added and the solution was extracted with ether. The combined ether extractions were dried (Na_2SO_4) and evaporated to dryness to give 75 g (61.5%) of crude XVIII as colorless crystallized solid. Recrystallization from pentane afforded 48 g (39.3%) of pure XVIII: mp 80–81°; nmr ($CDCl_3$) δ 3.35 (s, –OH), 4.93 (d, J = 8.3, –CH), 6.10 (d, J = 8.3, =CH); ir (KBr) main bands at *ca.* 3275, 1625, 1049, 875, 817, and 785 cm^{-1}.

Anal. Calcd for $C_4H_3Cl_5O$: C, 19.6; H, 1.2; Cl, 72.5. Found: C, 19.7; H, 1.4; Cl, 72.7.

***trans*-1,1,1,4,4,4-Hexachloro-2-butene (XXI).**—A solution of XVIII, 24.25 g (0.1 mol), in thionyl chloride, 96 g (0.8 mol), was heated to reflux for 5 hr until glpc indicated that the starting material had reacted completely. Excess thionyl chloride was removed under vacuum. The residue was recrystallized from pentane to give 25 g (95%) of XXI as white crystallized solid: mp 81°; nmr (CCl_4) δ 6.57 (s); ir (KBr) main bands at 3085, 1625, 1248, 1090, 1050, 945, 875 and *ca.* 750 cm^{-1}.

Anal. Calcd for $C_4H_2Cl_6$: C, 18.2; H, 0.8; Cl, 81.0. Found: C, 18.4; H, 0.9; Cl, 80.8.

1,1,1,2,3,4,4,4-Octachlorobutane (XXII).—Chlorine was passed into a solution of 3.3 g (12.5 mmol) of XXI in 15 ml of carbon tetrachloride under irradiation with uv light. After 2 hr, carbon tetrachloride was removed and the residue was purified by distillation under vacuum to give 3.85 g (92.1%) of XXII: bp 136° (10 mm); $n^{20}D$ 1.5498; d^{20}_4 1.8016; colorless viscous oil; ir (film) main bands at 2980, 1275, 1236, 1000, 970, 950 and *ca.* 800 cm^{-1}.

Anal. Calcd for $C_4H_2Cl_8$: C, 14.4; H, 0.6; Cl, 85.0. Found: C, 14.6; H, 0.7; Cl, 85.5.

Diethyl Fumarate (XXIII).—The mixture of 1 g of XXI and 3 ml of concentrated sulfuric acid was heated at 60–80° over a period of 16 hr, when 100 ml of ethanol was added and heating at reflux continued for an additional 24 hr. Ethanol (50 ml) was removed and the resulting reaction mixture was neutralized with aqueous Na_2CO_3. The neutralized solution was extracted several times with ether. The combined ether extractions were dried (Na_2SO_4); the solvent was removed under vacuum and the residue, 0.4 g (61.5%) of crude XXIII, was identified as follows: glpc and ir spectrum of XXIII were identical with those of an authentic sample, nmr (CCl_4) δ 6.79 (lit.[26] δ 6.83).

1,1,2,4,4,4-Hexachloro-1-buten-3-one (XXIV).—A solution of 313.5 g (1 mol) of XVI in 2000 ml of dry ether was prepared. Triethylamine, 101 g (1 mol), dissolved in 100 ml of dry ether was added with stirring at room temperature to the above solution. The reaction mixture was stirred for 15 min and suction filtered. The solid triethylammonium chloride was washed well with dry ether. The combined ether washings and the filtrate were evaporated to give a red liquid which was purified by distillation: bp 34° (0.01 mm); $n^{20}D$ 1.5300; d^{20}_4 1.6979; yield 267.4 g (96.5%); ir (film) main bands at 1745, 1585, 1488, 1159, 910, 840 and 690 cm^{-1}; uv max 205 mμ (ϵ 7139) and 245 (7430).

Anal. Calcd for C_4Cl_6O: C, 17.3; H, 0.0; Cl, 76.9. Found: C, 17.7; H, 0.2; Cl, 77.3.

1-Phenyl-4,5-dichloro-3-trichloromethylpyrazole (XXV).—To a solution of XXIV, 27.7 g (0.1 mol), in 200 ml of dry ether was added with stirring dropwise a solution of 21.6 g (0.2 mol) of phenylhydrazine in 50 ml of dry ether. The reaction mixture was stirred for additional 15 min and diluted with 200 ml of water. The organic layer was twice washed with 2 N sulfuric acid and dried ($CaCl_2$). Filtration and removal of ether gave a dark red viscous oil which was purified by distillation under vacuum to give 12.5 g (38%) of XXV, a pale yellow liquid: bp 144° (0.02 mm); $n^{20}D$ 1.6068; uv max 246 mμ (ϵ 10,300); nmr δ *ca.* 7.48 (phenyl H).

Anal. Calcd for $C_{10}H_5Cl_5N_2$: C, 36.3; H, 1.5; Cl, 53.7; N, 8.5. Found: C, 36.9; H, 1.7; Cl, 53.5; N, 8.5.

α,β,β-Trichloroacrylic Acid (XXVI).—Ketone XXIV, 2.77 g (0.01 mol), was added dropwise with stirring to 20 ml of 1 N sodium hydroxide at room temperature. After 2 hr, the reaction mixture was extracted with ether to remove chloroform. Acidification of the aqueous phase with concentrated hydrochloric acid gave a white crystalline solid which was collected and recrystallized from petroleum ether: yield 1.45 g (82%) of XXIV; mp 74° (lit.[27] mp 74–75°). The ether extract contained chloroform (glpc).

1,1,2,4,4,4-Hexachloro-1-buten-3-ol (XXVII).—To a solution of sodium borohydride, 2 g (52.9 mmol), in 80 ml of ethanol and 160 ml of water was added dropwise with stirring 55.4 g (0.2 mol) of XXIV. The temperature was maintained at 15–20° by external cooling with ice water. The reaction mixture was diluted with 100 ml of water and extracted several times with ether. The combined ether extractions were dried (Na_2SO_4). The solvent was removed under vacuum and the residual liquid was purified by distillation to give 39.8 g (71.6%) of XXVII: colorless liquid; bp 57° (0.01 mm) and 105° (9 mm); $n^{20}D$ 1.5486; d^{20}_4 1.7326; uv max 211 mμ (ϵ 9624); nmr (CCl_4) δ 4.14 (–OH), 5.48 (–CH).

Anal. Calcd for $C_4H_2Cl_6O$: C, 17.2; H, 0.7; Cl, 76.3. Found: C, 17.5; H, 1.0; Cl, 76.1.

***trans*-1,1,1,2,4,4,4-Heptachloro-2-butene (XXVIII).**—A solution of XXVII, 13.95 g (0.05 mol), in 25 ml of thionyl chloride was heated to reflux for 2 hr. Excess of thionyl chloride was removed under vacuum and the crude reaction product was distilled to give 13.6 g (90.3%) of colorless XXVIII: bp 105° (0.8 mm); $n^{20}D$ 1.5568; d^{20}_4 1.7812; estimated purity 95.3% (glpc); nmr (CCl_4) δ 6.57 (s).

Anal. Calcd for C_4HCl_7: C, 16.1; H, 0.3; Cl, 83.6. Found: C, 15.8; H, 0.6; Cl, 82.8.

Diethyl Chlorofumarate (XXIX).—A mixture of 8.5 g (28.6 mmol) of XXVIII and 10 ml of concentrated sulfuric acid was heated at 80° for 12 hr. Ethanol, 100 ml, was added and the reaction mixture was heated to reflux for a period of 8 hr. Water, 200 ml, was added to the brown reaction mixture, then the solution was neutralized with aqueous Na_2CO_3 and extracted with ether. The ether extract was dried and evaporated. The residue was distilled to give 2.85 g (48.2%) of XXIX: bp 112° (8 mm); $n^{20}D$ 1.4678; estimated purity 95.3% (glpc); nmr (CCl_4) δ 7.10 (s, =CH).

Anal. Calcd for $C_8H_{11}ClO_4$: C, 46.5; H, 5.3; Cl, 17.2. Found: C, 45.8; H, 5.4; Cl, 17.7.

Registry No.—I, 6900-33-0; III, 18767-18-5; IV, 18767-19-6; V, 18767-20-9; VI, 18767-21-0; XI, 15347-86-1; XV, 18767-23-2; XVI, 17334-13-3; XVIII, 18767-25-4; XXI, 18766-87-5; XXII, 18791-19-0; XXIV, 13340-11-9; XXV, 18767-27-6; XXVII, 18767-28-7; XXVIII, 18766-88-6; XXIX, 10302-94-0.

Acknowledgment.—The technical assistance of Mr. F. Görgen and valuable discussions with Mr. G. E. Pollard are gratefully acknowledged.

(26) N. S. Bhacca, L. F. Johnson, and J. N. Schooley, "High Resolution NMR Spectra Catalog," No. 213, Varian Associates, Palo Alto, Calif., 1962.

(27) Th. Zincke and A. Rohde, *Ann.*, **299**, 367 (1898).

Polychlorinated Ketones. II. Dechlorination of Highly Chlorinated Ketones with Trivalent Phosphorus Compounds[1]

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Highly chlorinated ketones undergo rapid α,β dechlorination when treated with an equivalent amount of triphenylphosphine, triphenyl phosphite or trialkyl phosphite. Decachloro-3-pentanone (I) reacted readily with triphenylphosphine or trimethyl phosphite (molar ratio 1:2) to give 1,1,2,4,5,5-hexachloro-1,4-pentadien-3-one (II). Decachloro-2-pentanone (VI) reacted analogously with triphenyl phosphite to give a mixture of the two geometrical isomeric 1,1,1,2,3,5,5,5-octachloro-2-penten-4-ones (VIIa and VIIb). Treatment of octachlorobutanone (IX) with triphenyl phosphite or triphenylphosphine (molar ratio 1:1) afforded 1,1,2,4,4,4-hexachloro-1-buten-3-one (X). With triphenylphosphine and IX (molar ratio 2:1) an enolphosphonium salt (XI) was formed which hydrolyzed spontaneously to give 1,1,2,4,4-pentachloro-1-buten-3-one (XII). With trialkyl phosphites and IX (molar ratio 2:1) dialkyl 1,1,3,4,4-pentachloro-1,4-butadien-2-yl phosphates (XVI) are obtained in addition to dialkylphosphorochloridates (IV) and alkyl chlorides (XVII). With trialkyl phosphites and X (molar ratio 1:1) XVI and XVII were obtained.

In connection with our work on chlorinated carbonyl compounds,[1] the reaction of highly chlorinated ketones with trivalent phosphorus compounds was studied. The reaction between trialkyl phosphites and α-halo ketones (Perkow reaction) has been considerably expanded in scope since its discovery and now embraces as coreactants for the trivalent phosphorus compound a large number of compound with replaceable halogen.[4,5a] Similarly, several α,β-dichloroaldehydes react normally with trialkyl phosphites to give vinyl phosphates.[6-9]

When the reaction was extended to α,β-dibrominated carbonyl compounds, however, it was found to take a different course in that the product containing the carbonyl moiety was not a vinyl phosphate or vinyl phosphonium salt, but was instead the debrominated carbonyl compound.[10-14] To the best of our knowledge, no higher α,β-halogenated carbonyl compounds have been employed in this reaction.

Our interest in investigating the reaction of highly chlorinated ketones with trivalent phosphorus compounds was to examine the nucleophilic reactivity of triphenylphosphine, triphenyl phosphite and trialkyl phosphites and determine the nature of the reaction products. Minor changes in structure often affect the choice between competing displacements on carbon and halogen and make it difficult to predict the nature of the products.[12] Nevertheless, in the case of perchlorinated ketones, the reactions with trivalent phosphorus compounds have been found to be less complex than anticipated. For example, decachloro-3-pentanone (I) with 2 mol equiv of triphenylphosphine in ether afforded 91.2% 1,1,2,4,5,5-hexachloro-1,4-pentadien-3-one (II) in addition to dichlorotriphenylphosphorane[15] (III). Trimethyl phosphite reacted much more vigorously with I to give 95.3% II in addition to methyl chloride and dimethyl phosphorochloridate (IVa) in almost quantitative yield. 1,1,2,4,4,5,5,5-Octachloro-1-penten-3-one has been shown to be an intermediate in this reaction (see Experimental Section). In analogy to the debromination of α,β-dibromocarbonyl compounds,[11] the dechlorination of I presumably proceeds *via* a concerted E2 mechanism. SN2 displacement of chlorine atoms was not observed. Reduction of II with sodium borohydride in aqueous ethanol afforded 1,1,2,4,5,5-hexachloro-1,4-pentadien-3-ol[16] (V).

The dechlorination of decachloro-2-pentanone (VI) with triphenyl phosphite in ether is much more sluggish, being complete after 1-hr reflux and leading to a mixture of the two geometrical isomeric 1,1,1,3,4,5,5,5-octachloro-3-penten-2-ones (VIIa and VIIb) (Scheme I) in addition to a reactive oil which appears to be dichlorotriphenoxyphosphorane (VIII) or its reaction products.[5b] The β elimination presumably involves neucleophilic attack on a positive α-chlorine atom. The *trans*-dechlorination of VI involves the conformer which is sterically more favored (eclipsed trichloroacetyl and chlorine). Because of the repulsion associated with eclipsing a trichloromethyl and trichloroacetyl group the other conformer is less favored.[17]

The reaction of octachlorobutanone (IX) with triphenyl phosphite in the presence or absence of ether was also found to give the dechlorinated product. 1,1,2,4,4,4-Hexachloro-1-buten-3-one (X) was formed in 82–96% yield. Similarly, ketone IX and triphenylphosphine afforded X and III. Ketone X is

(1) Previous paper: K. Pilgram and H. Ohse, *J. Org. Chem.*, **34**, 1586 (1969).

(2) To whom correspondence should be addressed at the Shell Development Co.

(3) Farbenfabriken Bayer, Werk Dormagen, Germany.

(4) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).

(5) B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, N. Y., 1965: (a) p 178; (b) p 143.

(6) E. C. Ladd and M. P. Harvey, U. S. Patent 2,631,162 (1949); *Chem. Abstr.*, **48**, 7048 (1954).

(7) R. R. Whetstone and D. Harman, U. S. Patent 2,765,331 (1952); *Chem. Abstr.*, **51**, 5816 (1957).

(8) W. Perkow, E. W. Krockow, and K. Knoevenagel, *Ber.*, **88**, 662 (1952).

(9) J. F. Allen and O. H. Johnson, *J. Amer. Chem. Soc.*, **77**, 2871 (1955).

(10) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem. USSR*, **26**, (1956); *Chem. Abstr.*, **51**, 1822 (1957).

(11) V. S. Abramov and S. Pall, *Tr. Kazansk. Khim. Tekhnol. Inst.*, **23**, 105 (1957); *Chem. Abstr.*, **52**, 9949 (1958).

(12) S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3959 (1961).

(13) A. J. Speziale and C. C. Tung, *ibid.*, **28**, 1353 (1963).

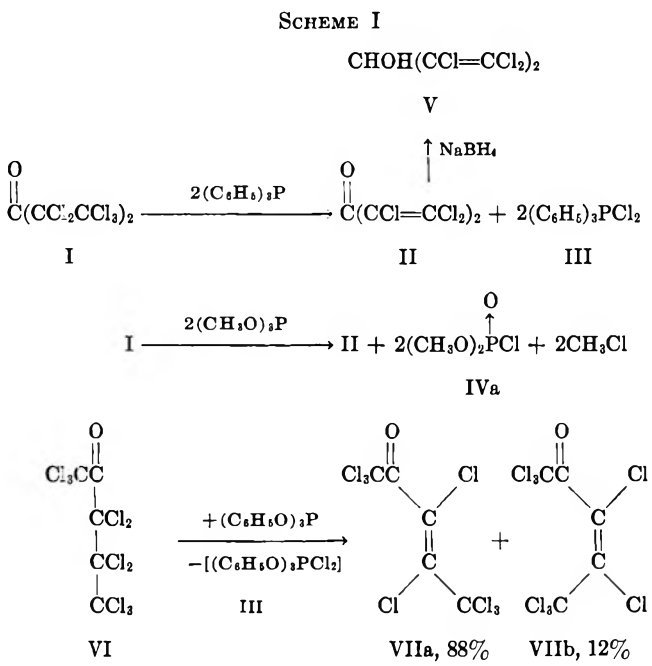
(14) C. C. Tung and A. J. Speziale, *ibid.*, **28**, 1521 (1963).

(15) Their spectrum was identical with that of an authentic sample prepared from triphenylphosphine and chlorine. In most cases III was not isolated; it is advantageous to hydrolyse it to triphenylphosphine oxide and hydrogen chloride before isolating the dechlorinated ketone.

(16) A. Roedig and H. J. Becker, *Ber.*, **89**, 1726 (1956).

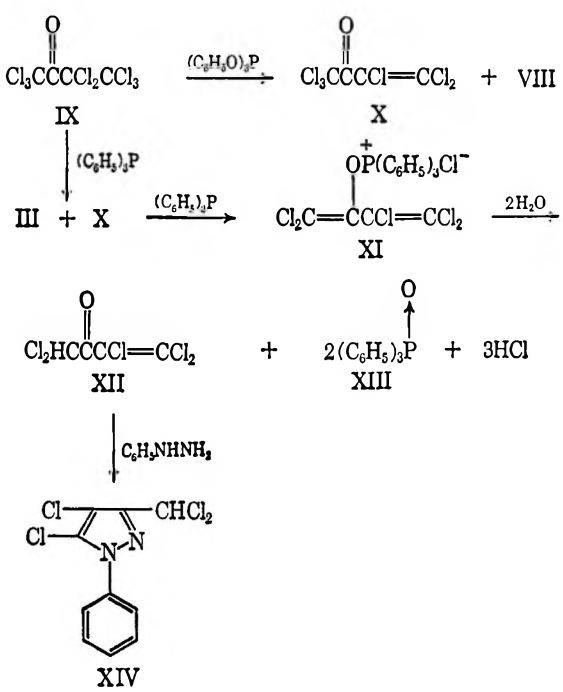
(17) M. Brown and B. W. Bremer [*J. Org. Chem.*, **32**, 1655 (1967)] have found that the nature of the elimination of bromine from vicinal dihalides by sodium selenide is a stereospecific *trans* elimination.

SCHEME I



identical with the product obtained by dehydrochlorination of 1,1,1,3,4,4,4-heptachloro-2-butanone.[1] In contrast to triphenyl phosphite which is unreactive to X,[18] 1 more mol equiv of triphenylphosphine was allowed to react with X to form vinyl phosphonium salt XI showing that triphenylphosphine is a stronger nucleophile than triphenyl phosphite (Scheme II).

SCHEME II



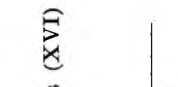
Several halogenated compounds, especially α-halocarbonyl compounds which give particularly stable carbanions, are known to form quasiphosphonium salts.[19]

(18) On dechlorination of IX, an excess of triphenyl phosphite does not alter the yield of X.

(19) H. Hoffmann and H. J. Diehr, *Angew. Chem.*, **76**, 948 (1964); *Angew. Chem. Intern. Ed. Engl.*, **3**, 742 (1964).

TABLE I

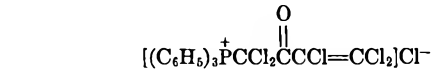
DIALKYL 1,1,3,4,4-PENTACHLORO-1,4-BUTADIEN-2-YL PHOSPHATES (XVI)



R	% yield	Bp, °C (mm)	Method of prepn	Calcd, % C	H	Cl	P	Found, % C	H	Cl	P
CH_3	95.5	85–86 (0.01)	A[a]	20.5	1.7	50.7	8.9	21.0	1.6	51.0	8.9
	76.0	88–89 (0.01)	B[b]					20.9	1.9	50.6	9.1
C_2H_5	96.8	98–99 (0.01)	A	25.4	2.6	46.5	8.2	25.6	2.8	46.6	8.0
	83.0	98–99 (0.01)	B					25.6	2.8	46.5	8.0
$CH(CH_3)_2$	94.5	99–100 (0.01)	A	29.5	3.4	43.8	7.6	31.3	4.0	42.4	8.2
	96.2	108 (0.01)	B					30.1	3.9	41.9	8.5
$CH_2CH{=}CH_2$	75.2	108–109 (0.03)	A	29.2	2.4	44.2	7.7	29.4	2.5	44.3	8.0
n-C_4H_9	74.0	121–122 (0.004)	B	33.2	4.1	40.8	7.2	33.6	4.1	40.8	7.4
n-C_5H_{11}	31.0	104–110 (0.001)	B	36.4	4.8	38.3	6.7	37.2	5.2	36.8	6.6
n-C_6H_{13}	86.0	170 (0.004)	A	39.2	5.3	36.2	6.3	40.5	5.9	33.4	6.7

[a] From X and $(RO)_3P$ (molar ratio 1:1). [b] From IX and $(RO)_3P$ (molar ratio 1:2).

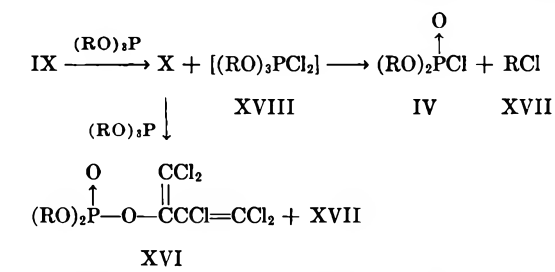
The structure of XI was proved by its quantitative conversion into 1,1,2,4,4-pentachloro-1-buten-3-one[20] (XII), triphenylphosphine oxide (XIII) and hydrogen chloride by addition of water. With phenylhydrazine and XII, the known pyrazole XIV is formed.[21] The alternate competitive reaction, formation of the β-ketophosphonium salt XV, was not observed. The



XV

absence of salt XV that would result from SN2 displacement of chlorine we regard as supporting evidence for the postulated mechanism.[22]

Trialkyl phosphites, $(RO)_3P$, reacted exothermically with IX (molar ratio 2:1) in ether and afforded dialkyl 1,1,3,4,4-pentachloro-1,4-butadien-2-yl phosphates (XVI), dialkyl phosphorochloridates (IV) and alkyl chlorides (XVII). Reaction of X with trialkyl phosphites gave XVI directly (see Table I). Again,



the anticipated attack of phosphorus on α-chlorine occurred, followed by simultaneous elimination of chloride ion to give X and the products of a rapid Arbuzov rearrangement of XVIII. A second mole equivalent of trialkyl phosphite was allowed to react with X *via* the Perkow reaction to give eventually the vinyl phosphates XVI in addition to alkyl chlorides (XVII).

Experimental Section

Melting points were taken in capillary tubes. They as well as boiling points are uncorrected. Gas chromatograms were recorded on a Model 500 linear programmed temperature gas chromatograph (F & M Scientific Corp., Avondale, Pa.). Nuclear magnetic resonance spectra were obtained on a KIS-2, 90-Mcps spectrometer, using hexadeuterioacetone as solvent and TMS as internal standard. Ultraviolet spectra were obtained in methanol with a Cary 14 spectrophotometer (200–350 mμ). Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer.

Materials.—Triphenylphosphine, triphenylphosphite, and trimethyl- and triethylphosphite were obtained commercially and recrystallized or redistilled before use. Triallyl, triisopropyl, tributyl, triamyl, and trihexyl phosphite were prepared from the corresponding alcohols and phosphorus trichloride in the presence of N,N-dimethyl- or -diethylaniline in ether according to published methods.

Dechlorination of Decachloro-3-pentanone (I). A. With Triphenylphosphine.—To a stirred solution (22°) of 86.2 g (0.2 mol) of I[23] in 200 ml of ether was added gradually a solution of 104.8 g (0.4 mol) of triphenylphosphine in 1000 ml of ether. The reaction was exothermic and the temperature rose to 35°. An ir spectrum indicated the mixture to contain II and III. After the reaction mixture was allowed to cool to room temperature, 500 ml of water was added dropwise with stirring. (*Caution:* during addition of the first milliliter of water, the reaction is vigorous.) Most of the triphenylphosphine oxide precipitated and was removed by filtration. The ether solution was dried ($CaCl_2$) and evaporated to dryness. The yellow residual oil was purified by distillation under vacuum to give 52.2 g (91.2%) of 1,1,2,4,5,5-hexachloro-1,4-pentadien-3-one (II): bp 69° (0.3 mm) [lit.[16] bp 94–95° (0.6 mm)]; $n^{20}D$ 1.5661; d^{20}_4 1.6963; ir (thin film) 5.73 (C=O) and 6.3 μ (C=C).

Anal. Calcd for C_5Cl_6O: C, 20.8; H, 0.0; Cl, 73.7. Found: C, 21.1; H, 0.2; Cl, 73.9.

B. With Trimethyl Phosphite.—Trimethyl phosphite, 49.6 g (0.4 mol), was dissolved in 50 ml of ether and then added dropwise with stirring to I, 86.2 g (0.2 mol), in 200 ml of ether. The reaction was vigorous and the flask was cooled with ice water. Methyl chloride was condensed in a cold trap. After 0.2 mol of trimethyl phosphite had been added, the reaction mixture contained dimethyl phosphorochloridate (IVa) and the following ketones: I (17.5%), 1,1,2,4,4,5,5,5-octachloro-1-penten-3-one (62.8%), identified by glpc comparison with an authentic sample,[16] and II (19.7%). After the second portion of trimethyl phosphite had been added, only II and IVa were detected by glpc. The cold trap contained 24.7 g (95%) of methyl chloride. Ether was removed from the reaction mixture and the products were separated by distillation under vacuum to give 57.6 g (99.6%) of dimethyl phosphorochloridate (IVa): bp 60° (8 mm); $n^{20}D$ 1.4184.

Anal. Calcd for $C_2H_6ClO_3P$: Cl, 24.6; P, 21.4. Found: Cl, 25.8; P, 20.5.

The second fraction distilled at 66° (0.005 mm) and afforded 55.1 g (95.3%) of II as light yellow oil which was identical with the product obtained in A.

1,1,2,4,5,5-Hexachloro-1,4-pentadien-3-ol (V).—To a solution of sodium borohydride, 1.0 g, in 80 ml of water and 20 ml of ethanol was added dropwise with stirring a solution of 28.9 g of II in 20 ml of ethanol. The flask was cooled with ice water during the addition. After 1 hr, 250 ml of water was added and the reaction mixture was thoroughly extracted with ether. The combined extractions were dried (Na_2SO_4) and evaporated to dryness. The residue, 29.0 g, was recrystallized from petroleum ether (bp 30–60°) to give 13.0 g (44.7%) of 1,1,2,4,5,5-hexachloro-1,4-pentadien-3-ol (V) as white crystalline solid, mp 53–53.5° (lit.[16] mp 53–53.5°).

Anal. Calcd for $C_5H_2Cl_6O$: C, 20.7; H, 0.7; Cl, 73.2. Found: C, 20.6; H, 0.9; Cl, 73.1.

Dechlorination of Decachloro-2-pentanone (VI).—To a solution of 129.3 g (0.3 mol) of VI in 100 ml of ether was added 93.0 g (0.3 mol) of triphenyl phosphite dissolved in 50 ml of ether. The mixture was heated to reflux for 1 hr. Ether was removed and the residual oil was distilled under vacuum at 90–120° (1–0.1 mm) to give 80 g of a crude material which was redistilled at 88–89° (0.05 mm) to give 73.0 g (67.6%) of 1,1,1,3,4,5,5,5-octachloro-3-penten-2-one (VIIa + VIIb). Glpc indicated a mixture of two compounds in a ratio of 88:12. The ir spectrum indicated the absence of CH bands and showed strong absorption at 1750 (C=O) and 1595 cm^{-1} (C=C).

Anal. Calcd for C_5Cl_8O: Cl, 78.9. Found: Cl, 78.6.

Dechlorination of Octachlorobutanone (IX). A. With Triphenyl Phosphite in Ether.—To a solution of IX, 174 g (0.5 mol), in 400 ml of ether was added dropwise with stirring triphenyl phosphite, 155 g (0.5 mol). Exothermicity was not observed, but the color of the solution changed to a grayish green. The solvent was removed under vacuum and the reaction mixture was distilled through a 30-cm Vigreux column. The temperature of the oil bath was gradually raised to 130° and the fraction at 40–50° (0.2 mm), 140 g, was redistilled at 44° (0.2 mm) to give 114 g (82.3%) of 1,1,2,4,4,4-hexachloro-1-buten-3-one (X): $n^{20}D$ 1.5321; ir (thin film) 1745 (C=O) and 1585 cm^{-1} (C=C); uv max 205 mμ (ϵ 7139) and 245 (7430).

Anal. Calcd for C_4Cl_6O: Cl, 76.9. Found: Cl, 76.8.

The residue which contained dichlorotriphenoxyphosphorane (VIII) or its reaction products[6b] solidified in the flask and was readily soluble in water.

B. Without Ether.—When triphenyl phosphite, 310 g (1.0 mol), and 174 g (0.5 mol) of IX were mixed at 22°, the temperature rose briefly to 40°. The mixture was immediately dis-

(20) The preparation of XII by acid-catalyzed thermolysis of the corresponding di(*sec*-butyl)vinyl phosphate analogous to XVI has been described recently: K. Pilgram and H. Ohse, *Angew. Chem.*, **78**, 820 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 836 (1966).

(21) A. Roedig and H. J. Becker, *Ann.*, **597**, 214 (1956).

(22) Vinylphosphonium salts are extremely sensitive to solvolytic reagents and decompose with water to give α-monodehalogenated carbonyl compounds whereas β-ketophosphonium salts are stable under neutral and acidic conditions.[19]

(23) M. Geiger, E. Usteri, and Ch. Grünacher, *Helv. Chim. Acta.*, **34**, 1340 (1951).

tilled under vacuum. The temperature of the oil bath was gradually raised to 160°. A forerun, 20 g, bp 39° (0.15 mm), was followed by the main fraction which afforded 132.7 g (96.3%) of X: bp 42–44° (0.15 mm); $n^{20}D$ 1.5324. The ir spectrum was superimposable with that of X, obtained above.

C. With Triphenylphosphine in Ether.—A solution of IX, 34.8 g (0.1 mol), in 50 ml of ether was added dropwise with stirring to a solution of triphenylphosphine, 52.4 g (0.2 mol), in 1000 ml of ether at 25–35°. After the addition was complete, no starting material could be detected in solution by means of glpc. Water, 500 ml, was added dropwise with stirring. Triphenylphosphine oxide precipitated out shortly afterward and was removed by suction-filtration. The ether layer was dried ($CaCl_2$) and evaporated to dryness. The crude product was purified by distillation to give 39.8 g (82.1%) of 1,1,2,4,4-pentachloro-1-buten-3-one (XII): bp 89° (9 mm); $n^{20}D$ 1.5440; d^{20}_4 1.6628 [lit.[24] bp 99–100° (13 mm); $n^{20}D$ 1.4442]; ir (film) 5.9 (C=O) and 6.5 μ (C=O); uv max 212 mμ (ε 7953) and 271 (3071); nmr δ 6.76.

Anal. Calcd for C_4HCl_5O: C, 19.8; H, 0.4; Cl, 73.2. Found: C, 20.0; H, 0.7; Cl, 73.2.

1-Phenyl-4,5-dichloro-3-dichloromethylpyrazole (XIV).—To a solution of 24.25 g (0.1 mol) of XII in 300 ml of ether was added dropwise a solution of 21.6 g (0.2 mol) of phenylhydrazine in 50 ml of ether. After 30 min 200 ml of water was added. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude pyrazole was purified by distillation under vacuum to give 12.43 g (42%) of pure XIV, which solidified: bp 142° (0.4 mm); mp 55–55.5° [lit.[21] mp 57.5–58°; bp 155° (0.8 mm)]; uv max 247 mμ (ε 11,566); nmr δ 7.00 (aliphatic H) and 7.45 (aromatic H).

Anal. Calcd for $C_{10}H_6Cl_4N_2$: C, 40.5; H, 2.0; Cl, 47.9; N, 9.5. Found: C, 40.4; H, 2.2; Cl, 47.5; N, 9.7.

(24) A. Roedig and H. J. Becker, *Ber.*, **89**, 906 (1956).

Reaction of Octachlorobutanone (IX) and 1,1,2,4,4,4-Hexachloro-1-buten-3-one (X) with Trialkyl Phosphites.—The results are summarized in Table I. The general procedures are illustrated by the reactions of IX and X with trimethyl phosphite.

A.—To a stirred solution of IX, 34.8 g (0.1 mol), in 50 ml of ether was added dropwise trimethyl phosphite, 24.8 g (0.2 mol). The reaction was exothermic and the ether started to boil. The reaction mixture was heated to reflux for 10 min. Ether was removed under vacuum and the residual oil was distilled to give 13.0 g (90%) of dimethyl phosphorochloridate (IVa), bp 60–62° (8 mm), identical (glpc) with the product obtained by dechlorination of I with trimethyl phosphite (see above). The vinyl phosphate XVI (R = CH_3) distilled at 88–89° (0.01 mm): 26.6 g (76%); $n^{20}D$ 1.5173; d^{20}_4 1.5869. The ester is a colorless liquid and turns light yellow on storage for several weeks when exposed to sunlight: uv max 208 mμ (ε 20,088) and max 247 (7375); ir (film) 6.35 (C=C) and 7.7 μ (P→O).

B.—To a stirred solution of X, 10.65 g (0.0385 mol) in 20 ml of ether, was added trimethyl phosphite, 6.2 g (0.05 mol), dissolved in 20 ml of ether. The reaction was exothermic. Ether was removed and the residual oil was purified by distillation to give 12.9 g (95.5%) of XVI (R = CH_3): $n^{20}D$ 1.5163; d^{20}_4 1.5899; uv and ir spectrum were identical with the product obtained in A.

Registry No.—II, 13340-09-5; IVa, 813-77-4; V, 18791-16-7; VIIa, 18766-86-4; VIIb, 18791-17-8; X, 13340-11-9; XII, 13340-10-8; XIV, 18767-09-4; XVI (R = Me), 18767-10-7; XVI (R = C_2H_5), 18767-11-8; XVI [R = $CH(CH_3)_2$], 18767-12-9; XVI (R = $CH_2CH{=}CH_2$), 18767-13-0; XVI (R = n-C_4H_9), 18767-14-1; XVI (R = n-C_5H_{11}), 18767-15-2; XVI (R = n-C_6H_{13}), 18791-18-9.

The Reactions of Triphenylphosphine with α-Halobenzyl Phenyl Ketones and with α-Mesyloxybenzyl Phenyl Ketone[1]

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The reactions of α-bromobenzyl phenyl ketone (**11**) and α-chlorobenzyl phenyl ketone (**14**) with triphenylphosphine are described. Both enol phosphonium and ketophosphonium halides are formed in ratios dependent upon reaction conditions. The enol phosphonium halides are solvolyzed to deoxybenzoin (**16**) and converted into diphenylacetylene (**17**). Debromination of **11** to **16** occurs with triphenylphosphine in the presence of methanol. α-Mesyloxybenzyl phenyl ketone (**19**) reacts with triphenylphosphine to give only the α-ketophosphonium mesylate *via* displacement of mesylate ion. Probable mechanisms for the observed reactions and the relationships of these reactions to the reactions of other α-halo ketones with phosphines are discussed.

Recent work has shown that the reactions of triphenylphosphine with α-bromoacetophenone (**1**) and with α-bromopropiophenone (**2**) give the corresponding α-ketotriphenylphosphonium bromides in aprotic solvents.[3,4] Our kinetic studies indicate that both **1** and **2** probably react with triphenylphosphine *via* displacement of bromide ion under aprotic conditions.[5,6]

We and others have previously postulated that the reactions of certain α-halo ketones such as 2-bromodimedone and the α-halobenzyl phenyl ketones (desyl halides) with triphenylphosphine can involve the formation of enol phosphonium salts.[7,8] Enol phosphonium salts including **7–10** have been isolated from the reaction of triphenylphosphine with chlorobenzhydryl phenyl ketone **3**,[9] the corresponding bromo ketone **4**,[10a] dibromobenzyl phenyl ketone **5**,[10b] dibromopropiophenone (**6**), and from other α-dihalo ketones[10a] (Scheme I).

It has been suggested that enol phosphonium salts may arise *via* displacement by triphenylphosphine on halogen of an α-halo ketone to give an enolate halotri-

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(2) To whom correspondence should be addressed at the Belfer Graduate School of Science, Yeshiva University.

(3) (a) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963); (b) I. J. Borowitz, K. C. Kirby, Jr., and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(4) (a) F. Ramirez and S. Dershowitz, *ibid.*, **22**, 41 (1957); (b) A. V. Dombrovskii and M. I. Shevchuk, *Zh. Obshch. Khim.*, **33**, 1263 (1963).

(5) I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

(6) H. Parnes, Yeshiva University, unpublished results.

(7) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, 471 (1962).

(8) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

(9) R. D. Partos and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 5068 (1965).

(10) (a) K. C. Kirby, Jr., Yeshiva University, unpublished results; (b) P. E. Rusek, Yeshiva University, unpublished results.

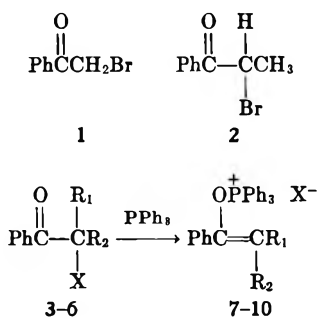
TABLE I

THE REACTIONS OF α-BROMOBENZYL PHENYL KETONE WITH TRIPHENYLPHOSPHINE

Reaction conditions	Time	Yields, %[a] α-Ketophosphonium bromide	Enol phosphonium bromide	Deoxybenzoin	Diphenylacetylene	Triphenylphosphine oxide
Benzene[b,c] (0.13 *M*)	24 hr	58		34[d]	4	44
Benzene–methanol[b]	23 hr	0		100[d]		100
Acetonitrile[b]	4 days	29		49	19	
Glyme[b] (1.3 *M*)	24 hr	79		15		
Glyme, room temp	2 weeks	13	73[f,g]			
Acetonitrile[e] (0.16 *M*)	7 days	21	70[f,g]	9		
Nitromethane[e]	7 days	15	70[f,g]	15		
Glyme–methanol[e]	24 hr			100[f]		100[f]
Nitromethane–methanol[e]	24 hr			100[f]		100[f]
Acetonitrile–methanol[e]	24 hr			100[f]		100[f]

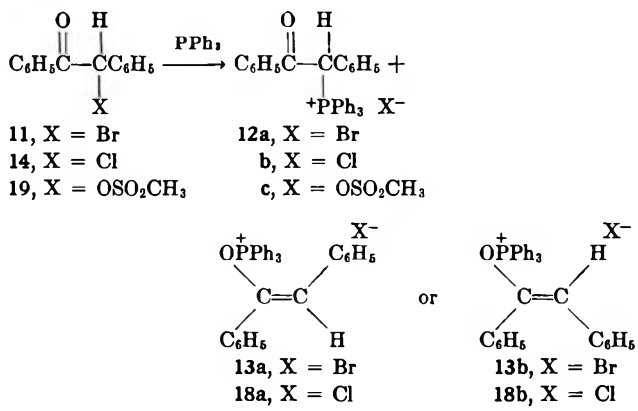
[a] 1.0–1.1 equiv of PPh_3 was used. Isolated yield unless otherwise indicated. [b] At reflux. [c] Same result from reaction in glyme (24 hr) or in toluene (24, 48 hr) at reflux. [d] By uv or vpc analysis. [e] At room temperature. [f] By nmr analysis. [g] Actually isolated.

SCHEME I



3, 7, X = Cl; $R_1 = R_2$ = Ph
4, 8, X = Br; $R_1 = R_2$ = Ph
5, 9, X = R_1 = Br; R_2 = Ph
6, 10, X = R_1 = Br; R_2 = CH_3

SCHEME II



phenylphosphonium ion pair. Such an ion pair could then recombine to give the observed enol phosphonium salt.[7,11] The actual mechanism of enol phosphonium salt formation has remained unsettled. It is being investigated by us with the aid of the related reactions of appropriate α-halo ketones with optically active methylpropylphenylphosphine.[12]

We now report our results on the reactions of triphenylphosphine with the α-halobenzyl phenyl ketones and with α-mesyloxybenzyl phenyl ketone. Ketophosphonium and enol phosphonium salts as well as derived products are formed in these reactions.

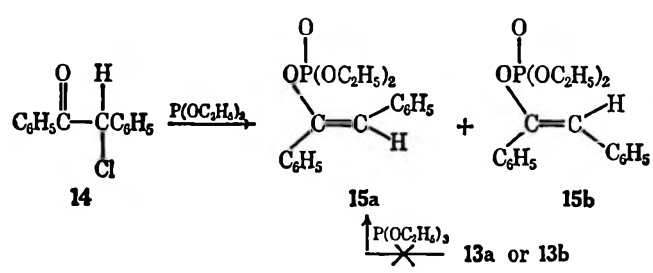
Results and Discussion

The Reactions of α-Bromobenzyl Phenyl Ketone.—α-Bromobenzyl phenyl ketone (desyl bromide) **11** reacts with triphenylphosphine in various solvents at room temperature (0.13–0.16 *M*) to give small yields (5–21%) of the α-ketophosphonium bromide **12** (Table I). High yields (58–85%) of **12** are obtained at higher temperature (80–111°) or with higher concentrations of the reagents. The best procedure for obtaining a high yield of **12** (79–85%) involves reaction of **11** with triphenylphosphine (1.3 *M* each) in dimethoxyethane (glyme) at reflux temperature (Scheme II).

The room-temperature reactions of **11** with triphenylphosphine, as followed by nmr spectroscopy, give the enol phosphonium bromide **13** as the main product (70–95%). The enol phosphonium bromide exhibits a vinyl proton doublet at τ 3.38 with J_{PH} = 1.8 Hz. The presence of one vinyl proton doublet probably indicates that only one isomer of **13** is present. It is anticipated that if both geometric isomers of **13** were present two vinyl proton doublets with different J_{PH} values would be observed. Two doublets are observed for several enol phosphates derived from the reactions of α-halo ketones with triethyl phosphite.[13] Thus α-chlorobenzyl phenyl ketone **14** reacts with triethyl phosphite to give a 1:2 ratio of **15b**:**15a** with vinyl doublets at τ 3.31 (J = 2.5 Hz) and 3.65 (J = 1.0 Hz).[14] Our evidence indicates that the smaller J_{HP} value most probably belongs to the *trans* isomer **15a**.

An attempt to convert **13** to **15a** and/or **15b** directly by treatment with triethyl phosphite was unsuccessful

SCHEME III



(11) A. J. Speziale and L. J. Taylor, *J. Org. Chem.*, **31**, 2450 (1966).

(12) (a) O. Korpiun and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 4784 (1967); (b) D. B. Denney and N. G. Adin, *Tetrahedron Lett.*, 2569 (1966); (c) L. Horner and H. Winkler, *ibid.*, 455 (1965).

(13) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(14) S. Firstenberg, Yeshiva University, unpublished results.

TABLE II
THE REACTIONS OF α-CHLOROBENZYL PHENYL KETONE (14) WITH TRIPHENYLPHOSPHINE

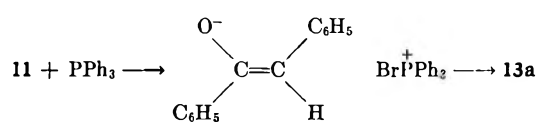
Reaction conditions	Time	Yields, %[a] α-Ketophosphonium bromide	Enol phosphonium bromide	Diphenylacetylene	Deoxybenzoin	Triphenylphosphine oxide
Benzene, reflux	20 hr	12[b,c]		17	31	82
Acetonitrile, reflux	10 days	31.5		14	41	*e*
Glyme, reflux	24 hr	12			78	*e*
Methanol[d]	38 days	41			*e*	*e*
Glyme[d]	14 days		100,[f] 85[g]			
Acetonitrile[d]	7 days	50[f]	50[f]			*e*
Nitromethane[d]	7 days	53–61			29	*e*
Glyme–methanol[d]	14 days				86	*e*
Acetonitrile–methanol[d]	14 days	48			32	*e*
Nitromethane–methanol[d]	14 days	56			33	*e*

[a] 1.0–1.1 equiv of PPh_3 was used. Isolated yield unless otherwise indicated. [b] Same yield from reaction in toluene (24 hr) at reflux. [c] Unreacted **14** was recovered (25%). [d] At room temperature. [e] Present by tlc. [f] Yield by nmr. [g] Actually isolated.

(Scheme III). The displacement of triphenylphosphine from an enol phosphonium salt with the more nucleophilic diethylphenylphosphine has been noted.[15] We have successfully used tributylphosphine in such a displacement (see Experimental Section). Even though displacement by triethyl phosphite should irreversibly lead to an enol phosphate, the poorer nucleophilicity of the phosphite when compared with that of triphenylphosphine[16] renders such displacement unlikely.

While there is yet no firm evidence for the stereochemical assignment for **13** we favor the *trans* geometry of **13a** on the basis of the observed J_{PH} value of 1.8 Hz and mechanistic reasoning as follows. If enol phosphonium salts are formed *via* the recombination of enolate halotriphenylphosphonium ion pairs then *trans* geometry is expected for **13** since the enolate of deoxybenzoin should be more stable in the *trans* configuration and should react in this configuration (Scheme IV).

SCHEME IV

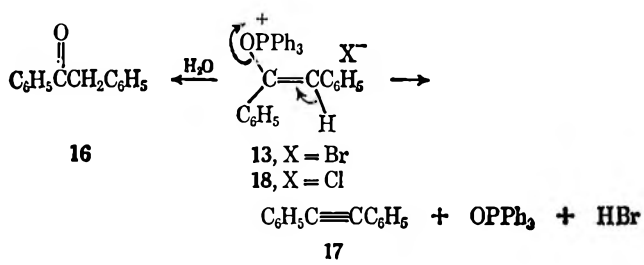


A similar argument can be made for the conversion of **14** into **18a.**

While the room temperature reactions of **11** with triphenylphosphine give only **12** and **13** the higher temperature reactions give **12** and several products derived from **13,** *i.e.*, deoxybenzoin (**16**) and diphenylacetylene (**17**). A number of enol phosphonium salts have been postulated to be or actually are solvolyzed by water to give the corresponding ketone.[9,10,17] We believe that the presence of **16** in our reactions is due to the hydrolysis of **13** by residual moisture in the reaction system or by hydrolysis during work-up.

The formation of **17** is of special interest in that it indicates a synthetic use for enol phosphonium salts. We[7] and others[17,18] have postulated that the previously observed[18,19] formation of **17** from **14** is *via* the enol phosphonium chloride **18.** We demonstrate as will follow that **17** does form from **18,** although to a small extent. Our evidence is sufficient to state that the formation of **17** from **11** is *via* **13** (Scheme V).

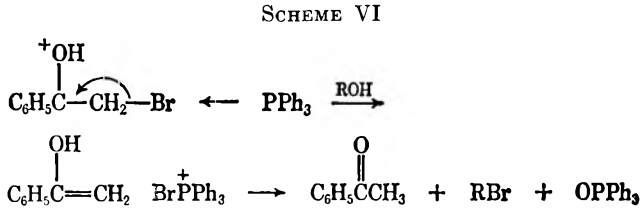
SCHEME V



The debromination of **11** to **16** with triphenylphosphine in the presence of methanol is quantitative in nonpolar or polar solvents (Table I). The debromination of α-bromo ketones by triphenylphosphine and a protic species has been found to be a general reaction[3,7,17,20a] failing only in the case of α-bromocamphor which presents an especially hindered situation.[15,20b]

Our most recent work[6] indicates that the debromination reaction is acid catalyzed in several cases including **2** and **11** and that it most probably involves a change of mechanism from the SN2 type of pathway which is involved in α-ketophosphonium salt formation from **1** or **2**[5,6] (Scheme VI).

SCHEME VI



It now appears that the debromination reaction probably involves attack by phosphine on the bromine of a protonated α-bromo ketone.[21]

The Reactions of α-Chlorobenzyl Phenyl Ketone (14).—The reactions of **14** with triphenylphosphine are summarized in Table II. Enol phosphonium chloride

(15) H. Hoffmann, *Angew. Chem. Intern. Ed. Engl.*, **3**, 737 (1964).
(16) G. Aksnes and D. Aksnes, *Acta Chem. Scand.*, **18**, 38 (1964).
(17) H. Hoffmann and H. J. Diehr, *Tetrahedron Lett.*, 583 (1962).
(18) S. Trippett, *J. Chem. Soc.*, 2337 (1962).
(19) S. Trippett and D. M. Walker, *ibid.*, 2976 (1960).
(20) I. J. Borowitz, K. C. Kirby, Jr., P. E. Rusek, and R. Virkhaus, *J. Org. Chem.*, **33**, 3686 (1968); (b) G. Gonis, Lehigh University, unpublished results.
(21) Our kinetic studies on the debromination reaction are in progress and will be reported elsewhere.

18 is the only product in glyme at room temperature. Reaction in polar solvents, acetonitrile or nitromethane, at room temperature gives 50–61% yields of the ketophosphonium chloride **12b**. The trend toward higher yields of ketophosphonium salt in reactions in polar solvents or those done at higher temperatures in nonpolar solvents noted for **11** is also evident for **14**. Thus reaction of **14** with triphenylphosphine in glyme, benzene, or toluene at reflux gives 12% **12b** as compared with none in glyme at room temperature.

Reaction of **14** with triphenylphosphine in the presence of protic species generally leads to about the same yields of **12b** as do the corresponding reactions in the absence of a protic species. It appears that the lack of dehalogenation in this case is related to the reactions of α-chloracetophenone,[3a] α-chloroacetone,[3a] or α-chloropropiophenone[10b] wherein the yields of α-ketophosphonium chloride are not significantly decreased by the initial presence of a protic species; *i.e.*, displacement of chloride ion occurs even in the presence of protic species.

The yields of desoxybenzoin observed in all of the reactions probably arises from the secondary hydrolysis of the enol phosphonium chloride which forms to some extent under all of the conditions studied. Evidence for the presence of the enol phosphonium chloride in room temperature reactions is based on proton nmr measurements and direct isolation of **18** (see the Experimental Section).

Diphenylacetylene is a minor product in the reactions of **14** with triphenylphosphine. We have not obtained the high yield (90%) of **17** from **14** as noted by Trippett and Walker.[19]

The recovery of starting material in the benzene reaction indicates that **14** reacts more slowly with triphenylphosphine than does **11**. This reactivity difference of bromo ketone > chloro ketone has been noted for numerous sets of α-bromo and α-chloro ketones in reaction with triphenylphosphine.[6,22]

We note that the presence of electron-withdrawing groups on the carbon bearing the halogen of an α-halo ketone enhances enol phosphonium salt formation. Thus, while chloroacetophenone and chloropropiophenone react with triphenylphosphine to give ketophosphonium chlorides, **14** gives both enol and ketophosphonium chlorides and α-chlorobenzhydryl phenyl ketone (**3**) gives only enol phosphonium chloride.[9] A similar distribution of products exists for the corresponding α-bromo ketones.[3,10b]

We believe that the above results are best explained by mechanistic pathways involving SN2 type of displacement of halide ion for the ketophosphonium halides, and attack on halogen followed by recombination of the resultant ion pair for the enol phosphonium halides.[23] The latter pathway will be elaborated upon in the next section of our Discussion. Attack on halogen is electronically enhanced by electron-withdrawing phenyl groups while displacement of halide ion is sterically retarded by them.

The major difference between the α-bromo ketone and the α-chloro ketone series is that the initial presence of protic species causes all of the α-bromo ketones to be debrominated completely while the chloro ketones still give α-ketophosphonium chloride formation. We presume that attack on bromine by triphenylphosphine is a more facile process than attack on chlorine since the latter is less polarizable, *i.e.*, not so "soft" as is bromine.[24]

The Reactions of α-Mesyloxybenzyl Phenyl Ketone (19).—Reaction of benzoin with methanesulfonyl chloride and triethylamine gives **19** in 69% yield. Reaction of **19** with triphenylphosphine in glyme at reflux gives the α-ketophosphonium mesylate **12c** in 81% yield. No other products are noted in this reaction which is the method of choice for the preparation of **12**. The yield of **12c** is not significantly decreased (80%) when **19** is treated with triphenylphosphine in a 4:1 mixture of glyme–methanol. Thus these reactions, as those of other α-keto mesylates with triphenylphosphine, involve simple displacement of mesylate ion. The α-keto mesylate reactions thus serve as simplified models for the more complex reactions of the comparable α-halo ketones with triphenylphosphine.

The lack of enol phosphonium salt formation from **19**, when compared with the behavior of **11** and **14**, again suggests that attack on halogen is involved in enol phosphonium salt formation. This is especially so since **19** reacts more slowly with triphenylphosphine than does **11** or **14**; *i.e.*, the possibility that the clean formation of **12c** from **19** merely involves a faster SN2-type reaction than is found for **11** or **14** is eliminated. It appears that other pathways are available to **11** or **14** that are not available to **19**. The most likely of these pathways is attack on halogen (Scheme IV).

Attack on oxygen by "soft" phosphorus, while found in certain cases where there is really no competitive alternative,[25] is an unlikely process for monohalo ketones. This is due to the lack of polarization for the oxygen atom which is "hard" as compared with the polarizable or "soft" bromine or chlorine atom.[24] Enol phosphonium salts may conceivably be formed by attack of triphenylphosphine at carbonyl oxygen[18,26] or by addition to carbonyl carbon and rearrangement of the phosphorus moiety to oxygen (as suggested by us for the formation of certain enol phosphates[13]). It is difficult to see why these pathways should be completely absent for the mesylate **19** in comparison with the α-halo ketones **11** or **14**.

Reactions of the Enol Phosphonium Salts.—The addition of water to a mixture of **12** and **13** causes the disappearance of the vinyl proton doublet at τ 3.38 and the appearance of the methylene singlet of deoxybenzoin (**16**) at τ 5.7 as followed by nmr spectrometry, *i.e.*, the enol phosphonium salt **13** is readily hydrolyzed by water to **16**.

No reaction occurs if **13** is heated at reflux in glyme for 24 hr or kept at room temperature for 1 week. A similar recovery of **13** occurs if it is treated with triphenylphosphine in glyme at reflux or room tempera-

(22) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, Inc., New York, N. Y., 1965, pp 146–151.

(23) Our results with optically active methyl-*n*-propylphenylphosphine agree with these conclusions and will be published elsewhere.

(24) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(25) For examples of organophosphorus reactions which are likely to involve addition to carbonyl oxygen, see (a) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968); (b) I. J. Borowitz and M. Anschel, *Tetrahedron Lett.*, 1517, 5032 (1967).

(26) F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *J. Org. Chem.*, **33**, 25 (1968).

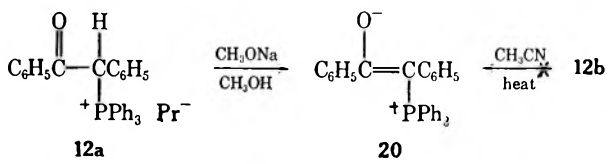
ture for 3 days. There is no formation of diphenylacetylene nor any conversion of **13** into the ketophosphonium salt **12.** Diphenylacetylene (**17**) is formed in 17% yield from the treatment of **13** with acetonitrile at reflux for 64 hr and in 28% yield from similar treatment of **18.**

These results indicate that the enol phosphonium salts **13** and **18** can be decomposed to diphenylacetylene as we had originally suggested. The origin of **17** in some of the reactions of **11** and **14** with triphenylphosphine is thus explained.

The Role of Ketoylide 20.—Conversion of **12a** into α-phenylphenacyltriphenylphosphorane (**20**) is accomplished in 88% yield upon treatment with sodium methoxide in methanol at room temperature (Scheme VII). Treatment of **20** with acetonitrile at reflux gives no reaction. It has been previously noted by Trippett and Walker[19] that **20** decomposes to give **17** under pyrolytic conditions at 300°. Our control experiment indicates that **20** is not involved in the formation of **17** under normal reaction conditions in solution. Furthermore **20** is reasonably stable to hydrolysis[27] and it cannot reasonably be the precursor of desoxybenzoin in the reactions outlined in Tables I and II.

As a further control, ketophosphonium chloride **12b** was shown to be stable to acetonitrile at reflux. No conversion to any other species was found. Thus the enol and keto phosphonium salts do not interconvert and seem to be forming *via* separate pathways.

SCHEME VII



12a **20**

Experimental Section[28]

All of the solvents used were distilled from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions were conducted under an atmosphere of dry nitrogen. Organic solutions were dried over magnesium sulfate.

α-Bromobenzyl phenyl ketone was prepared by the bromination of deoxybenzoin in ether in 84% yield, mp 54.5–56° (from EtOH), lit.[29] mp 54–56°.

α-Chlorobenzyl phenyl ketone was obtained from Aldrich Chemical Co., mp 66.5–68° (from hexane), or prepared as in the literature:[30] mp 66.0–67.0°, lit.[30] mp 66–67°.

α-Mesyloxybenzyl Phenyl Ketone.—Methanesulfonyl chloride (2.15 g, 0.0189 mol) in dry benzene (40 ml) was added dropwise over 1 hr to a well-stirred mixture of benzoin (4.0 g, 0.0189 mol) and triethylamine (3.82 g, 0.0378 mole) in benzene (20 ml). After 1 hr of stirring and removal of triethylamine hydrochloride by filtration, the resultant solution was washed with water, dried, evaporated *in vacuo*, and recrystallized from EtOAc and from cyclohexane to give **19** as a white solid (3.80 g, 0.0131 mol, 69%), mp 120–121°. The ir spectrum (CH_2Cl_2) exhibited peaks at 5.89 (C=O), 7.40, and 8.50 μ (OSO_2CH_3); nmr ($CDCl_3$), singlets at τ 6.95 (OSO_2CH_3) and 3.15 (COCH) and a multiplet at 2.0–2.9 (10 aromatic H).

Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.06; H, 4.85; S, 11.04. Found: C, 62.18; H, 5.00; S, 10.91.

The Reaction of α-Bromobenzyl Phenyl Ketone with Triphenylphosphine. A. In Nonpolar Solvents at Reflux.—α-Bromobenzyl phenyl ketone (2.00 g, 0.00727 mol) and triphenylphosphine (2.02 g, 0.00769 mol) were heated at reflux in benzene (55 ml) for 24 hr. Insoluble white material (2.70 g) was extracted with hot benzene to leave α-phenylphenacyltriphenylphosphonium bromide (**12a**) (2.26 g, 0.0042 mol, 58%), mp 239.5–241° dec, as an insoluble residue. The ir spectrum (KBr) exhibited peaks at 6.08 (s), 6.97 (s), 7.81 (m), 8.30 (m), 9.18 (s) and 10.06 μ (m); nmr ($CDCl_3$), multiplets at τ 1.5–3.0 (aromatic H) and a doublet centered at 1.04 (methine H, $J_{^{31}PH}$ = 12.5 Hz). The analytical sample had mp 243–244° dec (from aqueous EtOH).

Anal. Calcd for $C_{32}H_{26}OPBr$: C, 71.51; H, 4.88. Found: C, 71.72; H, 5.08.

The benzene extract gave crude triphenylphosphine oxide (0.88 g, 0.00317 mol, 44%), mp 149–155°, identified by tlc and its ir ($CHCl_3$) spectrum on a cyclohexane-insoluble fraction. The cyclohexane-soluble fraction gave diphenylacetylene (0.05 g, 0.00028 mol, 4%), identified *via* its uv absorption maximum at 292 mμ and desoxybenzoin (*ca.* 0.50 g, 0.0025 mol, 34%), identified *via* tlc, ir, and mixture melting point (as below).

Similar reactions in glyme (24 hr) or in toluene (24 or 48 hr) gave **12a** in 58% yield. Reaction of more concentrated solutions of α-bromobenzyl phenyl ketone and triphenylphosphine (1.3 *M* each in dry glyme at reflux for 6 hr) gave **12a** in 79–85% yield with desoxybenzoin and triphenylphosphine oxide as the other products.

B. In Acetonitrile at Reflux.—A mixture of α-bromobenzyl phenyl ketone (2.99 g, 0.0109 mol) and triphenylphosphine (3.09 g, 0.0118 mol) in acetonitrile (70 ml) was kept at reflux for 4 days. Removal of the solvent *in vacuo* gave an oil which was slurried in glyme to give **12a** (1.70 g, 0.00315 mol, 29%), mp 239.5–241.0° (ir, nmr spectra as above). The residual mixture was dried *in vacuo*, dissolved in benzene (3 ml), and chromatographed on a column of silica gel (100 g). Elution with benzene (progress monitored *via* tlc) gave diphenylacetylene (0.362 g, 0.00207 mol, 19%), mp 58–59.5°, mmp 57.5–59.5°. Further elution with benzene gave deoxybenzoin (1.05 g, 0.0054 mol, 49%), mp 54–56° (from methanol), mmp 53–56°.

C. In Various Solvents Containing Methanol.—A mixture of α-bromobenzyl phenyl ketone (3.00 g, 0.0159 mol), triphenylphosphine (2.85 g, 0.00159 mol), and methanol (1.50 g, 0.0477 mol) in acetonitrile (20 ml) was stirred at room temperature for 24 hr. After removal of the solvent *in vacuo*, the nmr spectrum of the residue indicated triphenylphosphine oxide and deoxybenzoin (100% yield); nmr ($CDCl_3$), a multiplet at τ 1.7–3.0 (25 aromatic H) and a singlet at 5.80 (2 methylene H). The same results were obtained from reactions in methanol–benzene at reflux and methanol–glyme or methanol–nitromethane at room temperature. Work-up of the benzene–methanol reaction by chromatography on acid-washed alumina gave (1) deoxybenzoin (99–100%) *via* elution with benzene and (2) triphenylphosphine oxide, mp 149–157° (100%), *via* elution with 95% ethanol.

D. In Aprotic Solvents at Room Temperature.—α-Bromobenzyl phenyl ketone (6.0 g, 0.0218 mol) and triphenylphosphine (6.06 g, 0.0231 mol) were stirred in glyme (15 ml) at room temperature until the lack of a precipitate with mercuric chloride indicated the absence of triphenylphosphine[3b] (2 weeks). The resultant solid was filtered under nitrogen and dried *in vacuo* to give a mixture of the ketophosphonium bromide **12a** and the enol phosphonium bromide **13** (10.2 g, 0.0187 mol, 86%). The mixture consisted of 15% **12a** and 85% **13** corresponding to a 13% yield of **12a** and a 73% yield of **13**: ir (CH_2Cl_2), 3.0–3.5, 6.00 (C=O), 7.0, 9.0, and 9.6–10.4 μ; nmr ($CDCl_3$), a doublet centered at τ 0.75 (methine H of **12a**, $J_{^{31}PH}$ = 12.5 Hz), a multiplet at 1.5–3.0 (25 aromatic H), and a doublet centered at 3.38 (vinyl proton of **13**, $J_{^{31}PH}$ = 1.8 Hz).

Similar results were obtained in acetonitrile and in nitromethane at room temperature (Table I).

The Reaction of α-Chlorobenzyl Phenyl Ketone with Triphenylphosphine. A. In Aprotic Solvents at Reflux.—α-Chlorobenzyl phenyl ketone (**14**) (11.30 g, 0.0491 mol) and triphenylphosphine (13.10 g, 0.050 mol) were heated at reflux in dry glyme (15 ml) for 24 hr to give α-phenylphenacyltriphenylphosphonium chloride (**12b**) (2.9 g, 0.0059 mol, 12%): mp

(27) H. J. Bestmann and B. Arnason, *Chem. Ber.*, **95**, 1513 (1962).

(28) The instrumental and other techniques used have been recorded previously.[3b]

(29) H. Limpricht and H. Schwanert, *Ann.*, **155**, 59 (1870).

(30) A. M. Ward, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 159.

237–240°; ir (CH_2Cl_2), 6.0 (C=O), 6.95, and 9.06 μ; nmr ($CDCl_3$), a multiplet at τ 1.4–3.1 (25 aromatic H) and a doublet centered at 0.35 (methine H, $J_{^{31}PH}$ = 12.5 Hz). Thin layer chromatography showed triphenylphosphine oxide and deoxybenzoin (isolated in 78% yield) to be the only other species formed. The same yield of **12b** was obtained from reactions in benzene or in toluene (Table II). Similar reaction of **14** (1.32 g, 0.0057 mol) in acetonitrile (40 ml) at reflux for 10 days, followed by a work-up as for the reaction of **11** (above), gave **12b** (0.90 g, 0.0018 mol, 31.5%), mp 237–240°, diphenylacetylene (0.143 g, 0.00081 mol, 14%), mp 57–59° [from petroleum ether (bp 30–60°)], deoxybenzoin (0.462 g, 0.0023 mol, 41%), and triphenylphosphine oxide.

B. In Aprotic Solvents at Room Temperature.—Reaction of **14** (11.3 g, 0.0491 mol) and triphenylphosphine (13.0 g, 0.050 mol) in glyme (15 ml) for 14 days at room temperature (reaction complete by lack of precipitate with mercuric chloride) gave the enol phosphonium chloride **18** as a white solid which could be filtered under nitrogen from the mixture (20.9 g, 0.0425 mol, 85% isolated yield, 100% yield by nmr): ir (CH_2Cl_2), 3.2–3.5, 7.0, 9.0, 9.9, and 10.1 μ; nmr ($CDCl_3$), a multiplet at τ 1.7–3.0 (25 aromatic H) and a doublet centered at 3.45 (1 vinyl H, $J_{^{31}PH}$ = 2.0 Hz).

Similar reaction of **14** and triphenylphosphine (0.050 mol each) in acetonitrile (15 ml) (Table II) gave, after removal of the solvent *in vacuo*, a 1:1 mixture of enol and ketophosphonium salts as an oil: nmr ($CDCl_3$), a multiplet at τ 1.7–3.0 (25 aromatic H) and doublets centered at 3.45 (vinyl H of **18**, $J_{^{31}PH}$ = 2.0 Hz) and 0.35 (methylene H of **12b**, $J_{^{31}PH}$ = 12.5 Hz). Similar reaction in nitromethane gave **14** (53–61%) and deoxybenzoin (29%), mp 54–56°. No diphenylacetylene was found in these reactions (tlc).

C. In Methanol or Methanol-Containing Solvents.—Reaction of **14** and triphenylphosphine (0.017 mol each) in methanol (20 ml) for 5.5 weeks at room temperature gave, after removal of the solvent *in vacuo*, an oil which was slurried in glyme to give **12b** (3.44 g, 0.007 mol, 41%), mp 238.5–240.5°. The residue contained triphenylphosphine oxide and deoxybenzoin (by tlc on silica gel using 5% EtOAc–C_6H_6 for development). Similar reaction and work-up as for **11** for reactions done in methanol-containing solvents gave yields indicated in Table II.

The Reactions of α-Mesyloxybenzyl Phenyl Ketone with Triphenylphosphine.—Reaction of **19** and triphenylphosphine (0.00655 mol each) in glyme (15 ml) at reflux for 24 hr gave **12c** as a white powder (3.05 g, 0.0053 mol, 81%): mp 247–248.5°; ir (CH_2Cl_2), 5.98 (C=O) and 8.3–8.5 μ ($^-OSO_2CH_3$); H^1 nmr ($CDCl_3$), a multiplet at τ 1.6–3.1 (25 aromatic H and 1 methine H) and a singlet at 7.25 (3 H of OSO_2CH_3); ^{31}P nmr ($CDCl_3$), −25.6 ppm (H_3PO_4 = 0).[31] A similar reaction in 4:1 (v/v) glyme–methanol gave **12c** in 80% yield.

The Conversion of the Enol Phosphonium Halides 13 and 18 into Diphenylacetylene.—A 1:1 mixture of the ketophosphonium chloride **12b** and the enol phosphonium chloride **18** (a total of 0.022 mol) was heated at reflux for 64 hr in acetonitrile (500 ml) to give recovered **12b** (4.87 g, 0.0099 mol, 45.5%), mp 239–241°, mmp 238–241.5°. The residual oil was chromatographed over silica gel (200 g). Elution with benzene gave diphenylacetylene (0.54 g, 0.0030 mol, 28% based on **18**), mp 57–57.5°, mmp 57.5–60°. The reaction mixture also contained deoxybenzoin and triphenylphosphine oxide (tlc).

Similar treatment of the enol phosphonium bromide **13** gave diphenylacetylene (17%), deoxybenzoin, and triphenylphosphine oxide.

Reaction of **13** in glyme at reflux with or without the presence of triphenylphosphine (1 equiv) for 3–7 days led to recovered **13** in 82 and 95% yields, respectively.

The Hydrolysis of the Enol Phosphonium Bromide 13.—Water (4 drops) was added to a solution of **13** (0.602 g, 0.0011 mol) in $CDCl_3$ (1 ml) in a nmr tube. After 5 min of shaking, **13** was completely hydrolyzed since the nmr spectrum showed the absence of the vinyl proton of **13** at τ 3.3 and the presence of the methylene protons of desoxybenzoin at 5.8.

Attempted Reaction of 13 with Triethyl Phosphite.—The enol phosphonium bromide **13** (2.0 g, 0.0037 mol) and triethyl phosphite (0.616 g, 0.0037 mol) were heated at reflux for 3 days in dry benzene (10 ml, distilled from $LiAlH_4$) to give a black mass which contained triethyl phosphate, triphenylphosphine oxide, and deoxybenzoin (tlc).

The Reaction of 13 with Tributylphosphine.—Tributylphosphine (0.189 g, 0.000934 mol) was added to **13** (0.501 g, 0.000934 mol) in $CDCl_3$ (1 ml). Triphenylphosphine was formed immediately (by tlc and formation of the adduct with mercuric chloride).

The Formation of α-Phenylphenacyltriphenylphosphorane (20).—Sodium methoxide (0.21 g, 0.0039 mol) in methanol (10 ml) was added to a stirred solution of **12a** (2.00 g, 0.0037 mol) in methanol (25 ml) and stirring was continued for 30 min.[4b] The resultant solution was poured into water (200 ml) to give a white precipitate which was washed with water and recrystallized twice from EtOAc to give **20** (1.5 g, 0.0033 mole, 88%): mp 195–197° (lit.[28] mp 192–194°); uv, λ_{max}^{MeOH} 320 (ϵ 7200), 275, 267.5, 262 mμ; ir ($CHCl_3$), 6.68 (vs), 6.75 (vs), 6.95 (s), 7.23, 8.85, 9.04 (s), 9.33, 9.73, 10.0, and 10.33 μ; tlc (25% MeOH–C_6H_6), R_f 0.74 *vs.* 0.59 for triphenylphosphine oxide.

A solution of **20** (0.253 g, 0.00055 mol), mp 190–195°, in acetonitrile (10 ml) was heated at reflux for 24 hr to leave only **20** (0.25 g, 100%), mp 187–194°.

The Stability of α-Phenylphenacyltriphenylphosphonium Chloride in Acetonitrile at Reflux.—A solution of **12b** (0.30 g, 0.00061 mol) in acetonitrile (10 ml) was heated at reflux for 24 hr to give recovered **12b** (0.31 g, 100%), mp 233–238°, ir ($CHCl_3$) identical with that of genuine **12b**.

Registry No.—Triphenylphosphine, 603-35-0; **11**, 1484-50-0; **12a**, 1530-47-8; **12b**, 19254-98-9; **12c**, 19254-99-0; **14**, 447-31-4; **19**, 19255-01-7.

Acknowledgment.—We are indebted to Professor Claibourne E. Griffin, University of Pittsburgh, for the early nmr spectra and to Professor Grace Borowitz, Upsala College, for stimulating discussions and aid in obtaining ^{31}P nmr spectra.

(31) The ^{31}P nmr spectrum was kindly determined by Jeolco, Inc., at 24.29 and at 40 MHz on JNM C-60HL and C-100 spectrometers.

Irradiation Studies and Novel Sodium Borohydride Reduction of 1,4-Cholestadien-3-one

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Irradiation of 1,4-cholestadien-3-one (I) in *t*-butyl alcohol gave four phenols, *i.e.*, 1-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene (II, 40%), 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10)-triene (III, 40%), 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene (IV, 10%), and 2-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene (V, 4%). Irradiation of dienone I in the presence of sodium borohydride afforded phenol II (15%), phenol III (45%), phenol IV (13%), 4-methyl-19-norcholesta-1,3,5(10)-triene (IX, 5%), and an unidentified sterol X (8%). Ground-state sodium borohydride reduction of dienone I gave 5β-cholest-1-en-3-one (VI, 10%), 4-cholesten-3-one (VII, 18%), 4-cholesten-3β-ol (VIII, 40%), hydrocarbon IX (8%), and starting material (12%). These reactions are discussed and compared with reductions of 4-cholesten-3-one reported previously.

The photoreduction of 3,17β-estradiol[1] and steroidal ketones[2] by ultraviolet irradiation in the presence of sodium borohydride has been described. A 22-fold rate increase in the photoreduction *vs.* ground-state reduction of 4-cholesten-3-one was observed. The products obtained by photo- and ground-state reduction in 2-propanol were essentially the same. We now describe the reactions of the cross-conjugated dienone 1,4-cholestadien-3-one (I), (i) under ultraviolet irradiation, (ii) with excess borohydride, and (iii) under irradiation in the presence of borohydride in *t*-butyl alcohol and 2-propanol. The unreactivity of ring-A steroidal dienones toward sodium borohydride coupled with the intriguing photochemical rearrangements of this system made this study especially desirable. In addition, the individual processes could be interrelated.

Methods and Results

Irradiations in the Absence of Borohydride.—A solution of 1,4-cholestadien-3-one (I, 0.7 mmol) in 150 ml of *t*-butyl alcohol was irradiated at 36° with a 450-W Hanovia medium-pressure mercury lamp (679A-36) equipped with a Pyrex filter. Aliquots of the solution were removed periodically from 0 to 60 min. The rate of photorearrangement of I was easily followed by the disappearance of the ultraviolet absorption band at 244 mμ; 90% of the reaction was complete within 29.5 min. A similar rate of rearrangement of I in 2-propanol was observed and tlc indicated the same composition of products.

The four compounds isolated from the preparative scale irradiation in *t*-butyl alcohol by column and preparative thin layer chromatography[3] were 1-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene[4-6] (II, 40%), 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10)-triene[7] (III, 40%), 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene (IV, 10%), and 2-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene[8] (V, 4%).

Phenol IV has been tentatively assigned the structure of 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene, based on spectral data which is in excellent agreement with that of the analogous phenol, *i.e.*, 4-hydroxy-2-methyl-17β-acetoxyestra-1,3,5(10)-triene.[9]

Sodium Borohydride Reduction of Dienone I in the Ground State.—The kinetic data of the sodium borohydride reduction of dienone I are summarized in Table III (Experimental Section). No reduction took place at the stoichiometric concentration of sodium borohydride. At increasing concentrations, the rate of reduction was proportionately increased. Figure 1 illustrates the reduction of I at several concentrations of borohydride.

Reduction of dienone I on a preparative scale in *t*-butyl alcohol with an 8 molar excess of sodium borohydride gave the following four reduction products which were isolated by careful chromatography: 5β-cholest-1-en-3-one[10] (VI, 10%), 4-cholesten-3-one[11] (VII, 18%), 4-cholesten-3β-ol[11] (VIII, 40%), and 4-methyl-19-norcholesta-1,3,5(10)-triene[12] (IX, 8%) (Scheme I).

Irradiations of Dienone I in the Presence of Sodium Borohydride.—Dienone I was irradiated in the presence of an 8 molar excess of sodium borohydride. The time required for 90% disappearance of dienone I (uv) in *t*-butyl alcohol was 30 min, comparable with the reaction in 2-propanol. The preparative run gave five compounds: phenols II (15%), III (45%), IV (13%), hydrocarbon IX (5%), and an unknown sterol X (8%). Phenols II, III, and IV were identical with those obtained from the irradiation without borohydride by mixture melting point, infrared spectra, and tlc. The spectral properties (infrared, ultraviolet, and nmr) of 4-methylcholestatriene IX were comparable with the oily hydrocarbon obtained from the borohydride reduction. The unidentified sterol X which was obtained as a colorless solid, mp 112–113.5°, $[\alpha]^{20}D$ −45.3°, may be a reduced bicyclohexenone, an intermediate in the formation of phenolic isomers. The products and yields from the irradiation, borohydride reduction, and attempted photoreduction of dienone I are correlated in Table I.

(1) J. A. Waters and B. Witkop, *J. Amer. Chem. Soc.*, **89**, 1022 (1967).
(2) J. A. Waters and B. Witkop, *ibid.*, **90**, 758 (1968).
(3) The per cent yields of the various compounds reported in this paper are *estimated* yields from the total reaction mixture as determined by tlc and glpc of the fractions obtained from column and preparative thin layer experiments.
(4) A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, **68**, 1712 (1946).
(5) H. H. Inhoffen and G. Zühlsdorff, *Ber.*, **74**, 604 (1941).
(6) This phenol has now been assigned the 1-hydroxy-4-methyl structure: G. I. Gregory and A. G. Long, *J. Chem. Soc.*, 3059 (1961).
(7) J. Romo, C. Djerassi, and G. Rosenkranz, *J. Org. Chem.*, **15**, 896 (1950).
(8) B. R. Davis and T. G. Halsall, *J. Chem. Soc.*, 1833 (1962).
(9) H. Dutler, C. Ganter, H. Ryf, E. C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2346 (1962).
(10) H. H. Inhoffen, G. Kolling, G. Koch, and I. Nebel, *Ber.*, **84**, 361 (1951).
(11) C. W. Shoppee, B. D. Agashe, and G. H. Summers, *J. Chem. Soc.*, 3107 (1957).
(12) H. Dannenberg and H. J. Gross, *Tetrahedron*, **21**, 1611 (1965).

TABLE I

IRRADIATION, BOROHYDRIDE REDUCTION, AND PHOTOREDUCTION OF CHOLESTADIENONE (I)

	Yields, %								
Dienone reaction	Phenol II	Phenol III	Phenol IV	Phenol V	Enone VI	Enone VII	Enol VIII	Hydrocarbon IX	Sterol X
$h\nu$	40	40	10	4					
$h\nu$ + $NaBH_4$	15	45	13					5	8
$NaBH_4$					10	18	40	8	

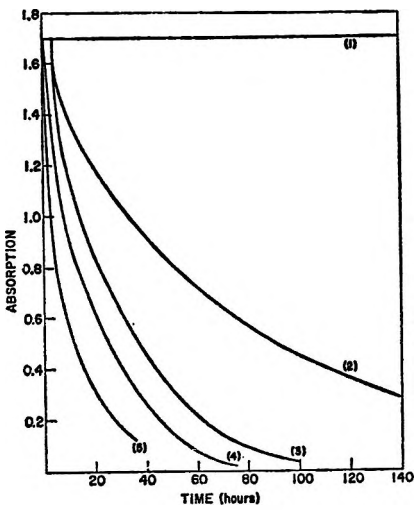
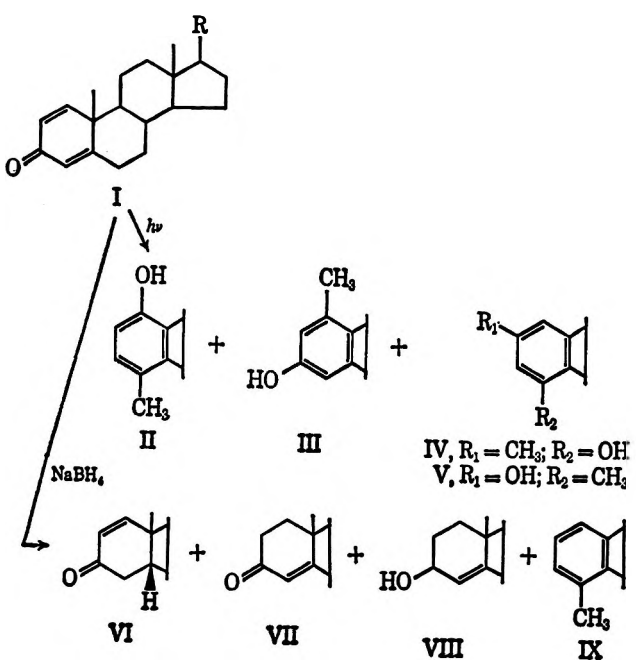


Figure 1.—Ultraviolet absorption of 1,4-cholestadien-3-one (0.023 mmol in 5.0 ml of *t*-butyl alcohol) at different $NaBH_4$ concentrations: (1) 0.006 mmol, (2) 0.031 mmol, (3) 0.056 mmol, (4) 0.12 mmol, and (5) 0.19 mmol.

SCHEME I



Discussion

Photorearrangement of 1,4-cholestadien-3-one (I)[13] to give phenols II–V parallels the irradiation of 1-dehydro-17-acetyltestosterone in neutral media[9,14,15] in which four phenols (9-hr reaction period) or four photoketones (1.5-hr reaction period) have been isolated. The cross-conjugated dienone, upon n–π^* excitation, is converted into a triplet species (singlet to triplet intersystem crossing), which is postulated to undergo bond alteration and formation of a mesoionic species.[16] This zwitterion may then rearrange to bicyclo[3.1.0]hexenones, which, in turn, undergo secondary photorearrangement to the spirocyclic 2,4-cyclohexadienones. The photoketones can then further rearrange to phenols of type II–V. Separate irradiation of each ketone has established this latter rearrangement.[9,15] The course of dienone rearrangement is greatly influenced by a 4-methyl substituent[9,15,17,18] or by the presence of acid.[15,17,18] Identical phenols may be formed by irradiation[19] or by the acid-catalyzed dienone–phenol rearrangement.[20]

To correlate photorearrangement with photoreduction, dienone I was reduced with sodium borohydride in the ground state. Figure 1 illustrates the kinetics of this reduction. At high borohydride concentration (0.187 mmol), 90% of the original dienone disappeared within 30 hr (extrapolation from Table III), whereas at low concentrations (0.006 mmol) no reduction took place, and in 0.03 mmol of $NaBH_4$ the reduction required 172 hr. Preparative-scale reduction at high borohydride concentration gave enones VI and VII, 4-cholesten-3β-ol (VIII), and hydrocarbon IX (Table I).

Steroidal ring-A dienones are usually resistant to reduction by sodium borohydride. Exceptions are the reductions of 1,4-androstadiene-3,17-dione[21] and prednisone[22] in which both the Δ^1 double bond and the carbonyl functions were reduced. Reduction of the Δ^4 double bond of I to give 5β-cholest-1-en-3-one (VI) and the Δ^1 double bond to 4-cholesten-3-one (VII) with preservation of the carbonyl group has no precedent. Reduction of both the 4,5 bond and the carbonyl group of a 1,4-dien-3-one with lithium aluminum hydride in boiling tetrahydrofuran has been noted.[23] Chemical[23] or enzymatic reduction of the 4,5 bond of the dienone[24] produced the 5β-1-en-3-one in analogy

(13) For reviews of the photochemistry of cross-conjugated dienones, see O. L. Chapmann, *Advan. Photochem.*, **1**, 330 (1963); K. Schaffner, *ibid.*, **4**, 85 (1966); N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 162; R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., New York, N. Y., 1966, p 105; D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corp., New York, N. Y., 1967, p 217.

(14) H. Dutler, H. Bosshard, and O. Jeger, *Helv. Chim. Acta*, **40**, 494 (1957).

(15) For a summary of their dienone investigations, see J. Frei, C. Ganter, D. Kägi, K. Kocsis, M. Miljkovic, A. Siewinski, R. Wenger, K. Schaffner, and O. Jeger, *ibid.*, **49**, 1049 (1966).

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(18) P. J. Kropp and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 2456 (1963).

(19) J. M. Erikson and D. L. Forbes, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 332.

(20) See ref 19, p 371.

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(22) J. A. Zderic and J. Iriarte, *J. Org. Chem.* **27**, 1756 (1962).

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(24) E. Caspi and M. M. Pechet, *J. Biol. Chem.*, **230**, 843 (1958).

to our study in which 5β-cholest-1-en-3-one (VI, 1-coprosten-3-one) is formed.

4-Cholesten-3-one (VII) is reduced to 4-cholesten-3β-ol as described previously.[2] Hence VII is apparently formed to a much greater extent initially than the final yield indicates (Table I). Additional evidence that the Δ^1 double bond in 1,4-diene-3-keto steroids is more readily reduced than the Δ^4 double bond comes from the homogeneous catalytic hydrogenation technique.[25]

Formation of 4-methyl-19-norcholesta-1,3,5(10)-triene (IX) is analogous to the lithium aluminum hydride reduction of 1,4-dien-3-ones (to the 3ξ-ols) and subsequent rearrangement of the reaction mixture by alumina or Florisil chromatography.[23,26,27]

When I was irradiated in the presence of sodium borohydride, the dienone disappeared at the same rate as without borohydride. The products were predominantly phenolic (Table I). However, phenol II was formed in a much lower yield.

There is a striking contrast between this dienone photoreduction and the photoreduction of 4-cholesten-3-one[2] in which the same reduction products are formed as in the ground state, but at a rate increase of 22.5. The irradiation of dienone I in the presence of borohydride leads instead to phenolic rearrangement rather than reduction products. In the photoreduction of 4-cholesten-3-one in 2-propanol the solvent could be a source of hydrogen atoms. However, little or no difference in the rate of formation or composition of products was observed between *t*-butyl alcohol or 2-propanol, in contrast to the easy photoreduction of saturated 3-keto steroids in isopropyl alcohol solution.[28]

The rate and quantum efficiency of triplet rearrangement in dienones is up to 10,000-fold faster and 200-fold more efficient than in enones.[16,29] In addition, borohydride reduction of the dienone in the ground state is extremely slow. The intermediate zwitterionic bicyclic or spirocyclic photoproducts from the dienone[15] apparently rearrange to phenols fast enough that nucleophilic attack of hydride becomes negligible. Addition of a triplet quencher, such as 1,3-pentadiene,[28] should differentiate between these reactions by retarding the photorearrangements. Such attempted quenching experiments have so far been inconclusive, since interaction between borohydride and piperylene prevents attainment of desirable concentrations of quenching agent.

Experimental Section

Materials and Apparatus.—*t*-Butyl alcohol (Eastman Kodak) and 2-propanol (Fisher Spectroanalyzed grade) were used as solvents. Silica gel G tlc plates (0.25 mm thick) were used routinely and were developed in hexane–acetone–ether 8:1:1 unless designated otherwise. Melting points were taken on a Kofler hot stage and are corrected. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141) in chloroform. The glpc data were obtained on a Barber–Coleman Series 5000 gas chromatograph using a 1% QF-1 column on Gaschrome P (80–100 mesh) at a temperature of 220° (30 psi). The ultraviolet spectra were recorded on a Beckman DB-G grating spectrophotometer in absolute ethanol unless stated otherwise. The infrared spectra were measured on a Perkin-Elmer spectrometer (Model 21) in chloroform, unless designated otherwise. The mass spectra were obtained on the LKB mass spectrometer and the nmr spectra on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as the internal standard. Samples were irradiated with a 450-W Hanovia mercury-vapor lamp, 679A-36, using a water-cooled quartz immersion well equipped with a Pyrex filter. Nitrogen was passed through the solution during the entire irradiation period.

1,4-Cholestadien-3-one (I).—Cholestan-3-one was converted into 2,4-dibromocholestan-3-one.[4] Dehydrobromination of the dibromo compound by redistilled collidine[30] gave 1,4-cholestadien-3-one, mp 113–114° (lit.[30] mp 111–111.5°). The compound was pure as indicated by tlc and glpc.

Irradiations of 1,4-Cholestadien-3-one. A. Kinetic Runs.—In all irradiation experiments the Hanovia lamp was turned on 10 min before the addition of the solutions to the photolysis chamber. This time period was required for the alcohol solutions to reach and maintain a constant temperature of 36°. A solution of 267 mg (0.7 mmol) of 1,4-cholestadien-3-one in 150 ml of *t*-butyl alcohol was warmed to 36° and placed in the irradiation cell. Aliquots (0.2 ml diluted to 10 ml) were removed periodically and the ultraviolet absorption band at 244 mμ was recorded (time in minutes, OD units): 0, 1.70; 5, 1.25; 15, 0.51; 30, 0.16; 60, 0.12. On completion of the reaction period (75 min), the solvent was evaporated under reduced pressure. Tlc of the mixture showed the presence of four compounds. Glpc of the material displayed four peaks: 4.1 min (minor), 4.7 min (major), 4.9 min (minor), and 5.8 min (major). The two major compounds displayed a 1:1 peak area ratio. Isolation of these compounds will be described in the preparative scale experiment.

A solution of 154 mg (0.4 mmol) of 1,4-cholestadien-3-one in 150 ml of 2-propanol was irradiated and ultraviolet data were recorded in the manner described above (time in minutes, OD_{244}): 0, 1.20; 5, 1.05; 15, 0.58; 30, 0.22; 60, 0.07. Examination of the reaction mixture by tlc showed compounds with the same R_f value and intensity as the *t*-butyl alcohol irradiation. No products were isolated from the 2-propanol reaction.

B. Preparative Run.—A solution of 5.34 g (14 mmol) of 1,4-cholestadien-3-one in 3.0 l. of *t*-butyl alcohol was warmed to 36° and then placed in the photolysis chamber. The reaction was followed by noting the disappearance of the ultraviolet absorption as stated above (time in minutes, OD units): 0, 2.00; 20, 1.48; 80, 0.44; 120, 0.24; 150, 0.15. On completion of the irradiation period (180 min), the solvent was evaporated under reduced pressure. Tlc of the pale yellow semisolid showed the presence of four closely related compounds (R_f 0.42, 0.35, 0.32, 0.28). The crude mixture was subjected to column chromatography on alumina (Woelm, grade 3, 160 g). The following fractions were eluted as shown in Table II.

Table II

Fractionation of Phenolic Rearrangement Products from the Irradiation of Dienone I

Fraction	Solvent (vol)	Material, g
1	Hexane (1 l.)	Solid (II), 1.04
2	Benzene–hexane 1:9 (1 l.)	Solid (II), 1.30
3	Benzene–hexane 1:3 (1 l.)	Oil (IV), 0.46
4	Benzene–hexane 1:1 (1 l.)	Oil (V), 0.65
5	Benzene (1 l.)	Oil (III), 1.81
6	Benzene–ether and ether–methanol mixtures (9 l. total)	Oil, 0.22

Fractions 1 and 2 contained the compound with R_f 0.42, 40% of total reaction mixture, in highly purified form as shown by tlc. Fraction 2 (1.3 g) was recrystallized from petroleum ether (bp 30–60°) to give 595 mg of colorless needles, mp 144.5–145.5°. The mother liquor, on standing, yielded a second crop, 171 mg, mp 145–146°. The combined material was recrystallized a

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TABLE III

KINETIC STUDY OF THE REDUCTION OF CHOLESTADIENONE WITH SODIUM BOROHYDRIDE

Tube no.[a]	$NaBH_4$, mg (mmol)	OD, Time, hr: 0	4	8	12	24	36	48	76	100	150	192
1	0.22 (0.0058)	1.70	1.70	1.70	1.70	1.70		1.70	1.70	1.70	1.70	1.70
2	1.17 (0.031)	1.70	1.70	1.38	1.35	1.16		0.80	0.62	0.43	0.25	0.10
3	2.10 (0.0556)	1.70	1.70	1.20	1.08	0.74		0.39	0.09	0.03		
4	3.07 (0.081)	1.70	1.60	1.20	0.87	0.57		0.28	0.09	0.02		
5	4.00 (0.106)	1.70	1.25	0.97	0.76	0.49	0.31	0.16	0.02	0.02		
6	4.93 (0.130)	1.70	1.36	0.82	0.67	0.35	0.26	0.06				
7	5.90 (0.156)	1.70	1.30	0.86	0.58	0.31	0.17	0.04				
8	7.07 (0.187)	1.70	1.04	0.74	0.49	0.22	0.12	0.01				

[a] Each tube contained 8.9 mg (0.023 mmol) of 1,4-cholestadien-3-one made up to a final volume of 5.0 ml of *t*-butyl alcohol.

second time from the same solvent to yield 532 mg of 1-hydroxy-4-methyl-19-norcholesta-1,3,5-(10)-triene (II) as colorless needles, mp 146.5–147.5°, $[\alpha]^{20}D$ +158.4°. An analytical sample was recrystallized a third time and gave mp 147.5–148° (lit. mp 145.5–146°, $[\alpha]^{24.5}D$ +161°[4,6] and mp 145–146°[5]); ultraviolet spectrum λ_{max} 284 mμ (ε 2400), 226 (5200); infrared spectrum 3595, 1587, 1480, 1465, 1382, 1300, 1155 cm^{-1}; in CS_2 900, 850, 810, 796, and 733 cm^{-1}; nmr spectrum (δ) 2.28 (s, aromatic CH_3), 6.97 (m, 2-CH and 3-CH).

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.41; H, 10.81.

Additional amounts of phenol II, in less pure form, were obtained by recrystallization of fraction 1 from petroleum ether (bp 30–60°).

Fraction 3 (0.46 g) was highly enriched in compound R_f 0.35 (10% of total reaction mixture), but attempts to crystallize this compound from a variety of solvents was unsuccessful. The material was therefore chromatographed on alumina (grade 3, 12 g). Elution of the column with 2.5, 5, and 10% benzene in hexane gave a total of 204 mg of oil which started to crystallize on standing. Two recrystallizations of the combined fraction from petroleum ether (bp 30–60°) gave pure phenol IV, tentatively formulated as 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene, as a colorless crystalline solid of mp 124.5–125°, $[\alpha]^{20}D$ +77.1°. An analytical sample was recrystallized again from a small amount of petroleum ether (bp 30–60°) to give colorless rods: mp 125.5–126.5°; ultraviolet spectrum λ_{max} 283 mμ (ε 1800), 277 (1700), 227 (5400); infrared spectrum 3600, 1620, 1580, 1470, 1385, 1305, 1264, 1158, 976 cm^{-1}; in CS_2 845, 825, 752, 715 cm^{-1}; KBr 839 and 825 cm^{-1};[9] nmr spectrum (δ) 2.27 (s, aromatic CH_3), 6.52 and 6.78 (1-CH and 3-CH).[9]

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.56; H, 10.78.

Fraction 4 (0.65 g) contained *ca.* 25% of the R_f 0.32 compound (4% of total mixture). Column chromatography of the fraction on alumina (grade 3, 20 g) and elution with benzene–hexane (1:3) gave the desired compound (151 mg) which crystallized on standing. Recrystallization from petroleum ether gave 57.6 mg of colorless crystalline solid, mp 119–121°. A second recrystallization from the same solvent gave 2-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene (V) as a crystalline solid: mp 120.5–121°; $[\alpha]^{20}D$ +74.1° (lit.[8] mp 120–120.5°); ultraviolet spectrum λ_{max} 282 mμ (ε 2300), 223 (6200); infrared spectrum 3595, 1610, 1470, 1382, 1315, 1300, 1175, 1140, 1012, 980 cm^{-1}; in CS_2 890, 852, 828, 753, 744, 712 cm^{-1}; nmr spectrum (δ) 2.17 (s, aromatic CH_3), 6.57, 6.72 (1-CH and 3-CH).

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.95; H, 10.93.

Fraction 5 (1.81 g) was highly enriched in compound R_f 0.28 (40% of total reaction mixture). Crystallization of the product from petroleum ether (bp 30–60°) gave 1.678 g of crystals, mp 125–126.5°. Two additional recrystallizations from petroleum ether gave 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10)-triene (III) as colorless needles: mp 127.5–128°; $\alpha^{20}D$ +141.2° (lit.[7] mp 126.5–128°, $[\alpha]^{20}D$ +135.6°); ultraviolet spectrum λ_{max} 284 mμ (ε 1900), 225 (8300); infrared spectrum 3600, 1614, 1590, 1475, 1385, 1305, 1175, 1142, 970, 860 cm^{-1}; in CS_2 896, 860, 852, 832, 718 cm^{-1}; nmr spectrum (δ) 2.42 (s, aromatic CH_3), 6.80 (m, 2-CH and 4-CH).

Sodium Borohydride Reduction of 1,4-Cholestadien-3-one. A. Kinetic Study.—To each of eight centrifuge tubes was added 8.9 mg of 1,4-cholestadien-3-one. *t*-Butyl alcohol (0.2 ml) was added to dissolve the dienone. From a stock solution of 150 mg of sodium borohydride in 100 ml of *t*-butyl alcohol was pipeted the desired amount of borohydride for each tube (*cf.* Table III). Each tube was then brought to a total volume of 5.0 ml by the addition of *t*-butyl alcohol. The tubes were then stoppered and immediately placed in a constant-temperature bath at 36°. Periodically, 0.2 ml was pipeted from each tube and diluted to 10 ml of absolute ethanol. The uv spectrum was then taken and the optical density of the 244-mμ band recorded. The results are summarized in Table III.

On completion of the rate study, 4 ml of water was added to the solution remaining in each tube. Each mixture was then extracted three times with 2 ml of ether. The ether was evaporated and each residue was spotted on a single tlc plate. The developed plate showed identical patterns for each of the eight tubes, both in R_f values and intensity of spots (five compounds indicated). Glpc of the reaction mixture from tube 8 displayed six peaks at 12.8, 9.0, 4.3, 2.1, 1.3 and 1.1 min. Isolation of five of the main compounds will be described in the preparative-scale experiment.

To a solution of 154 mg (0.4 mmol) of 1,4-cholestadien-3-one in 150 ml of 2-propanol (36°) was added 362 mg (9.6 mmol) of sodium borohydride and the spectral data were recorded (time in hours, OD_{244}): 0, 1.20; 1, 1.15; 3, 0.76; and 20, 0.06. Tlc of the reaction material gave the same pattern of compounds as the chromatogram from the *t*-butyl alcohol reduction.

B. Preparative Run.—To a solution of 2.67 g (7 mmol) of 1,4-cholestadien-3-one in 1.5 l. of *t*-butyl alcohol (36°) in a 2-l. erlenmeyer flask was added 2.12 g (56 mmol) of sodium borohydride. The flask was stirred for a brief period, stoppered and placed in a constant-temperature bath (36°). Aliquots were removed periodically and absorption at λ_{max} 244 mμ was recorded as optical density units (time in hours): 0 (1.60), 16 (0.42), 24 (0.25), 40 (0.10) and 45 (0.07). After the 46-hr reaction period most of the solvent was removed under reduced pressure, 500 ml of water was added and the resulting mixture was extracted three times with 50-ml portions of chloroform. The combined chloroform extracts were washed three times with saline water, dried over sodium sulfate and evaporated under reduced pressure. An additional 5.35 g of dienone was reduced in the same manner. Tlc of the pale yellow crude product showed the presence of five compounds (R_f 0.76, 0.53, 0.42, 0.34, 0.27). The crude mixture (8.0 g) was subjected to column chromatography on alumina (230 g, Woelm grade 1). The fractions obtained are listed in Table IV.

Fraction B-1 contained a nonpolar product (R_f 0.76, 8% of total reaction mixture) besides several more polar compounds. Fraction B-1 was chromatographed on alumina (grade 1, 26 g). Elution with hexane (180 ml) gave 263 mg of colorless oil. On standing at room temperature for a period of 2–3 weeks, the pure oil was apparently partly autoxidized as shown by tlc. The material (263 mg) was then subjected to preparative tlc (two plates, 20 × 20 × 0.5 mm). After development of the plates in hexane–acetone–ether (8:1:1), the top portion of the plates was eluted with acetone to give 109 mg of pure IX as a pale yellow oil, $\alpha^{20}D$ +52.3°. The compound was stored in frozen benzene: ultraviolet spectrum $\lambda_{max}^{n\text{-hexane}}$ 269, 260, 254, 248, 242, 228 mμ; infrared spectrum 1582, 1468, 1382, 1368, 1085, 965, 940, 851 cm^{-1}; nmr spectrum in CCl_4 (δ) 2.15 (s, aromatic CH_3) and 6.75–7.03 (m, aromatic CH) [lit.[12] 2.15 ppm (s) and 6.75–7.05 (m)].

Fraction B-2 (680 mg) which contained two compounds (R_f

Table IV

Fractionation of Reduction Products of Cholestadienone

Fraction	Solvent (vol)	Amount, g
B-1	Hexane to benzene:hexane 1:1 (6 l.)	0.87
B-2	Benzene (1.5 l.)	0.68
B-3	Ether–benzene 1:9 (1.5 l.)	1.20
B-4	Ether–benzene 1:3 (1.5 l.)	0.57
B-5	Ether–benzene 1:1 (1.5 l.)	1.09
B-6	Ether (1.5 l.)	1.77
B-7	1% methanol in ether (1.5 l.)	0.81
B-8	2.5–10% methanol in ether (4.5 l.)	0.44
B-9	25% MeOH in ether (1.5 l.)	0.17
B-10	Chloroform–ethyl acetate–methanol 1:1:1 (1.5 l.)	0.08

0.53 and 0.42) was chromatographed on alumina (grade 1, 20 g) and eluted with benzene–hexane (1:3) to give 101 mg of colorless crystals, R_f 0.53 (10% of total crude yield), pure by tlc. Recrystallization from petroleum ether gave 61.7 mg of colorless crystals, mp 98–106. Further recrystallization from petroleum ether gave 5β-cholest-1-en-3-one (VI) as colorless rectangles, mp 107–108°, $[\alpha]^{20}D$ +135.9° (lit.[10] mp 104°).

An additional recrystallization from the same solvent did not alter the melting point: ultraviolet spectrum λ_{max} 233 mμ (ε 8700); infrared spectrum 1675, 1468, 1378, 1270, 1112, 975, 840 cm^{-1}; nmr spectrum (δ) 6.98, 6.80, 6.03, 5.87 (AB quartet).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31, H, 11.53. Found: C, 84.02, H, 11.33.

Further elution of the fraction B-2 column with benzene gave 120 mg of colorless crystals (R_f 0.42, 18% total reaction mixture). Two recrystallizations of the material from petroleum ether gave 72.3 mg of 4-cholesten-3-one (VII) as clusters of needles: mp 82–82.5°, $\alpha^{20}D$ +93.2°; ultraviolet spectrum 239 mμ (ε 15,600). A mixture melting point of the sample with authentic 4-cholesten-3-one was undepressed at 81.5–82.5°. The infrared spectrum of VII was identical with that of the authentic sample.

Fraction B-6 (1.77 g) after chromatography on alumina (grade 1, 45 g) gave compound R_f 0.27 (40% of total reaction mixture). Elution of the column with ether–benzene (1:3) gave 585 mg of purified material (tlc). Crystallization of the product from acetone–methanol gave 460 mg of 4-cholesten-3β-ol (VIII) as colorless needles: mp 128–130°; $[\alpha]^{20}D$ +49.3 (lit.[11] mp 130–132°, $\alpha^{20}D$ +46°). The mixture melting point with authentic sample was undepressed and the infrared spectra were identical.

Fraction B-3 (1.20 g) contained the desired R_f 0.34 compound (12% of total reaction mixture) together with 4-cholesten-3-one (VII). Column chromatography of this fraction on alumina (grade 1, 36 g) and elution with 4% ether in benzene gave 101 mg of highly purified compound (tlc). Recrystallization of this material from petroleum ether gave 71 mg of colorless crystals: mp 114–115°; $[\alpha]^{20}D$ +31.2°; λ_{max} 244 mμ (ε 16,800), identical with starting material I by mixture melting point (no depression) and comparison of infrared spectra.

Irradiation of 1,4-Cholestadien-3-one in the Presence of Sodium Borohydride. A. Kinetic Studies.—A solution of 267 mg (0.7 mmol) of 1,4-cholestadien-3-one in 50 ml of *t*-butyl alcohol (36°) was added to a solution of 212 mg of sodium borohydride in 100 ml of *t*-butyl alcohol (36°). The mixture was immediately placed in the irradiation chamber. Aliquots were removed periodically and absorption at λ_{max} 244 mμ was recorded. Time is given in minutes (optical density units): 0 (1.70); 5 (1.15), 15 (0.62), 30 (0.17) and 60 (0.10). After 75 min, the solution was added to 300 ml of water. The mixture was extracted three times with 50 ml of chloroform. The combined extracts were washed several times with saline water and then dried over sodium sulfate. Evaporation of the solvent gave 290 mg of crude product as a viscous pale yellow oil. Tlc of the reaction mixture showed the presence of five compounds. Glpc showed the presence of six main peak areas at retention times of 1.1 min (minor), 2.1 (major), 3.0 min (major), 4.1 (minor), 4.9 min (major) and 5.8 min (major). For isolation of five of these compounds; *cf.* preparative-scale experiment.

A solution of 154 mg (0.4 mmol) of 1,4-cholestadien-3-one in 100 ml of 2-propanol (36°) was added to a solution of 362 mg (9.6 mmol) of sodium borohydride in 50 ml of 2-propanol (36°). The mixture was irradiated and the ultraviolet absorption was recorded as previously described (time in minutes, OD): 0, 1.20; 5, 0.98, 15, 0.48; 30, 0.14; 60, 0.07. Examination of the reaction mixture by tlc showed identical compounds (R_f and intensity) in comparison with the tlc of the *t*-butyl alcohol reaction product. 2-Propanol irradiation products were not isolated.

B. Preparative Run.—A solution of 5.34 g (14 mmol) of 1,4-cholestadien-3-one in 1 l. of *t*-butyl alcohol (36°) was added to a solution of 4.24 g (115 mmol) of sodium borohydride in 2 l. of *t*-butyl alcohol (36°). The resulting solution was immediately added to the irradiation chamber. Aliquots of the solution were removed periodically during the irradiation period in order to record ultraviolet absorption data as previously described (time in minutes, OD_{244}): 5, 1.50°, 20, 1.20; 40, 0.80; 80, 0.30; 120, 0.14; 150, 0.11. After the reaction was quenched by the addition of 100 ml of water, most of the solvent evaporated under reduced pressure. To the concentrated mixture was added 1 l. of water, followed by extraction with three 75-ml portions of chloroform. The combined chloroform extracts were washed with water, saline water, and then dried over sodium sulfate. Evaporation of the solvent gave 5.45 g of tan solid. The above reaction was repeated to give a total amount of 10.89 g of irradiated material. Tlc of the product showed the presence of one nonpolar compound and four closely related polar compounds (R_f 0.76, 0.53, 0.44, 0.40, 0.36) and several substances near the origin in trace amounts. The crude mixture (10.89 g) was chromatographed on alumina (grade 1, 475 g). The various fractions obtained are summarized in Table V.

Table V

Fractionation of Products Resulting from the Irradiation of Cholestadienone in the Presence of Borohydride

Fraction	Solvent (vol)	Amount, g
BH-1	Hexane (2 l.)	0.06
BH-2	Benzene–hexane (1:9) to ether (16 l. total)	1.67
BH-3	1% methanol in ether (2 l.)	4.02
BH-4	2.5% methanol in ether (2 l.)	2.11
BH-5	5% methanol in ether to chloroform–ethyl acetate–methanol (8 l. total)	2.234

Fraction BH-2 contained the nonpolar R_f 0.76 compound (5% of total crude mixture) together with more polar substances. Approximately 250 mg of this fraction was applied to two preparative tlc plates (20 × 20 × 0.5 mm). The chromatograms were developed with hexane–acetone–ether (8:1:1) and the upper portion of the plates eluted to give a total of 72 mg of pale yellow oil, $[\alpha]^{20}D$ +41.4°. The fraction was dissolved in benzene and the solution frozen to prevent autoxidation of the compound. The R_f value (tlc) of the compound was identical with that of hydrocarbon IX: ultraviolet spectrum λ_{max}^{hexane} 269 mμ (ε 310), 260 (570), 254 (700), 248 (650), 242 (760), and 230 (1110). The nmr spectrum was identical with that of IX. The mass spectrum of this compound showed M^+ 366, *m/e* 364, *m/e* 351 ($M^+ - CH_3$), and *m/e* 211 (ring C fragmentation).

Fraction BH-3 (4.02 g) was chromatographed on 120 g of alumina (grade 3) and eluted with benzene–hexane (1:9) to give 820 mg of thick oil which consisted largely of the R_f 0.53 compound (15% of total). Attempts to crystallize this compound from two solvent systems failed. The material was then rechromatographed on alumina (25 g, grade 3). Elution with benzene–hexane (1:9) gave 68 mg of colorless crystals which were recrystallized from petroleum ether to give 11.4 mg of colorless crystals, mp 142–144°. A second recrystallization from the same solvent gave pure 1-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene (II) as needles, mp 145–146°. The compound was identical with phenol II obtained from the irradiation experiment as shown by mmp 145–147° and identical infrared spectra.

Further elution of the BH-3 column with benzene–hexane (1:3) gave 1.0 g of material containing the R_f 0.40 compound (8% of total reaction mixture) contaminated by two other compounds (tlc). This material was rechromatographed on alumina (30 g, grade 3). Elution with 1, 2.5, 5, and 10% benzene in hexane gave a combined fraction of 531 mg as a

thick yellow oil. Rechromatography of this fraction with grade 2 alumina and elution with benzene–hexane (1:1) and benzene gave 243 mg of the desired compound as a colorless solid contaminated by a compound with lower R_f as shown by tlc. Final purification of the compound was achieved by two preparative tlc procedures. In the final procedure, 96 mg of the mixture was placed on two preparative tlc plates (20 × 20 × 1 mm silica gel G plates containing fluorescein dye). The plates were developed continuously for 6 hr (hexane–acetone–ether, 9:0.5:0.5). Elution of the top uv zone from each plate gave a combined yield of 44 mg of colorless solid. Recrystallization of the solid from methanol gave 21.6 mg of colorless crystalline clusters, mp 108–112°. A second recrystallization from methanol gave 17.3 mg (X): mp 112–113.5°; $[\alpha]^{20}D$ −45.3°; infrared spectrum 3618, 1470, 1385, 1114, 1068, 1032, 1020, 918, 832 cm^{-1}; nmr spectrum (δ) 5.25 (m, olefin), 1.26 (s, C-19 methyl), 0.67 (s, C-18 methyl).

Further elution of the BH-3 column with benzene–hexane (1:1) gave 997 mg of impure compound R_f 0.44 (13% of total). The material was then rechromatographed two times on alumina. The final procedure on elution with benzene and ether–benzene (1:9) (grade 2 alumina) gave a combined yield of 325 mg of product highly enriched in the desired compound, but not crystalline. The material was therefore applied to three preparative tlc plates (1-mm plates containing fluoroscein dye). After continuous development for 3 hr and uv lamp inspection of the plates, the lower portion of the top uv zone was eluted with acetone to give a combined yield of 147 mg. The product was recrystallized from petroleum ether to give two crops of colorless crystals, 20.7 mg, mp 122–123°, and 61.0 mg, mp 125–125.5°. The combined crops were recrystallized from petroleum ether to give 68.4 mg of 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene (IV), as colorless crystals, mp 124.5–125.5°. The compound was identical with IV obtained from the irradiation experiment as shown by mmp 125–126.5° and infrared and ultraviolet spectra.

Fraction BH-4 (2.11 g) was subjected to column chromatography on alumina (grade 1, 63 g). Elution with 0.1, 0.25 and 0.5% methanol in ether gave 1.03 g of combined material containing the desired compound, R_f 0.36 (45% of total reaction mixture), accompanied by minor impurities. The material was then rechromatographed two more times on alumina, the final procedure (17 g, grade 3) after elution with benzene–hexane (1:1) gave 220 mg of pure product. Recrystallization from petroleum ether gave colorless fine needles, mp 126.5–127.5°. A second recrystallization from the same solvent gave pure 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10)-triene (III), mp 128–128.5°. The compound was identical with III obtained from the irradiation experiment with regard to infrared spectrum and mmp 126.5–127.5°.

Registry No.—I, 566-91-6; II, 19202-72-3; III, 17605-79-7; IV, 19202-74-5; V, 19202-75-6; VI, 19202-76-7; IX, 2603-79-4; sodium borohydride, 1303-74-8.

Steroids. LXXX.[1] The Effect of C-12 Substitution on the Reactivity of Δ^{16}-20-Keto Steroids toward 1,4-Nucleophilic Addition[2,3]

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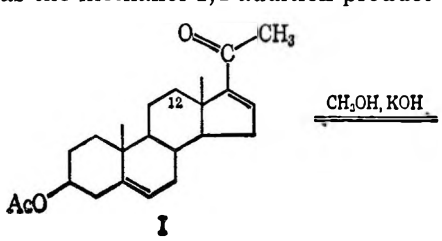
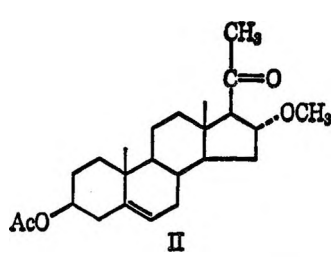
The presence of a ketone function at C-12 has a marked rate accelerating effect on 1,4 additions to Δ^{16}-20-keto steroids. The rates of the base-catalyzed 1,4 addition of methanol to a wide variety of 12-substituted Δ^{16}-20-keto steroids have been measured. On the basis of nmr and ultraviolet spectral data it is concluded that the rapid rate of reaction exhibited by the 12-keto steroids is anomalous. A mechanism is proposed to explain the unexpected rate of 1,4 addition displayed by Δ^{16}-12,20-diketo steroids. This effect is shown to be applicable to a number of nucleophiles, some of which undergo further reaction to produce polycyclic derivatives.

In 1951, Fukushima and Gallagher[4] characterized the product obtained from the action of methanolic potassium hydroxide on Δ^{16}-pregnenolone acetate (I) as the methanol 1,4-addition product II.

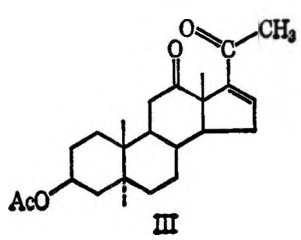


I



II

Mueller, *et al.*,[5] have shown that the presence of a ketone at C-12 greatly increases the rate of this reaction. Adams, *et al.*,[6] have also observed this effect and attributed the increased reactivity to the polar effect of the 12-ketone on the adjacent conjugated system. In an earlier publication[7] we reported the facile base-catalyzed 1,4 addition of acetone to the 12-keto compound III.[8] The 12-deoxy analog I[9] failed to



III

react with acetone under the same conditions. It occurred to us that the increased reactivity of III could

(1) Previous paper in this series (Steroids. LXXIX): C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.* **33**, 2789 (1968).

(2) (a) The research in this paper was supported under Contract SA-43-ph 4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. (b) Presented at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov, 1967.

(3) Taken from the M.S. Thesis of G. S. Abernethy, Jr., North Carolina State University, 1967.

(4) D. F. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.*, **73**, 196 (1951).

(5) G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *ibid.*, **75**, 4888 (1953).

(6) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuard-Webb, *J. Chem. Soc.*, 2209 (1954).

(7) M. E. Wall, S. Serota, H. E. Kenney, and G. S. Abernethy, *J. Amer. Chem. Soc.*, **85**, 1844 (1963).

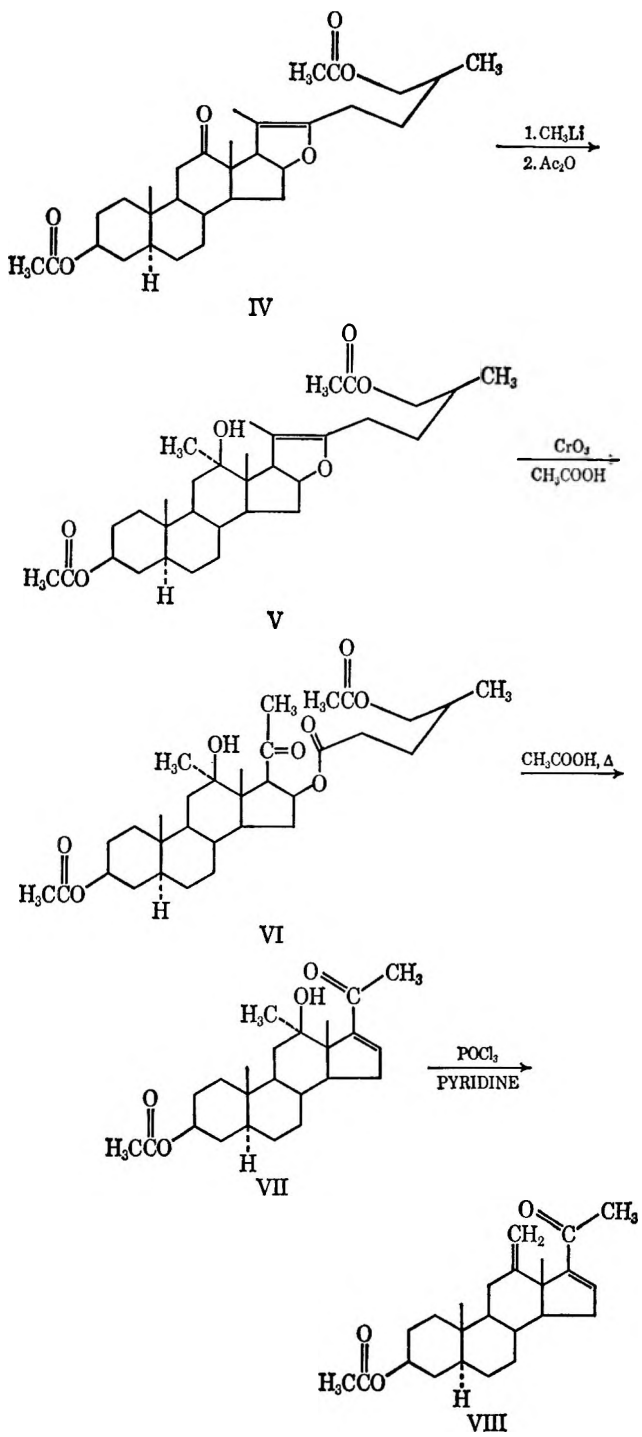
(8) R. B. Wagner, J. A. Moore, and R. F. Forker, *ibid.*, **72**, 1856 (1950).

(9) D. H. Gould, H. Staeudle, and E. B. Hershberg, *ibid.*, **74**, 3685 (1952).

be attributed to ring strain imposed by sp^2 hybridization at C-12 added to that already present in the Δ^{16}-20 keto moiety.

With this in mind, we undertook the synthesis of the 12-methylene analog. This moiety incorporates the steric requirements of III while lacking the polar contributions of the ketone. After several unsuccessful attempts employing the Wittig reaction, a successful synthesis was accomplished as outlined in Scheme I.

SCHEME I



Treatment of pseudohecogenin diacetate (IV)[5] with methyllithium[10] and reacetylation gave 12β-hydroxy-12α-methylpseudotigogenin diacetate (V). Low temperature chromic acid oxidation led to the formation of triester VI. The side chain was cleaved in refluxing acetic acid to give 3β-acetoxy-12β-hydroxy-12α-methyl-5α-pregn-16-en-20-one (VII). The structure of VII and the stereochemistry of the 12β-hydroxy-12α-methyl moiety rests on the evidence, which includes (1) method of preparation; (2) correct analysis for the calculated molecular formula; (3) λ_{max} 242 mμ (ϵ 8250) in accord with postulated Δ^{16}-20 keto moiety; (4) the infrared spectrum indicating strong intramolecular hydrogen bonding (of the 12β-hydroxy and the C-20 carbonyl groups) identical with that observed with the known 12β-hydroxy-12α-methoxy and 12β-hydroxy Δ^{16}-20-ketone compounds.[11] This establishes the configuration at C-12. The nmr spectrum is in accord with the proposed structure showing the presence of five methyl groups and an olefinic proton appearing at δ 6.95. Treatment of the tertiary alcohol with phosphorus oxychloride in pyridine afforded the desired product, 3β-acetoxy-12-methylene-5α-pregn-16-en-20-one (VIII). The structure of VIII derives from its method of preparation[12] and correct analytical values. In particular the presence of the C-12 methylene moiety is shown by the nmr spectrum which shows two singlets at δ 4.38 and 4.63. Molecular models explain the nonequivalency of the C-12 methylene protons as one of them is in close proximity to the C-20 carbonyl.

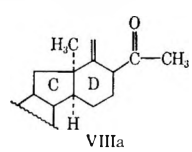
The rates of 1,4 addition of the various steroids were compared by treating the steroid (10^{-4} *M*) with 0.1 *N* methanolic potassium hydroxide. Because of the large excess of methoxide ion employed pseudo-first-order kinetics are observed. The reaction rates were measured by observing the rate of decrease of the ultraviolet absorption maxima. The specific first-order rate constants of a variety of Δ^{16}-20-keto steroids are listed in Table I. These values must be regarded as approximate due to slight variations in temperature.

It is seen that the 12-methylene steroid VIII reacts at

(10) The reaction of methyllithium with steroidal 12-ketones was first described by P. Bladon [*J. Chem. Soc.*, 2191 (1960)] and G. Just [*Can. J. Chem.*, **39**, 548 (1961)].

(11) (a) M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960); (b) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955).

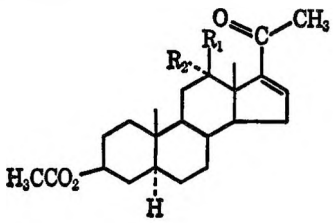
(12) One of the referees has suggested that an alternative structure VIIIa, a C-nor-D-homo product, is not excluded by the data presented. It is indeed



difficult *via* the physical data (ir, uv, nmr, and C and H analysis) to differentiate VIII and VIIIa, particularly since appropriate model compounds are lacking. S. G. Levine and M. E. Wall [*J. Amer. Chem. Soc.*, **82**, 391 (1960)] characterized the 12-methyl-12-hydroxy epimers produced by Grignard reaction of methylmagnesium bromide with the 12-ketosapogenin, hecogenin. On dehydration of the epimers with thionyl chloride in pyridine, *a method closely analogous* to that used in our procedure, a separable mixture of *endo* and *exo* olefins was obtained. Treatment of the *exo* olefin with osmium tetroxide followed by periodate oxidation gave the starting product *hecogenin in 65% yield.* Hence, the methylene group must be at position 12 in the product of Levine and Wall and by close analogy is placed similarly in our compound VIII. It can be stated parenthetically that the C-nor-D-homo rearrangement is characteristically observed on solvolysis of 12β-mesylates or -tosylates (an excellent review of this rearrangement is found in N. L. Wendler, "Molecular Rearrangements," Part II, Paul de Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, Chapter 16). In these compounds only the C-13–C-14 bond is located in an appropriate position to participate in this reaction, whereas in dehydration of the 12β-hydroxy-12α-methyl tertiary alcohol VIII, the formation of the exo-methylene would (from the data of Levine and Wall) be favored [*cf.* D. H. R. Barton, A. Campus-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956), for similar *exo*-methylene formation by dehydration of 3β-hydroxy-3α-methylcholestane].

TABLE I

FIRST-ORDER SPECIFIC RATE CONSTANTS FOR THE REACTION OF Δ^{16}-20-KETO STEROIDS WITH 0.1 *M* METHANOLIC POTASSIUM HYDROXIDE

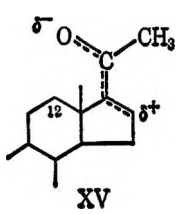


Compd no.	C-12 substituents	Specific rate constant, min^{-1}
IX	R_1 = OH, R_2 = H	0.30[a]
X	R_1R_2 = O=, $\Delta^{9(11)}$	0.072
XI	R_1 = R_2 = H, 11-ketone	0.043
III	R_1R_2=O=	0.028
XII	R_1 = H, R_2 = OH	0.0075
I	R_1 = R_2 = H, Δ^5	0.0055
XIII	R_1 = R_2 = H	0.0051
VIII	R_1R_2=H_2C=	0.0027
VII	R_1 = OH, R_2 = CH_3	0.0013
XIV	R_1R_2= 	0.00066

[a] Minimum value.

a rate slower than either of the 12-unsubstituted analogs I and XIII. Thus the rapid reaction rate exhibited by the 12,20-diketo-Δ^{16}-pregnenes cannot be attributed to sp^2 hybridization at C-12.

The Electrostatic Effect.—The reaction of Δ^{16}-20-keto steroids with a nucleophile requires the development of a partial positive charge at C-16. This positive center is attained through a number of resonance forms which may be summarized as the resonance hybrid (XV).



XV

In order to determine the nature of the effect of substituents at C-12 on the susceptibility of the conjugated system to nucleophilic attack, it was desirable to obtain a measurement of the relative electron densities at C-16. It was found that this information could be obtained by observing the chemical shift of the C-16 proton in the nmr spectra of these compounds. These data are presented in Table II. If the 12-unsubstituted moieties, I and XIII[13] are taken as reference compounds, it is evident that the presence of an ethylene ketal at C-12 (compound XIV)[14] produces a shielding effect on the olefinic C-16 proton. This indicates a relatively high electron density at C-16 in XIV. We believe that this shielding is due to electrostatic repulsion between the ketal oxygens and the C-20 carbonyl which inhibits the formation of the resonance hybrid XV. This effect is similar to that of a 12β-acetoxy group on the Δ^{16}-20-ketone system discussed by Snatzke and Schwinum.[15]

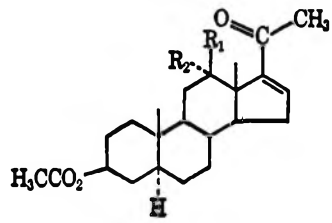
(13) P. A. Plattner, L. Ruzicka, H. Heusser, and E. Angliker, *Helv. Chim. Acta.*, **30**, 385 (1947).

(14) The preparation and physical constants of this compound are given in the Experimental Section.

(15) G. Snatze and E. Schwinum, *Tetrahedron*, **22**, 761 (1966).

TABLE II

NMR CHEMICAL SHIFT OF THE C-16 PROTON IN Δ^{16}-20-KETO STEROIDS[a]



Compd no.	C-12 substituents	Chemical shift of proton, ppm (δ)
XIV	R_1R_2 =	6.55
III	R_1R_2 = O=	6.62
X	R_1R_2 = O=, $\Delta^{9(11)}$	6.62
XIII	R_1 = R_2 = H	6.72
I	R_1 = R_2 = H, Δ^5	6.74
VIII	R_1R_2 = H_2C=	6.75
XII	R_1 = H, R_2 = OH	6.76
XI	R_1 = R_2 = H, 11-ketone	6.80
VII	R_1 = OH, R_2 = CH_3	6.95
IX	R_1 = OH, R_2 = H	6.98

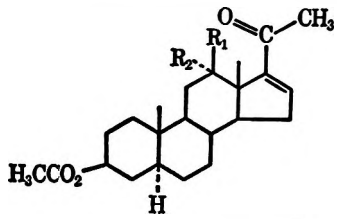
[a] Spectra were obtained in deuteriochloroform solution using a Varian spectrometer operating at 60 Mc and calibrated against internal tetramethylsilane.

As these data predict, XIV exhibits a very slow rate of 1,4 addition as shown in Table I. The two 12-keto moieties III and X[16] also show a high field shift of the 16-proton. In analogy to the ketal XIV, this observation can be attributed to oxygen–oxygen repulsion between the C-12 and C-20 ketones. In view of these data, III and X would be expected to display a relatively slow rate of 1,4 addition. However, as shown in Table I both of the 12-keto moieties react very rapidly with methanolic potassium hydroxide. The chemical shift of the 16 proton in the 12-methylene derivative VIII and 12α- (axial) hydroxy analog[14] approximates those of the 12-unsubstituted compounds I and XIII. Table I shows that XII reacts slightly faster than the dihydro compounds while VIII reacts at a slower rate. The 11-keto moiety XI[17] shows a slight shift of the 16 proton to lower field indicating a relatively low electron concentration in this region. This observation provides an explanation for the rapid rate of 1,4 addition displayed by XI as shown in Table I. The olefinic protons of the 12β-hydroxy-12α-methyl compound VII and the 12β-hydroxy analog IX exhibit the greatest downfield shift, indicating an electron-deficient center at C-16. This observation can be explained by the strong intramolecular hydrogen bond[15] between the 12β- (equatorial) hydroxyl and the C-20 carbonyl which would stabilize the resonance hybrid XV. These data predict that VII and IX would undergo 1,4-nucleophilic addition at a very rapid rate. This prediction is realized in the case of the 12β-hydroxy compound IX (Table I) while the 12β-hydroxy-12α-methyl derivative VII reacts at a slow rate. Molecular models indicate that the 12α- (axial) methyl function of VII offers considerable steric interaction with the α face of C-16. This interaction could effectively hinder the rear-side attack of a

(16) D. Rosenthal and J. P. Gratz, *J. Org. Chem.*, **34**, 409 (1969).

(17) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, *J. Amer. Chem. Soc.*, **73**, 2396 (1951).

TABLE III
ULTRAVIOLET ABSORPTION MAXIMA OF Δ^{16}-20-KETO STEROIDS

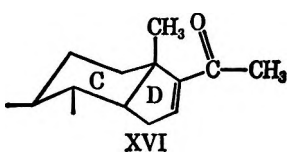


Compd no.	C-12 substituents	λ_{max}, mμ	ϵ_{max}, M^{-1} cm^{-1}	Ref
III	R_1R_2 = O=	227–230	8,510	8
X	R_1R_2 = O=, $\Delta^{9,11}$	229[a]	17,000[a]	16
XI	R_1 = R_2 = H, 11-ketone	234.5	9,050	17
XIV	R_1R_2 = 	236	7,500	
VIII	R_1R_2 = H_2C=	237	7,800	
XII	R_1 = H, R_2 = OH	237.5	8,850	
I	R_1 = R_2 = H, Δ^5	239	9,100	4
XIII	R_1 = R_2 = H	240	10,000	13
IX	R_1 = OH, R_2 = H	242	8,800	*b*
VII	R_1 = OH, R_2 = CH_3	242	8,250	

[a] ϵ_{max} of the Δ^{16}-20-ketone chromophore is taken as 8500. [b] M. E. Wall, F. I. Carroll, and G. S. Abernethy, Jr., *J. Org. Chem.*, **29**, 604 (1964).

nucleophile at C-16 and thus decrease the rate of reaction. The nmr data correlate well with the reaction rates in Table I with the exception of the 12-keto moieties I and X. The reaction rates of these compounds seem to be anomalous.

The Steric Effect.—Mueller, *et al.*,[5] have demonstrated that Δ^{16}-20-keto steroids exist predominantly in the *s-trans* conformation (XVI). The most stable



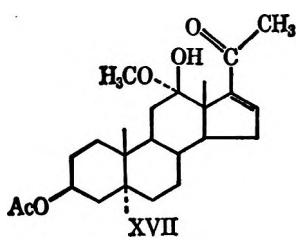
XVI

conformation is that in which the 16,17 double bond and the C-20 carbonyl are coplanar. This conformation allows maximum π-orbital overlap which is necessary for the formation of the resonance hybrid (XV). Any factor which disrupts the planarity of the conjugated system will effectively inhibit the formation of the resonance hybrid by decreasing the π-orbital overlap. Molecular models indicate that the spacial proximity of an equatorial substituent at C-12 to the C-20 carbonyl of a Δ^{16}-20-keto steroid in the *s-trans* coplanar conformation is sufficient to cause considerable steric interaction between the two functions.

Braude, *et al.*,[18] found that this deviation from planarity of a conjugated system may be measured by ultraviolet spectroscopy. A structural change which causes the conjugated system to twist slightly from planarity results in a decrease in absorption with little change in wavelength. A more severe twist in the chromophore results in a decrease in absorption accompanied by a shift to shorter wavelength. The ultraviolet spectral parameters for the steroids studied are listed in Table III. It has been shown by circular dichroism measurements[15] that the conjugated enone system of the 12β-hydroxy compound IX is essentially *s-trans* and coplanar. If this compound is taken as a reference, the degree of steric distortion of the conjugated system of the remaining steroids can be estimated. The 12-ethylenedioxy compound XIV and the 12-methylene analog VIII shows a distinct decrease in absorption indicating a slight out of plane distortion of the enone system. Accordingly, Table I shows that these compounds undergo 1,4 addition at a slower rate than does the 12β-hydroxy moiety. The 12-keto steroids III and X exhibit a hyposchromic shift accompanied by a slight decrease in absorption. This indicates a rather severe distortion of the conjugated system and predicts a slow rate of 1,4 addition. However, both 12-keto steroids display a rapid rate of 1,4 addition as shown in Table I.

The reactivity of the 12-keto steroids is thus apparently anomalous. The nmr spectra indicate a relatively high electron density at C-16 which is not conducive to nucleophilic addition. Also the ultraviolet spectra indicate a severe distortion of the conjugated system which inhibits the development of a positive center at C-16; yet these compounds display a rapid rate of nucleophilic addition.

Proposed Mechanism for 1,4 Addition to Δ^{16}-12,20-Diketo Steroids.—Bearing in mind the rapid reaction rate displayed by the 12β-hydroxy compound IX (Table I), a possible mechanism occurred to us. Wall and Serota[11] have isolated the hemiketal XVII from a methanolic solution of diketone III.



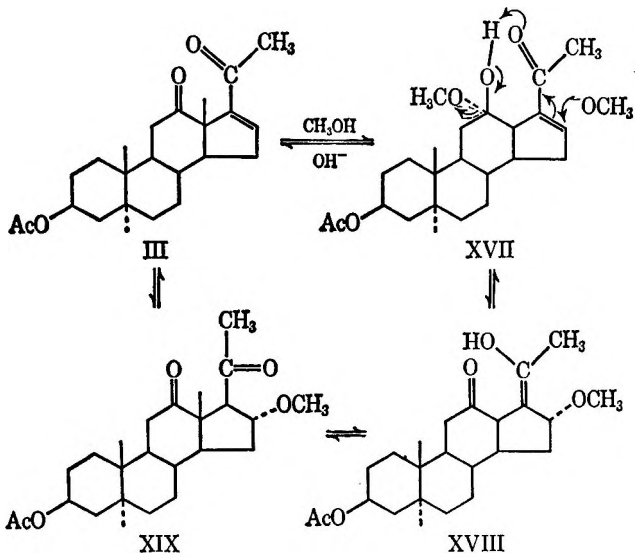
XVII

It was impossible to measure effectively the rate of 1,4 addition of methanol to XVII owing to rapid decomposition to diketone III in the strong basic media. This observation does not preclude the existence of XVII in basic solution, although its concentration is undoubtedly low.

(18) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 1890 (1949).

In view of these considerations, we can rationalize the apparently anomalous rate of 1,4 addition displayed by Δ^{16}-12,20-diketo steroids by Scheme II. The first step involves solvolysis of the 12-ketone to form hemiketal XVII. Attack of methoxide ion at C-16 is followed by abstraction of the hydrogen from the 12β-hydroxyl group. This leads to the expulsion of the 12α-methoxyl group to yield enol XVIII. This enol can rapidly

SCHEME II

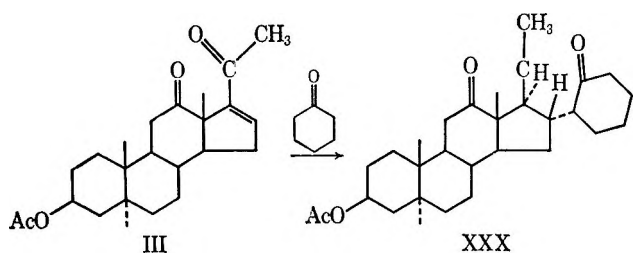


ketonize to form the expected 1,4-addition product XIX.[19] In consideration of the data presented thus far, it is unlikely that XIX is formed directly from III to an appreciable extent.

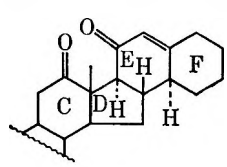
Consideration of certain physical data makes this mechanism more attractive. The strong intramolecular hydrogen bond of the hemiketal XVII should stabilize the resonance hybrid XV, producing a region of low electron density at C-16 and making this moiety more susceptible to nucleophilic attack. The C-16 proton of XVII appears at δ 6.96 in the nmr spectrum, indicating a relatively low electron concentration in this region (see Table II).

The Reaction of Δ^{16}-20-Keto Steroids with Various Nucleophiles.—The addition of nucleophiles to Δ^{16}-20-keto steroids to give 16α-substituted steroids has been reported by many authors.[4,7,20,21] In the previous section we have presented data which explain the greater reactivity of Δ^{16}-12,20-diketopregnenes toward attack by methoxide ion. In this section we wish to show that this is a *general* reaction with applicability to a variety of nucleophiles. As substrates we have chosen the readily available 3β-acetoxy-pregna-5,16-dien-20-one (I) and 3β-acetoxy-5α-pregn-16-ene-12,20-dione (III). In the previous section we have shown that steroids with a Δ^5 or 5α fusion had identical first-order rate constants with respect to the addition of methoxide ion to C-16. Hence I and III should be reasonably comparable in regard to the rate of nucleophilic attack on the conjugated system. If appropriate reaction conditions are selected, the increased reactivity of III becomes evident as shown in Table IV. It is seen that both substrates react with strong nucleophiles such as cyanide ion, ethylenimine and benzyl mercaptide anion under mild conditions. Under comparable conditions in the presence of a quaternary ammonium hydroxide, nitromethane, nitroethane, acetylacetone, ethyl cyanoacetate, cyclohexanone, and cyclopentanone react only with the 12-keto moiety. Cycloheptanone also reacted with III under these conditions, but the product was not crystalline. It is interesting to note that Mazur and Cella[21b] were able to effect the addition of acetylacetone and ethyl cyanoacetate to the 12-deoxy analog I by employing a stronger base. Similarly, as shown in Table IV, nitromethane and cyclohexanone react with I under more stringent conditions.

Reaction of I and III with cyclohexanone has led to some novel polycyclic compounds containing two rings fused at C-16 and C-17 in addition to the tetracyclic steroid nucleus. Cyclohexanone under mild basic conditions reacts with III to give the normal Michael adduct XXX. The stereochemistry at C-16,C-17 is



based on analogy with many previous similar studies.[20,21] In the presence of a stronger base such as sodium methoxide, XXX smoothly undergoes an aldol condensation to yield XXXIII. The structure and



XXXIII

stereochemistry is postulated on the following grounds: (1) agreement of analytical values with the postulated structure; (2) the presence of a conjugated carbonyl as shown by the ultraviolet spectrum, λ_{max} 240 mμ; (3) the infrared spectrum showing strong bands at 1735, 1712, and 1685 cm^{-1} in accord with the presence of the expected acetate, 12-ketone, and conjugated ketone moieties; (4) the nmr spectrum (*cf.* Experimental Section), also in accord with the proposed structure. The ring fusion at C-16,C-17 is based on analogy to a

(19) *A priori* this mechanism may seem to be precluded by the slow rate of 1,4 addition displayed by the 12β-hydroxy-12α-methyl moiety VII which was attributed to steric inhibition of the rear-side attack of methoxide ion at C-16 by the 12α-methyl group. The 12α-methoxyl group in XVII might be expected to hinder the axial attack in a similar fashion. However, molecular models indicate that a 12α-methyl group offers considerably more steric interaction with the α face of C-16 than does a 12α-methoxyl group. This observation is supported by the work of R. W. Taft, Jr. [*J. Amer. Chem. Soc.*, **74**, 3120 (1952)], who found that the rate of acid-catalyzed hydrolysis of *o*-methoxybenzamide is considerably faster than that of *o*-methylbenzamide. It is stated that this effect is steric in nature, and that polar effects are negligible.

(20) (a) J. Romo, M. Romo, C. Djerassi, and G. Rosencrantz, *ibid.*, **73**, 1528 (1951); (b) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954).

(21) (a) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956). (b) R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959). (c) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961). (d) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. Maekellar, *ibid.*, **28**, 2499 (1963). (e) F. Schneider, J. Hamsher, and R. E. Beyler, *Steroids*, **8**, 553 (1966).

TABLE IV

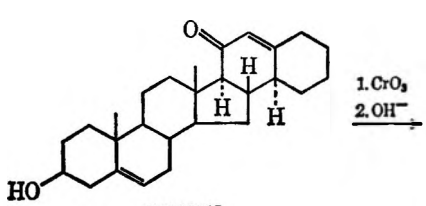
COMPARISON OF THE REACTIVITY OF 12-DEOXY AND 12-KETO-Δ^{16}-20-KETO STEROIDS WITH VARIOUS NUCLEOPHILES

Reactant	Reaction conditions[a]	Product, 16α substituent: 12-Deoxy	Product, 16α substituent: 12-Keto
Sodium cyanide	A	XX, –CN	XXI, –CN
Ethylenimine	B	XXII,	XXIII,
Benzyl mercaptan	C	XXIV,	XXV,
Nitromethane	C	NR[b]	XXVI, $-CH_2NO_2$
Nitroethane	C	NR	XXVII, $-CH(CH_3)NO_2$
Acetylacetone	C	NR	XXVIII, $-CH(COCH_3)C(=O)CH_3$
Ethyl cyanoacetate	C	NR	XXIX, $-CH(CN)COC_2H_5$
Cyclohexanone	C	NR	XXX,
Cyclopentanone	C	NR	XXXI,
Nitromethane	D	XXXII, $-CH_2NO_2$	
Cyclohexanone	D	XXXIV,	

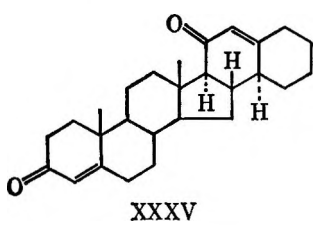
[a] A, 95% ethanol, heat; B, triethylamine catalyst; C, $R_4N^+OH^-$, tetrahydrofuran, heat; D, $(CH_3)_3CO^-K^+$ in $(CH_3)_3COH$. [b] NR, no appreciable reaction.

similar reaction of III with acetone[7] in which the stereochemistry was carefully determined. The assignment of the fusion of rings E and F is based on the fact that the reaction product is thermodynamically controlled. Thus the stable chair form of rings E and F would be predicted by conformational analysis.

As described previously, cyclohexanone failed to react with I under mild conditions. Under more rigorous conditions with potassium *t*-butoxide, Michael addition and aldol cyclization took place to give XXXIV. The physical properties are in accord with



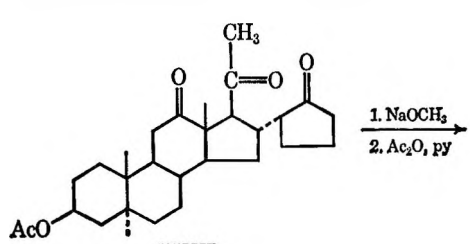
XXXIV



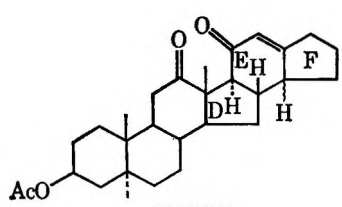
XXXV

the assigned structure. The stereochemistry is assigned on the same basis as described for XXXIII above.

Jones oxidation as described by Djerassi[22] gave the Δ^5-3-ketone which was not isolated, but was isomerized under basic conditions to XVIII, λ_{max} 240 mμ (ε 28,900). Cyclopentanone failed to react with I under mild conditions, but formed the Michael adduct XXXI when treated with III. Aldol cyclization of XXXI to XXXVI proceeded in poor yield presumably because of the ring strain involved in the fusion of a five-membered and a six-membered ring. The stereochemistry of the fusion of rings D and E is based on arguments previously



XXXI



XXXVI

(22) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

cited. The fusion of rings E and F cannot be firmly predicted on the basis of the evidence at hand.

Experimental Section[23]

3β-Acetoxy-12β-hydroxy-12α-methyl-5α-pregn-16-en-20-one (VII).—To 119 ml of a 5.2% solution of methyllithium in ether was added dropwise with stirring a solution of 10.29 g of pseudohecogenin diacetate[5] in 200 ml of dry ether. The resulting mixture was stirred at room temperature for 48 hr and 300 ml of water and 200 ml of ethyl acetate were added. The phases were separated and the aqueous layer was extracted several times with an ether–ethyl acetate solution. After drying the combined organic extracts over sodium sulfate, evaporation of the solvent under reduced pressure gave 8 g of a colorless solid. The infrared spectrum shows a very weak carbonyl absorption.

This solid was dissolved in a solution of 30 ml of pyridine and 20 ml of acetic anhydride. After standing at room temperature overnight, the liquid was removed *in vacuo* to give 10.9 g of a glassy residue. This material was dissolved in methylene chloride and the solution was washed with successive portions of 10% hydrochloric acid solution, 10% sodium bicarbonate solution and water. After drying over anhydrous magnesium sulfate, the solvent was evaporated, leaving 10.1 g of a solid residue. The infrared spectrum of this material showed a weak hydroxyl band at 3600 cm^{-1} and a strong carbonyl absorption at 1720 cm^{-1}. To a stirred solution of 10 g of this material in 50 ml of ethylene dichloride and 50 ml of acetic acid at −5° was added dropwise a precooled solution of 5 g of chromium trioxide in 50 ml of 90% acetic acid. After the addition was complete, the solution was stirred at −5° for 1 hr and 50 ml of a 10% aqueous sodium metabisulfite solution was added. The temperature was maintained below 0° during the addition. The organic layer was separated, and the aqueous layer was extracted several times with methylene chloride. The combined extracts were washed with water and with sodium bicarbonate solution until neutral. After drying over sodium sulfate, evaporation of the solvent afforded 9.3 g of a green glass. The infrared spectrum shows a strong carbonyl absorption at 1730 cm^{-1} with a shoulder at 1700 cm^{-1}.

An 8-g sample of this residue was dissolved in 120 ml of glacial acetic acid and the solution was heated under reflux for 2 hr. The hot solution was poured into a large volume of water, and the resulting suspension was extracted several times with methylene chloride. The combined extracts were washed with water and with sodium bicarbonate solution until neutral. After drying, the solvent was removed *in vacuo* to give 6 g of a brown, glassy residue. This material was chromatographed on 300 g of activity III neutral alumina using a gradient elution system consisting of benzene and a solution of 10% ether in benzene. A fraction weighing 2.01 g crystallized from heptane to give 1.93 g of the desired product: mp 164–166; $[\alpha]D$ +40°; λ_{max} 242 mμ (ε 8250); $\nu_{max}^{CS_2}$ 3050, 1728, 1650, 1375, 1248, 1025, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.87, 0.93, 1.16, 2.02, 2.37 (singlets, 3 H each), 4.71 (multiplet, 1 H), 6.97 (multiplet, 1 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.73.

3β-Acetoxy-12-methylene-5α-pregn-16-en-20-one (VIII).—A solution of 1.5 g of VII in 60 ml of dry pyridine and 1.35 ml of phosphorus oxychloride was allowed to stand at room temperature overnight. The solution was cooled to 0° and 7.5 ml of water was added. After removal of the liquid under reduced pressure, water was added to the residue and the resulting suspension was extracted with several portions of ether. After washing with sodium bicarbonate solution and drying, the solvent was evaporated to give 1.25 g of a solid. Crystallization from 95% ethanol afforded 0.87 g of needles which melted at 151–155.5°. An analytical sample crystallized from 95% ethanol: mp 156–157°; $[\alpha]D$ +164°; λ_{max} 237 mμ (ε 7800); $\nu_{max}^{CS_2}$ 3085, 3045, 1728, 1670, 1245, 1030, 885, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.90, 1.12, 2.02, 2.33 (singlets, 3 H each), 4.38, 4.63 (singlets, 1 H each), 4.60 (multiplet, 1 H), 4.05 (multiplet, 1 H), 6.75 (multiplet).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.49; H, 9.36.

3β-Acetoxy-12-ethylenedioxy-5α-pregn-16-en-20-one (XIV).—A mixture consisting of 10 g of III, 250 ml of benzene, 0.6 g of *p*-toluenesulfonic acid, and 40 ml of ethylene glycol was heated under reflux with vigorous stirring for 0.5 hr. The water formed was continuously removed with a Dean–Stark water trap. The two-phase mixture was cooled and washed with sodium bicarbonate solution and with water. After drying over magnesium sulfate, removal of the solvent *in vacuo* gave 12.5 g of a glassy residue. This material was dissolved in benzene and chromatographed on 200 g of Florisil. A fraction eluted with 5% ethyl acetate–95% benzene crystallized from isopropyl alcohol to give 8.1 g of crystals which melted at 131–134°. A pure sample was crystallized from the same solvent: mp 140–143°; $[\alpha]D$ +30°; λ_{max} 236 mμ (ε 7500); $\nu_{max}^{CS_2}$ 3050, 1730, 1680, 1365, 1245, 1075, 1032, 975, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.85, 1.15, 2.02, 2.30 (singlets, 3 H each), 3.92 (singlet, 4 H), 4.68 (broad multiplet, 1 H), 6.55 (doublet, 1 H).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.82; H, 8.75.

3β-Acetoxy-12α-hydroxy-5α-pregn-16-en-20-one (XII) and 3β-Acetoxy-12β-hydroxy-5α-pregn-16-en-20-one (IX).—To a solution of 20 g of dione III in 400 ml of tetrahydrofuran at 6° was added 16.4 g of lithium tri-*t*-butoxyaluminohydride. The resulting solution was maintained at 6–8° for 2 hr and 25 ml of saturated sodium sulfate solution was added slowly with stirring. This mixture was dried over anhydrous sodium sulfate and the solid was removed by filtration. The solvent was removed under reduced pressure to give 19.4 g of a colorless glass. Crystallization from 95% ethanol afforded 10.2 g of crystals, mp 212–217°. The infrared spectrum of this material was identical with that of an authentic sample of 3β-acetoxy-12β-hydroxy-5α-pregn-16-en-20-one. Concentration of the filtrate yielded an additional 2.4 g of crystals. A thin layer chromatogram (silica gel G–15% acetone, 85% benzene) indicated a mixture of two components. This mixture was chromatographed on 60 g of Florisil using a gradient elution system consisting of 500 ml of benzene and 500 ml of a 5% acetone–85% benzene solution. This procedure gave 0.72 g of IX and 1.6 g of a mixture.

Preparative thin layer chromatography of 0.2 g of this mixture on a silica gel plate (40 × 20 × 0.2 cm) eluted with a solution of 15% acetone in benzene afforded 0.081 g of IX. The second component crystallized from ether–petroleum ether (bp 30–60°) to give 0.093 g of pure 3β-acetoxy-12α-hydroxy-5α-pregn-16-en-20-one: mp 191.5–192.5°; $[\alpha]D$ +74°; λ_{max} 237.5 mμ (ε 8850); $\nu_{max}^{CS_2}$ 3610, 3057, 1735, 1663, 1365, 1245, 1030, 822; nmr ($CDCl_3$) δ 0.89 (singlet, 6 H), 2.30, 2.01 (singlets, 3 H each), 4.46 (triplet, 1 H), 4.70 (broad multiplet, 1 H) 6.76 (multiplet, 1 H).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.90; H, 9.17.

3β-Hydroxy-16α-cyanopregn-5-en-20-one (XX).—To 1 g of I in 50 ml of 95% ethanol was added 0.69 g of sodium cyanide. This mixture was refluxed for 1 hr and cooled to room temperature and the solvent was removed under reduced pressure. Water was added to the residue and the resulting suspension was extracted several times with dichloromethane. After drying over anhydrous sodium sulfate, the combined extracts were evaporated under reduced pressure to give 0.92 g of solid. This material was crystallized from ethyl acetate to give 0.65 g: mp 225–228° [a second crystallization from ethyl acetate raised the melting point to 230–232° (lit.[21b] mp 231–234°)]; $\nu_{max}^{CH_2Cl_2}$ 3600, 2245, 1710, 1362, 1048 cm^{-1}; nmr δ 0.60, 1.02, 2.22 (singlets, 3 H each), 3.53 (broad multiplet, 2 H), 5.36 (multiplet, 1 H).

3β-Acetoxy-16α-cyano-5α-pregnane-12,20-dione (XXI).—A mixture of 1 g of III, 0.72 g of sodium cyanide, and 50 ml of 95% ethanol was refluxed for 1 hr. After cooling, the solvent was removed *in vacuo* and water was added to the residue. This suspension was extracted with methylene chloride and the extracts were dried over anhydrous sodium sulfate. Removal of the solvent gave 0.92 g of a solid. This material was dissolved in a solution consisting of 2 ml of pyridine and 2 ml of acetic anhydride and allowed to stand at room temperature overnight. The liquid was removed *in vacuo* and the residue was dissolved in dichloromethane. This solution was washed with successive portions of dilute hydrochloric acid solution, dilute sodium bicarbonate and water. After drying over sodium sulfate, the solvent was removed and the residue was crystallized from methanol to give 0.72 g of crystals, mp 221–224°. A pure sample crystallized from methanol: mp 225–228°; $[\alpha]D$ +125°; $\nu_{max}^{CH_2Cl_2}$ 2246, 1728, 1710, 1370, 1270, 1030 cm^{-1}; nmr δ 0.90, 0.93, 2.04, 2.35 (singlets, 3 H each), 3.66 (multiplet, 2 H), 4.66 (multiplet, 1 H).

(23) Unless otherwise noted, all melting points were obtained on the Kofler hot stage, optical rotations in chloroform solution and ultraviolet spectra in methanol solution. Nmr spectra were obtained in deuteriochloroform solution using a Varian spectrometer operating at 60 Mc and calibrated against internal tetramethylsilane.

Anal. Calcd for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33. Found: C, 72.07; H, 8.23.

3β-Acetoxy-16α-(1′-aziridinyl)pregn-5-en-20-one (XXII).—A solution of 12 g of I in 100 ml of ethylenimine containing 2 ml of triethylamine was allowed to stand at room temperature overnight. The liquid was removed under reduced pressure and the residue was crystallized from ether to give 11.7 g of fine needles, mp 156–158°. A pure sample crystallized from ether: mp 158–159° (lit.[21e] mp 152–154°); $[\alpha]D$ −16°; $\nu_{max}^{CS_2}$ 3060, 1735, 1704, 1360, 1240, 1032 cm^{-1}; nmr δ 0.62, 1.02, 2.03, 2.20 (singlets, 3 H each), 4.67 (broad multiplet, 1 H), 5.45 (multiplet, 1 H).

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51. Found: C, 74.91; H, 9 34; N, 3.54.

3β-Acetoxy-16α-(1′-aziridinyl)-5α-pregnane-12,20-dione (XXIII).—A solution of 10 g of III in 100 ml of ethylenimine containing 2 ml of triethylamine was allowed to stand at room temperature for 2.5 hr. The liquid was removed *in vacuo* and the residue was crystallized from petroleum ether (bp 30–60°) to give 9.9 g, mp 141–144°. An analytical sample crystallized from ether: mp 146–148°; $[\alpha]D$ +104°; $\nu_{max}^{CS_2}$ 3059, 1735, 1709, 1245, 1035 cm^{-1}; nmr δ 0.92 (singlet, 6 H) 2.02, 2.36 (singlets, 3 H each), 3.47 (doublet, 1 H), 4.70 (broad multiplet, 1 H).

Anal. Calcd for $C_{26}H_{37}NO_4$: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.43; H, 9.03; N, 3.59.

3β-Acetoxy-16α-thiobenzylpregn-5-en-20-one (XXIV).—A mixture of 1.0 g of I in 4 ml of freshly distilled tetrahydrofuran containing 2 ml of benzyl mercaptan and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide was heated under reflux for 1 hr. After cooling, the mixture was diluted with 10 ml of ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 1.3 g of a yellow glass. This residue was dissolved in benzene and percolated through 10 g of Florisil. The fractions eluted with 10% chloroform–90% benzene crystallized from ethanol to give 1.21 g, mp 123–126°. A pure sample had mp 126–127.5° (lit.[20a] mp 124–125°); $[\alpha]D$ −37°; $\nu_{max}^{CS_2}$ 3088, 3068, 3033, 1736, 1708, 1240, 1033, 835 cm^{-1}; nmr δ 0.62, 1.00, 2.01, 2.05 (singlets, 3 H each), 3.72 (singlet, 2 H), 4.63 (broad multiplet), 5.37 (multiplet, 1 H), 7.30 (singlet, 5 H).

Anal. Calcd for $C_{30}H_{40}O_3S$: C, 74.96; H, 8.39. Found: C, 75.12; H, 8.43.

3β-Acetoxy-16α-thiobenzyl-5α-pregnane-12,20-dione (XXV).—To a solution of III in 4 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added 2 ml of benzyl mercaptan and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. The resulting mixture was refluxed for 0.5 hr. The reaction mixture was cooled, diluted with 10 ml of ether and washed with dilute sodium hydroxide solution and with water. After the solution was dried over anhydrous magnesium sulfate, evaporation of the solvent yielded 1.6 g of a viscous oil. The residue was dissolved in benzene and chromatographed on 20 g of Florisil. The fractions eluted with 20% chloroform–80% benzene crystallized from 95% ethanol to give 1.12 g, mp 133–135°. An analytical sample had mp 138.5–139.5°; $[\alpha]D$ +64°; $\nu_{max}^{CS_2}$ 3090, 3068, 3033, 1735, 1708, 1230, 1025, 688 cm^{-1}; nmr δ 0.90 (singlet, 6 H), 2.02, 2.26 (singlets, 3 H each), 3.71 (singlet, 2 H), 4.70 (broad multiplet, 1 H), 7.31 (singlet, 5 H).

Anal. Calcd for $C_{30}H_{40}O_4S$: C, 72.54; H, 8.12. Found: C, 72.72; H, 8.12.

3β-Acetoxy-16α-nitromethyl-5α-pregnane-12,20-dione (XXVI).—A mixture of 1 g of III, 2 ml of nitromethane and 0.2 ml of a 1 *M* aqueous solution of tetrabutylammonium hydroxide in 4 ml of tetrahydrofuran was refluxed for 1.5 hr. The reaction was worked up in the usual manner to give 0.928 g of a glassy residue. This material was crystallized from ethanol to give 0.816 g, mp 166–169°. A pure sample had mp 170–171°; $[\alpha]D$ +97°; $\nu_{max}^{CS_2}$ 1722, 1710, 1702, 1550, 1357, 1223, 1028, 1020 cm^{-1}; nmr δ 0.93, 1.00, 2.02, 2.30 (singlets, 3 H each), 3.24 (multiplet, 1 H).

Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.14. Found: C, 66.28; H, 8.11.

3β-Acetoxy-16α-(1′-nitroethyl)-5α-pregnane-12,20-dione (XXVII).—To 1 g of III in 4 ml of tetrahydrofuran was added 2 ml of nitroethane and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. After refluxing for 3 hr, the usual work-up provided 0.96 g of residue. This material was dissolved in benzene and chromatographed on Florisil (20 g). The material eluted with 10% ether–90% benzene crystallized from 95% ethanol to give 0.65 g, mp 126–130°. Concentration of the mother liquor afforded an additional 0.09 g, mp 120–128°. Crystallization from 95% ethanol provided a pure sample: mp 139–141.5°; $[\alpha]D$ +127°; $\nu_{max}^{CS_2}$ 1732, 1705, 1543, 1353, 1224, 1023 cm^{-1}; nmr δ 0.95, 0.97, 2.03, 2.34 (singlets, 3 H each), 1.42 (doublet), 3.30 (multiplet, 2 H), 4.58 (broad multiplet, 1 H).

Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33. Found: C, 67.31; H, 8.19.

3β-Acetoxy-16α-diacetylmethyl-5α-pregnane-12,20-dione (XXVIII).—A mixture of 5 g of III in 20 ml of tetrahydrofuran, 10 ml of acetylacetone and 1 ml of a 1 *M* aqueous solution of tetrabutylammonium hydroxide was refluxed for 3 hr. The usual work-up followed by crystallization from ethanol afforded 4.1 g of crystals mp 161–164°. A pure sample had mp 166–167.5°; $[\alpha]D$ +141°; $\nu_{max}^{CS_2}$ 1737, 1709, 1362, 1242, 1030 cm^{-1}; nmr δ 0.92, 0.95, 2.03, 2.10, 2.15, 2.23 (singlets, 3 H each), 3.37 (multiplet, 3 H), 4.67 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.29; H, 8.72.

3β-Acetoxy-16α-(α-carbethoxycyanomethyl)-5α-pregnane-12,20-dione (XXIX).—To 1 g of III in 4 ml of tetrahydrofuran was added 2 ml of ethyl cyanoacetate and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. After refluxing for 3 hr, the mixture was worked up in the usual manner to give 1.2 g of a syrup. Crystallization from ethanol afforded 0.97 g of crystals, mp 172–176°. An analytical sample had mp 177–179°; $[\alpha]D$ +105°; $\nu_{max}^{CH_2Cl_2}$ 1740, 1712, 1242, 1030 cm^{-1}; nmr δ 0.93, 0.95, 2.02, 2.33 (singlets, 3 H each), 1.30 (triplet, 3 H), 3.50 (doublet + broad multiplet, 2 H), 4.18 (quartet, 2 H), 4.71 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.10. Found: C, 69.57; H, 8.35.

3β-Acetoxy-16α-(2′-oxocyclohexyl)-5α-pregnane-12,20-dione (XXX).—A mixture of 15 g of III in 60 ml of tetrahydrofuran, 30 ml of cyclohexanone and 6 ml of a 25% aqueous solution of tetraethylammonium hydroxide was refluxed for 2.5 hr. After the standard work-up procedure, the residue was chromatographed on Florisil (300 g). The material eluted with 20% ethyl acetate–80% benzene crystallized from 95% ethanol to give 12.6 g of crystals, mp 175–179°. Recrystallization from 95% ethanol afforded a pure sample: mp 181–183.5°; $[\alpha]D$ +83°; $\nu_{max}^{CS_2}$ 1735, 1708, 1230, 1023 cm^{-1}.

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.13; H, 8.95.

3β-Acetoxy-16α-(2′-oxocyclopentyl)-5α-pregnane-12,20-dione (XXXI).—A solution of 15 g of III in 60 ml of freshly distilled tetrahydrofuran containing 30 ml of cyclopentanone and 6 ml of an aqueous 25% tetraethylammonium hydroxide solution was heated under reflux for 1.5 hr. After the standard work-up, the syrupy residue was chromatographed on 300 g of Florisil. The fractions eluted with 10% ethyl acetate–90% benzene crystallized from ethanol to give 10.1 g of material which melted at 167–170°. A pure sample was crystallized from ethanol: mp 172–174°; $[\alpha]D$ +115°; $\nu_{max}^{CS_2}$ 1735, 1705, 1238, 1028 cm^{-1}; nmr δ 0.93 (singlet, 6 H), 2.02, 2.35 (singlets, 3 H each), 4.72 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{40}O_5$: C, 73.56; H, 8.83. Found: C, 73.56; H, 8.75.

3β-Hydroxy-16α-nitromethylpregn-5-en-20-one (XXXII).—To 5 g of 3β-hydroxypregn-5,16-dien-20-one dissolved in 100 ml of *t*-butyl alcohol was added 0.9 g of potassium *t*-butoxide and 10 ml of nitromethane. The resulting mixture was maintained at 50° overnight and poured into 500 ml of water with stirring. The precipitated solid was removed by filtration and dried *in vacuo*. A cream colored solid (5 g) was obtained which crystallized from 95% ethanol to give 3.3 g of crystals, mp 219–223°. Concentration of the mother liquor afforded 0.9 g of crystals, mp 217–221°. Several crystallizations from 95% ethanol provided an analytical sample: mp 226–229°; $[\alpha]D$ +21°; $\nu_{max}^{CH_2Cl_2}$ 3600, 1706, 1550, 1370, 1049 cm^{-1}; nmr δ 0.70, 1.03, 2.16 (singlets, 3 H each), 3.44 (broad multiplet, 2 H), 4.31 (doublet, 2 H), 5.39 (multiplet, 1 H).

Anal. Calcd for $C_{22}H_{33}O_4N$: C, 70.37; H, 8.86. Found: C, 70.42; H, 8.79.

3β-Acetoxy-1′,2′-tetramethylene-16β,17α,5α-[16,17-butanoandrost-2′-ene]-4′,12-dione (XXXIII).—A mixture of 1 g of XXX in 10 ml of dry benzene and 0.27 g of sodium methoxide was refluxed for 1.5 hr using a water removal trap. After cooling, the solution was washed several times with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue refluxed in 5 ml of acetic anhydride for 0.5 hr and the solution was poured into a large volume of water with stirring. The resulting suspension was extracted several times with ether

and the extracts were evaporated to dryness *in vacuo*. Trituration of the residue with 95% ethanol afforded 0.66 g of crystals, mp 242–244°. A pure sample was crystallized from methanol: mp 242.5–244°; $[\alpha]D$ +140°; λ_{max} 239 mμ (ε 14,000); $\nu_{max}^{CS_2}$ 3025, 1735, 1712, 1685 cm^{-1}; nmr δ 0.92, 1.20, 2.00 (singlets, 3 H each), 4.72 (broad multiplet, 1 H), 5.73 (singlet, 1 H).

Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.09; H, 8.95.

3β-Hydroxy-1′,2′-tetramethylene-16β,17α-[16,17-butanoandrosta-2′,5-dien]-4′-one (XXXIV).—To a solution of 1 g of 3β-hydroxypregn-5,16-dien-20-one in 25 ml of dry *t*-butyl alcohol containing 0.896 g of potassium *t*-butoxide was added 2 ml of cyclohexanone. After 15 min crystals began to form. After standing for 1.5 hr, the mixture was poured into a large volume of water with stirring. The resulting precipitate was removed by filtration and dried *in vacuo* giving 1.14 g of powder. This material was percolated through 5 g of Florisil. A fraction eluted with 5% ethyl acetate in chloroform crystallized from methanol to give 0.71 g of tiny plates, mp 230–232°. A pure sample prepared by vacuum sublimation at 210–215° (0.02 mm) had mp 238–240°; $[\alpha]D$ −7°; λ_{max} 239 mμ (14,000); $\nu_{max}^{CH_2Cl_2}$ 3600, 1670, 1605, 1040, 835 cm^{-1}; nmr δ 0.88, 1.05 (singlets, 3 H each), 3.49 (broad multiplet, 1 H), 5.35 (multiplet, 1 H), 5.70 (singlet, 1 H); *m/e* 394.2859 (calcd 394.2872).

Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 81.65; H, 9.74.

1′,2′-Tetramethylene-16β,17α-[16,17-butanoandrosta-2′,4-diene]-3,4′-dione (XXXV).—To a solution of 8 g of XXXIV in 500 ml of acetone at 10° was added with stirring 7.85 ml of a standard chromium trioxide reagent.[22] Nitrogen was bubbled through all solutions before and during the reaction. After 5 min the reaction mixture was diluted with 2500 ml of water and the resulting precipitate was filtered and dried to give 7.6 g of a white powder. The crude product was dissolved in 600 ml of warm methanol and 10 drops of 10% potassium hydroxide solution was added. This solution was heated on a steam bath for 10 min and neutralized with acetic acid. Concentration of this solution gave 6.5 g of crystals: mp 249–253°; $[\alpha]D$ +82°; λ_{max} 240 mμ (ε 28,900); $\nu_{max}^{CS_2}$ 3025, 1675, 1195, 860, 832 cm^{-1}; nmr δ 0.92, 1.22 (singlets, 3 H each), 5.74 (singlet, 2 H).

Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.36; H, 9.17.

3β-Acetoxy-1′,2′-trimethylene-5α,16β,17α-[16,17-butanoandrost-2′-ene]-4′,12-dione (XXXVI).—A mixture of 20 g of XXXI and 5.8 g of sodium methoxide in 200 ml of benzene was refluxed with stirring for 2 hr. The water formed was continuously removed using a Dean–Stark water trap. The mixture was cooled and the insoluble material was removed by filtration. The infrared spectrum of this material shows only saturated ketone absorption. The filtrate was evaporated to give 6.5 g of a syrupy residue. This material was refluxed in 30 ml of acetic anhydride for 2 hr and the liquid was removed *in vacuo*. The residue crystallized from methanol to give 5.4 g of crystals, mp 244–248°. A pure sample was prepared by vacuum sublimation at 215–220° (0.02 mm): mp 249–251°; $[\alpha]D$ +128°; λ_{max} 240 mμ (ε 13,800); $\nu_{max}^{CS_2}$ 3035, 1737, 1715, 1674, 1240, 1030 cm^{-1}; nmr δ 0.97, 1.19, 2.02 (singlets, 3 H each), 4.68 (broad multiplet, 1 H), 5.86 (singlet, 1 H); *m/e* 438.2767 (calcd 438.2769).

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.25, H, 8.66.

Registry No.—I, 979-02-2; III, 2611-38-3; VII, 19459-49-5; VIII, 19459-50-8; IX, 6384-56-1; X, 18267-02-2; XI, 2724-68-7; XII, 19459-54-2; XIII, 1169-20-6; XIV, 19459-56-4; XX, 1434-54-4; XXI, 19459-58-6; XXII, 19459-59-7; XXIII, 19459-60-0; XXIV, 19459-61-1; XXV, 19459-62-2; XXVI, 19459-63-3; XXVII, 19459-64-4; XXVIII, 6953-90-8; XXIX, 19459-66-6; XXX, 19459-67-7; XXXI, 19459-68-8; XXXII, 19459-69-6; XXXIII, 19459-70-2; XXXIV, 19459-19-9; XXXV, 19459-20-2; XXXVI, 19459-21-3.

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16-Oxa Steroid. Synthesis and Structural Assignment

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A relatively simple procedure for the opening of ring D followed by the removal of C-16 was utilized for the synthesis of 16-oxa steroids.

The study of the effects of structural modifications of natural steriod hormones upon the biological activities has received considerable attention in the last few years and has led to a number of highly active synthetic modifications. Two recent publications[1,2] on the synthesis of 16-oxa steroid prompts us to report our work on the preparation of some of these compounds. In contrast to previous methods our procedure is stereospecific, consists of fewer steps and gives a higher yield. Moreover, one of the key intermediates (**3b**) in our synthetic project could be utilized in the synthesis of variety of heterocyclic steroids including D-nor oxa[3] and D-nor aza steroids.

The starting material in our synthesis is 3β-hydroxy-16,17-seco-16-norandrostan-15-(2′-indoxyliden)-17-oic acid (**2a**) which was obtained in 80% yield by allowing 3β-acetoxy-5α-androstan-17-one (**1**) to react with *o*-nitrobenzaldehyde, following essentially Hassner's procedure[4] (Scheme I).

Oxidation of methyl 3β-acetoxy-16,17-seco-16-norandrostan-15-(2′-indoxyliden)-17-oate (**2b**) with chromium trioxide in acetic acid at room temperature for 16 hr yielded 3β-hydroxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester (**3a**) in 75% yield. The compound on acetylation with acetic anhydride and pyridine gave the corresponding acetate **3b**. 3β-Acetoxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester, on treatment with diazomethane, gave the corresponding methyl ester **4**. The α configuration and the axial conformation of the 14 hydrogen in compounds **3a**, **3b**, and **4** is based on the observation of a doublet center around δ 2.5 in the nmr spectrum having a *coupling constant of 10.5 cps* which is characteristic of *trans-diaxial hydrogens*.

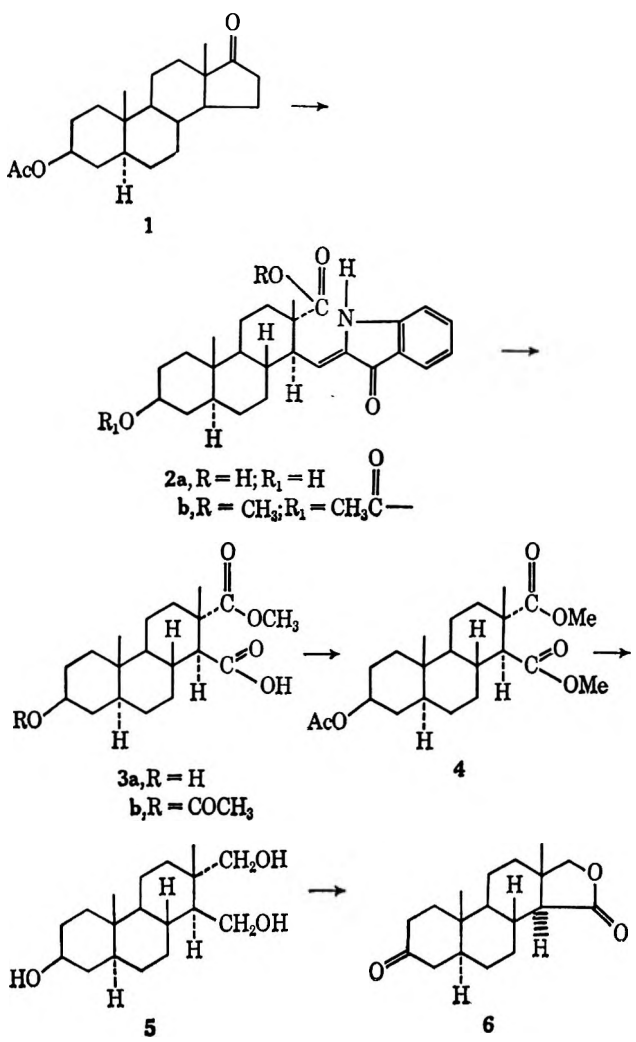
(1) R. W. Kierstead and A. Faraone, *J. Org. Chem.*, **32**, 705 (1967).
(2) J. S. Baran, *J. Med. Chem.*, **10**, 1039 (1967).
(3) A. K. Banerjee and M. Gut, *Tetrahedron Lett.* 51, (1969).
(4) A. Hassner, M. J. Haddadin, and P. Catsoulacos, *J. Org. Chem.*, **31**, 1363 (1966).

Table I

Compound	Predicted from sector rule	Exptl sign	Amplitude
16-Oxo-5α-androstane-3,15-dione	+	+	ϕ_{225} +3,183
16-Oxa-5α-androstane-3,17-dione[a]	+	+	ϕ_{223} +2,970
3β-Hydroxy-5α,14β-isoandrostan-15-one	−	−	ϕ_{220} −19,800
3β,15β-Dihydroxy-16-oxa-5α,14β-isoandrostan-17-one 3-acetate[b]	−	−	ϕ_{226} −5,320
3β-Acetoxy-17-oxa-5α-androstan-16-one[c]	−	−	ϕ_{221} −5,362

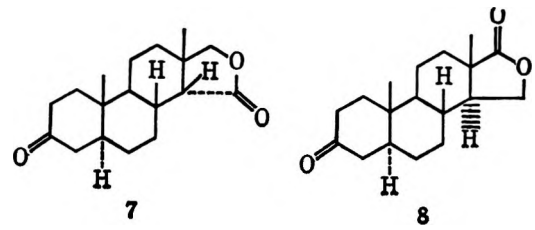
[a] Kindly supplied by Dr. R. W. Kierstead, Hoffmann-La-Roche Inc., Nutley, N.J., [b] Unpublished work by A. K. Banerjee. [c] S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

Scheme I



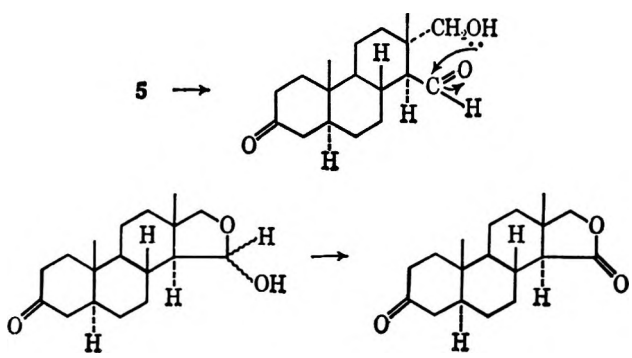
3β-Hydroxy-15,17-seco-D-norandrostane-15,17-dioic acid dimethyl ester, on reduction with lithium hydride in tetrahydrofuran, gave 15,17-seco-D-norandrostane-3β,15,17-triol (**5**), which on oxidation with Jones reagent[5] gave almost quantitatively lactone **6**: ν_{max}^{KBr} 5.70 (γ-lactone) and 5.90 (3-ketone). Its nmr spectrum in deuteriochloroform showed an ill-defined quartet for a 2-hydrogen center around δ 3.91 which could be assigned to the 17 hydrogens. The quartet became clear and distinct when the solvent was changed from deuteriochloroform to benzene. It is conceivable that compound **5** on oxidation could give rise to either of the products **6**, **7** or **8**.

The nmr spectrum of **8** would show the presence of ABX system whereas **6** and **7** would show the AB



system. Since the lactone showed a quartet, its structure could be either **6** or **7**. From the discussion (see below) of the ORD (lactone region) which showed a positive Cotton effect, it can be stated that the lactone is best represented by **6**. The exclusive formation of **6** rather than **8** can be explained from steric considerations and could be mechanistically expressed as in Scheme II.

Scheme II



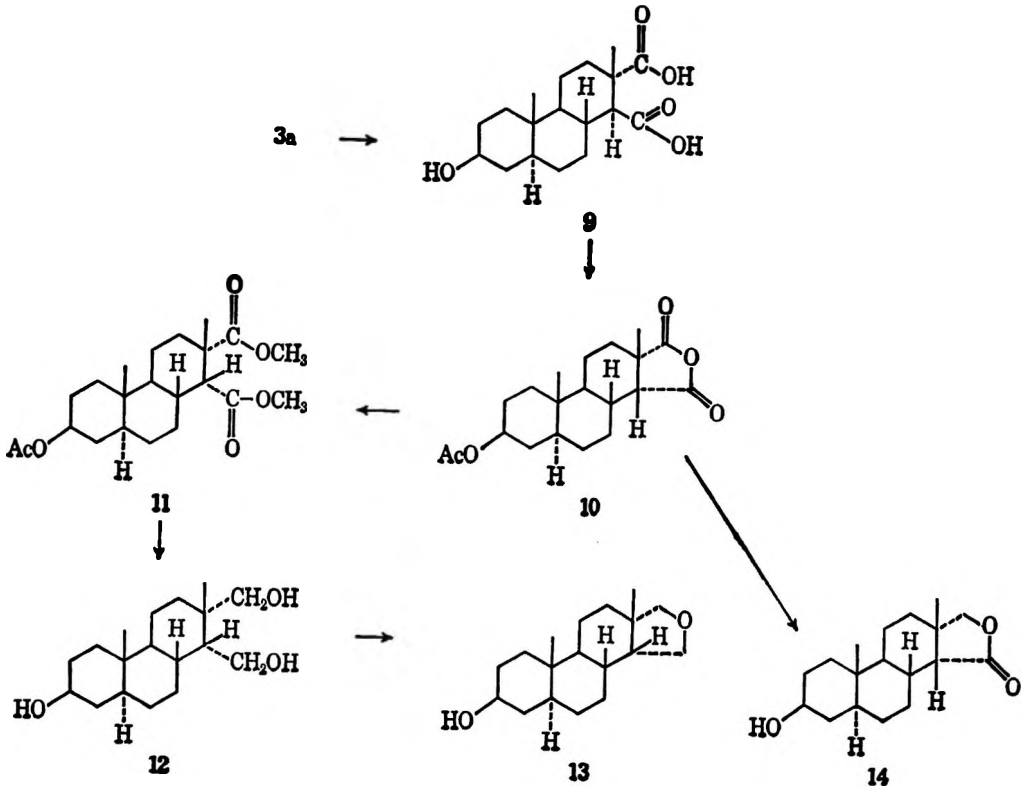
At this stage it was desirable to prepare stereospecifically the two 14 isomers and compare their spectral properties (Scheme III).

3β-Hydroxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester **3a**, upon refluxing with 20% methanolic potassium hydroxide for 48 hr, gave dibasic acid **9**, which, on treatment with boiling acetic anhydride, gave a cyclic anhydride: ν_{max}^{KBr} 5.40, 5.61, 5.80 and 8.00 μ. The *cis* configuration of anhydride **10** is based on the following observations. (a) The nmr spectrum showed the presence of a doublet center around δ 2.69, having a coupling constant, J = 2.5 cps, which confirmed the presence of a 14β hydrogen (axial–equitorial coupling). (b) The anhydride, on treatment with anhydrous methanol, gave a mixture of half-esters which, on methylation with diazomethane, gave a single diester **11**. It has a infrared spectrum similar to that of **4**, but differs considerably in its nmr spectrum, *i.e.*, the presence of a doublet center around δ 2.69 having J = 2.5 cps in contrast to the doublet at δ 2.50 having J = 10.5 cps in the *trans* series. Its fragmentation pattern in the mass spectrum corresponds to that of the *trans* series.

The exclusive formation of one anhydride under the

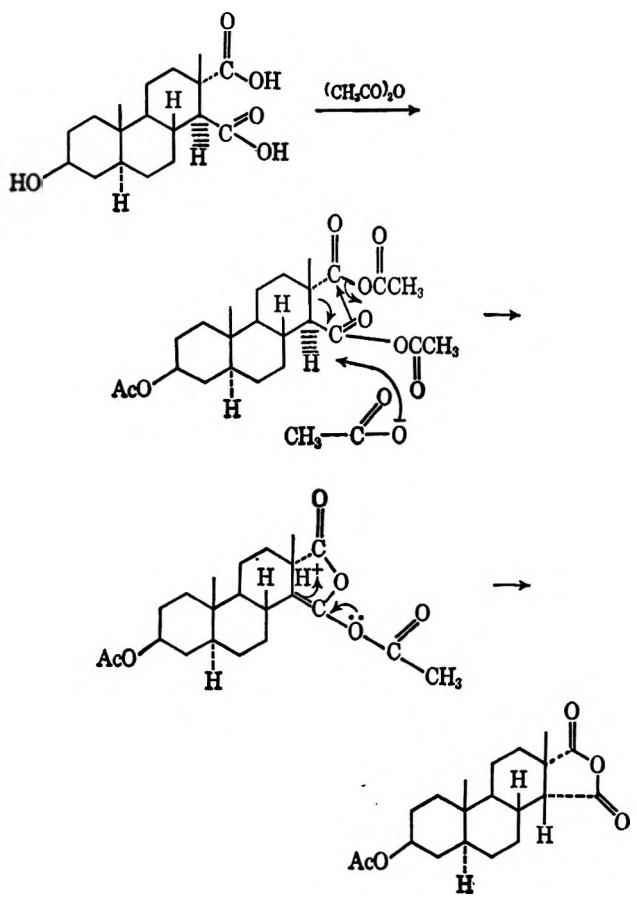
(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. Weeden, *J. Chem. Soc.*, **39**, (1946).

SCHEME III



reaction conditions is rather interesting. Examination of Dreiding models shows that both the *cis* and *trans* anhydride are free of strain. Since our starting material was the *trans* dibasic acid, the exclusive formation of the *cis* anhydride may be illustrated by Scheme IV.

SCHEME IV



Diester **11**, on reduction with lithium aluminum hydride in refluxing tetrahydrofuran for 16 hr, gave 15,17-seco-14-iso-D-norandrostane-3β,15,17-triol (**12**) (80% yield), which upon treatment with dimethyl sulfoxide[6] at 150° for 6 hr gave 16-oxa compound **13**. Lithium aluminum hydride reduction of anhydride **10** gave[7] besides other products a lactone to which structure **14** was assigned on the basis of the following observations: ν_{max}^{KBr} 2.85 (-OH) and 5.70 (γ-lactone); nmr δ 3.68 (2 H, singlet 17-H's) and 2.10 (1 H, doublet $J_{axial-equitorial}$ = 2.5 cps, 14β-H).

In recent years Klyne[8] and his coworkers have utilized the ORD method for the determination of the configuration of lactones. By applying the lactone sector rule it became possible to predict correctly the sign of the Cotton effect. Application of the lactone sector rule to the following lactones showed that the predicted values agreed well with the experimental data (Table I).

Experimental Section

Unless otherwise stated, combustion analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points were taken on a Fisher-Johns hot stage and were not corrected. The infrared spectra were recorded from a pressed potassium bromide pellet on a Perkin-Elmer Infracord spectrophotometer; nmr spectra were obtained on a Varian V-4300 B spectrophotometer in deuteriochloroform solution using tetramethylsilane as internal standard. Mass spectra were recorded on a Varian M-66 mass spectrometer. Preparative layer chromatography was done on a 20 × 20 cm and 20 × 40 cm plate with a thickness of 2.5 mm using silica gel H_{254} (Brinkmann).

3β-Hydroxy-16,17-seco-16-norandrostan-15-(2'-indoxyliden)-

(6) B. T. Grillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

(7) For discussion of mechanism, see J. J. Bloomfield and S. L. Lee, *ibid.*, **32**, 3919 (1967).

(8) W. Klyne and P. M. Scopes in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden & Son Ltd., London, 1967, Chapter 12, p 193.

17-oic Acid (2a).—To a solution of 5 g of 3β-acetoxyandrostan-17-one (1) in 150 ml of 3% methanolic potassium hydroxide, there was added a solution of 3 g of *o*-nitrobenzaldehyde in 10 ml of methanol. The solution was stirred at room temperature under nitrogen for 18 hr, then diluted with water and acidified with 2 *N* hydrochloric acid. The resulting yellow precipitate was collected by filtration, washed repeatedly with water and dried. Recrystallization from methanol–water gave 4.5 g of bright yellow crystals, mp 260–262° dec (lit.[4] mp 258–260° dec). A second crop of 500 mg was obtained, mp 260–262° dec (total yield 79%). In several runs the yield varied from 75 to 85%.

3β-Hydroxy-16,17-seco-16-norandrostan-15-(2′-indoxyliden)-17-oic Acid 17-Methyl Ester (2b) and Its 3β-Acetate (2c).—Methyl ester **2b** was obtained in almost quantitative yield from acid **2a** with diazomethane by the usual procedure. Crystallization from methylene chloride–ether afforded bright yellow prisms, mp 262–264° (lit.[4] mp 263–265°).

Acetylation with acetic anhydride–pyridine gave yellow needles, **2c**, mp 262–264° (lit.[4] mp 261–262°), in almost quantitative yield.

3β-Hydroxy-15,17-seco-D-norandrostane-15,17-dioic Acid 17-Methyl Ester (3a).—To a solution of 6 g of **2b** in 250 ml of glacial acetic acid there was added slowly a solution of 4.5 g of chromium trioxide in 5 ml of water under nitrogen. The yellow solution turned reddish brown with evolution of heat (the temperature was kept below 60° by external cooling). After stirring overnight at room temperature under nitrogen, the solution was diluted with 750 ml of water and the resulting turbid solution was thoroughly extracted three times with 150 ml of ether. The yellow ether layer was repeatedly washed with water to remove the isatin. The ethereal layer was then extracted three times with 50 ml of 2 *N* sodium hydroxide solution. Acidification of the basic solution with 2 *N* hydrochloric acid precipitated **3a** as a white solid. This was filtered, washed thoroughly with water and dried. One crystallization from aqueous methanol (Norit) gave 3.2 g (66%) of needles, mp 232–234°. In several runs the yield varied from 65 to 70%. An analytical sample was prepared by crystallizing from methanol–water to give needles: mp 234–235°; ν_{max} 2.82 (–OH), 3.00–3.10 (hydrogen bonded $-CO_2H$), 5.78 (methyl ester) and 5.85 and 5.90 μ (broad, unbonded and bonded CO_2H); nmr (pyridine) δ 3.64 (3 H, singlet, 17-CO_2Me), 2.86 (1 H, doublet, J = 10.5 cps, 14α-H), 1.00 (3 H, singlet, 18-methyl) and 0.82 (3 H, singlet, 19-methyl); mass spectrum (70 eV) *m/e* 338 (M^+), 320 ($M - H_2O)^+$ and 306 $(M - MeOH)^+$.

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.37, H, 8.81.

3β-Acetoxy-15,17-seco-D-norandrostane-15,17-dioic Acid 17-Methyl Ester (3b).—The solution of 10 g of **3a** in 15 ml of anhydrous pyridine was added to 15 ml of acetic anhydride, the flask stoppered and left overnight at room temperature. It was then poured onto crushed ice containing 20 ml of methanol and 15 ml of 2 *N* hydrochloric acid. After standing at room temperature for 1 hr, the acetate slowly crystallized out. It was filtered, washed repeatedly with water and dried. On crystallization from acetone–benzene it gave 10 g (95%) of prisms, mp 203–204°. An analytical sample was crystallized from ether–hexane: mp 205–207°; ν_{max} 3.15 (hydrogen-bonded CO_2H), 5.78 (acetate and methyl ester) and 5.9 μ (CO_2H); nmr δ 4.65 (1 H, multiplet, 3α-H), 3.63 (3 H, singlet, 17-CO_2Me), 2.56 (1 H, doublets, J = 10.5 cps, 14α-H), 2.01 (3 H, singlet, 3β-$OCOCH_3$), 1.26 (3 H, singlet, 18-methyl) and 0.82 (3 H, singlet, 19-methyl); mass spectrum (70 eV) *m/e* no molecular ion peak 348 (M − MeOH)$^+$ 320 (M − acetic acid)$^+$.

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.57; H, 8.50.

3β-Acetoxy-15,17-seco-D-norandrostane-15,17-dioic Acid Dimethyl Ester (4).—Methylation of 1 g of **3b** with diazomethane by the usual procedure gave, upon removal of the solvent, an oil which was obtained in almost quantitative yield. It crystallized from aqueous methanol in needles, mp 118–120°. An analytical sample was crystallized from methanol–water: mp 120–121°; ν_{max} 5.79 μ (broad, acetate and methyl ester); nmr δ 4.65 (1 H, multiplet, 3α-H), 3.62 (3 H, singlet, 15-CO_2CH_3), 3.59 (3 H, singlet, 17-CO_2Me), 2.50 (1 H, doublet, J = 10 cps, 14α-H), 2.00 (3 H, singlet, 3β-$OCOCH_3$), 1.20 (3 H, singlet, 18-methyl), and 0.82 (3 H, singlet, 19-methyl); mass spectrum (70 eV) *m/e* 394 (M^+), 362 $(M - CH_3OH)^+$ base peak.

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.04; H, 8.72.

15,17-Seco-D-norandrostane-3β,15,17-triol (5).—A solution of 500 mg of **3b**, in 5 ml of anhydrous tetrahydrofuran was added to the suspension of 500 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran in a three-necked flask, fitted with a reflux condenser, dropping funnel and nitrogen inlet dropwise, during 20 min. The mixture was then refluxed for 16 hr and then the excess of lithium aluminum hydride was decomposed by following the procedure of Micovic and Mihailovic.[9] The mixture was filtered, the residue washed with a small amount of tetrahydrofuran and then the filtrate was evaporated under vacuum whereby a crystalline solid was obtained. The residue was suspended in water, filtered, washed with water and dried to give 300 mg (80%) of crude **5**. On crystallization from acetone it gave rectangular plates: mp 228–230°; ν_{max} 2.85 μ (OH); nmr $[CD_3S(\rightarrow O)CD_3]$ δ 3.50 (4 H, broad, 15- and 17-CH_2OH) and 0.75 (6 H, two superimposed singlets, 18 and 19 methyl; mass spectrum (70 eV) *m/e* 278 $(M - H_2O)^+$ and 265 $(M - CH_2OH)^+$.

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 72.98; H, 10.98.

16-Oxa-5α-androstane-3,15-dione (6).—The solution of 200 mg of **5** in 20 ml of anhydrous acetone was cooled to 0° and to this Jones reagent[5] was added dropwise (until the faint color of the reagent persists) over a period of 5 min. It was then allowed to stand an additional 10 min at 0°. The mixture was then poured into ice water and extracted with ether. The etheral layer was washed sodium bicarbonate, water and dried. On removal of the solvent 180 mg (91%) of oil was obtained which could be crystallized. On recrystallization from methanol it gave needles: mp 165–166°; ν_{max} 5.70 (γ-lactone) and 5.90 μ (3-ketone); nmr δ 3.90 (2 H, quartet, 17-H's and 1.08 (6 H, two superimposed singlet, 18- and 19-methyl); mass spectrum (70 eV) *m/e* 290 M^+.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.48; H, 8.90. Found: C, 74.40; H, 8.86.

3β-Hydroxy-15,17-seco-D-norandrostane-15,17-dioic Acid (9).—To the solution of 2 g of **3a** in 5 ml of methanol was added 40 ml of 20% methanolic potassium hydroxide and refluxed for 48 hr under nitrogen. It was then cooled, diluted with 50 ml of water and acidified, whereby a white precipitate was obtained. This was filtered, washed repeatedly with water and dried to give 1.6 g (84%) of **9**. Crystallization from methanol–water furnished white flakes: mp 225–256° (one more recrystallization raised the melting point to 256–258°); ν_{max} 2.85 (OH), 3.00–3.15 (broad CO_2H) and 5.9 μ (broad CO_2H); nmr $[CD_3S(\rightarrow O)CD_3]$, 3.65 (1 H, multiplet, 3α-H), 2.35 (1 H, doublet, J = 10.8, 14α-H), 1.10 (3 H, singlet, 18-methyl) and 0.75 (3 H, singlet, 19-methyl); mass spectrum (70 eV), no molecular ion peak, *m/e* 306 $(M - H_2O)^+$, 288 $(M - 2H_2O)$.

Anal. Calcd for $C_{18}H_{28}O_5 \cdot MeOH$: C, 66.64; H, 8.70. Found: C, 66.46, H, 8.60.

3β-Acetoxy-15,17-diketo-16-nor-16-oxa-14β-androstane (10).—The solution of 1 g of **9** in 10 ml of acetic anhydride was refluxed for 6 hr. Excess acetic anhydride and the small amount of acetic acid formed during the reaction were removed under vacuum when 600 mg (59%) of crystalline solid was obtained. This was crystallized from ether–hexane in rectangular plates, mp 208–210°. An analytical sample, mp 210–212°, was obtained by further recrystallizations: ν_{max} 3.43, 5.40, 5.61, 5.80 and 8.00 μ; nmr δ 4.65 (1 H, multiplet, 3α-H), 2.77 (1 H, doublet, J = 2.5 cps, 14β-H), 2.01 (3 H, singlet, 3β-$OCOCH_3$), 1.38 (3 H, singlet, 18-methyl) and 0.81 (3 H, singlet, 19-methyl); mass spectrum (70 eV), no molecular ion peak, *m/e* 288 base peak (M − acetic acid)$^+$, 273 (M − methylacetic acid)$^+$.

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.87; H, 7.95.

3β-Acetoxy-15,17-seco-D-nor-14-isoandrostane-15,17-dioic Acid Dimethyl Ester (11).—The solution of 500 mg of **10** in 20 ml of anhydrous methanol refluxed for 4 hr (reflux was continued until disappearance of the anhydride band in the infrared spectrum) and then the solvent was removed under vacuum, whereby a crystalline solid was obtained. A thin layer chromatography, using the solvents methylene chloride–methanol–acetic acid (95:4:1) gave a plate that showed two spots, indicating that the mixture contained the two half-esters. No attempt was made to separate them. The eluate gave a crude solid of 500 mg

(9) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

which was dissolved in ether and methylated with diazomethane in the usual way. The crude diester was crystallized from methanol–water, giving pure **11**, mp 120–21°. An analytical sample was prepared by recrystallization from aqueous methanol: mp 121–122°; ν_{max} 5.80 (acetate and methyl ester) and 8.00 μ; nmr δ 3.63 (1 H, multiplet, 3α-H), 3.60 (6 H, singlet, 15-COOCH$_3$ and 17-COOCH$_3$), 2.00 (3 H, singlet, 3β-OCOCH$_3$), 2.69 (1 H, doublet, J = 2.5 cps, 14β-H), 1.26 (3 H, singlet, 18-methyl) and 0.81 (3 H, singlet, 19-methyl); mass spectrum (70 eV) m/e 394 (M^+, strong), 362 [$(M - CH_3OH)^+$, weak].

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.78; H, 8.59.

15,17-Seco-D-nor-14-isoandrostane-3β,15,17-triol (12).—To the suspension of 500 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran was added 500 mg of **11**, dissolved in 5 ml of anhydrous tetrahydrofuran, over a period of 15 min. The mixture was then heated under reflux under nitrogen for 16 hr. Excess of reagent was decomposed following the procedure of Micovic and Mihailovic.[9] It was then filtered, washed with a small amount of tetrahydrofuran and the filtrate along with the washings were concentrated under vacuum, when a crystalline solid was obtained. The mixture was diluted with water, filtered and the residue was washed thoroughly with water and dried to give 300 mg (80%) of **12**. Recrystallization from methanol gave needles: mp 263–264° (transformation at 250°); ν_{max} 2.98, 3.42, 9.55, 9.71 and 10.9 μ; nmr[$CD_3(S\rightarrow O)CD_3$] δ 0.93 (3 H, singlet, 18-methyl) and 0.70 (3 H, singlet, 19-methyl), mass spectrum (70 eV) m/e 278 $(M - 18)^+$.

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.98; H, 10.88. Found: C, 72.78, H, 10.68.

3β-Hydroxy-16-oxa-16-nor-5α-androstane (13).—The solution of 150 mg of **12** in 5 ml of anhydrous dimethyl sulfoxide was heated at 150° for 6 hr. It was then cooled, diluted with 15 ml of water and extracted with ether. The etheral extract was washed thoroughly with water and dried over sodium sulfate. On removal of solvent, an oil was obtained, which was purified through preparative thick layer chromatography using the system ethyl acetate–benzene 15:85. After elution a crystalline solid was obtained, which was recrystallized from aqueous methanol to give needles: mp 163–164°; ν_{max} 2.85 (OH) and 9.00 μ; mass spectrum (70 eV) m/e 278 (M^+), 260 $(M - 18)^+$.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.36; H, 10.68.

3β-Hydroxy-16-oxa-5α,14β-androstan-15-one (14).—To the suspension of 300 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran was added over a period of 15 min 300 mg of **8**, dissolved in 5 ml of anhydrous tetrahydrofuran. The mixture was refluxed overnight under nitrogen. It was then cooled and the excess of reagent was decomposed by following the procedure of Micovic and Mihailovic.[9] The mixture was then filtered, washed with a small amount of tetrahydrofuran and the filtrate along with its washings was concentrated under vacuum when a crystalline solid was obtained. More solids were precipitated when 10 ml of water was added to the filtrate. The solids were collected by filtration, washed repeatedly with water and dried. Recrystallization from methylene chloride–hexane gave needles: mp 208–210°; ν_{max} 2.85 (OH) and 5.40 μ (γ-lactone); nmr δ 3.78 (2 H, singlet, 17-H's), 2.10 (1 H, doublet, J = 3 cps, 14β-H), 1.29 (3 H, singlet 18-methyl), and 0.80 (3 H, singlet, 19-methyl); mass spectrum (70 eV) m/e at 292 (M^+).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 73.93; H, 9.65. Found: C, 73.69; H, 9.55.

Registry No.—**3a**, 19018-69-0; **3b**, 19018-70-3; **4**, 19018-71-4; **5**, 19018-72-5; **6**, 19018-73-6; **9**, 19018-74-7; **10**, 19018-75-8; **11**, 19018-76-9; **12**, 19018-77-0; **13**, 19018-78-1; **14**, 19018-79-2.

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Lead Tetraacetate Oxidation of the Oxime of Pregna-5,16-dien-3β-acetoxy-20-one[1]

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Since the lead tetraacetate promoted free-radical reaction between a secondary hydroxyl group and an otherwise nonactivated hydrogen atom was first described in the steroid series by Jeger, *et al.*,[3] many similar reactions have been reported in the literature.[4]

A modification of the method was introduced by Heusler, *et al.*,[5] who added iodine to the reaction medium. Under these conditions both alternate products and a different reaction mechanism are often observed. It was of interest to determine if similar transformations could be achieved with a hydroxyl group attached to nitrogen. As an example we selected the oxime of 3β-acetoxypregna-5,16-dien-20-one (I) (Scheme I) which could possibly lead to heterocyclic products of biological interest. Treatment of oxime I with lead tetraacetate in dry benzene and also in the presence of iodine gave a high-melting crystalline compound as the major product. A dimeric structure II was assigned to this compound on the basis of the following spectroscopic evidence (Scheme I).

In the mass spectrum of II, there are peaks at m/e 680 and 620 clearly indicating the dimeric nature of the sample with a one degree higher oxidation state than the corresponding monomer (ion m/e 680 = 2 × monomer

(1) Contribution No. 346 from the Institute of Steroid Chemistry, Syntex Research, Palo Alto, Calif.

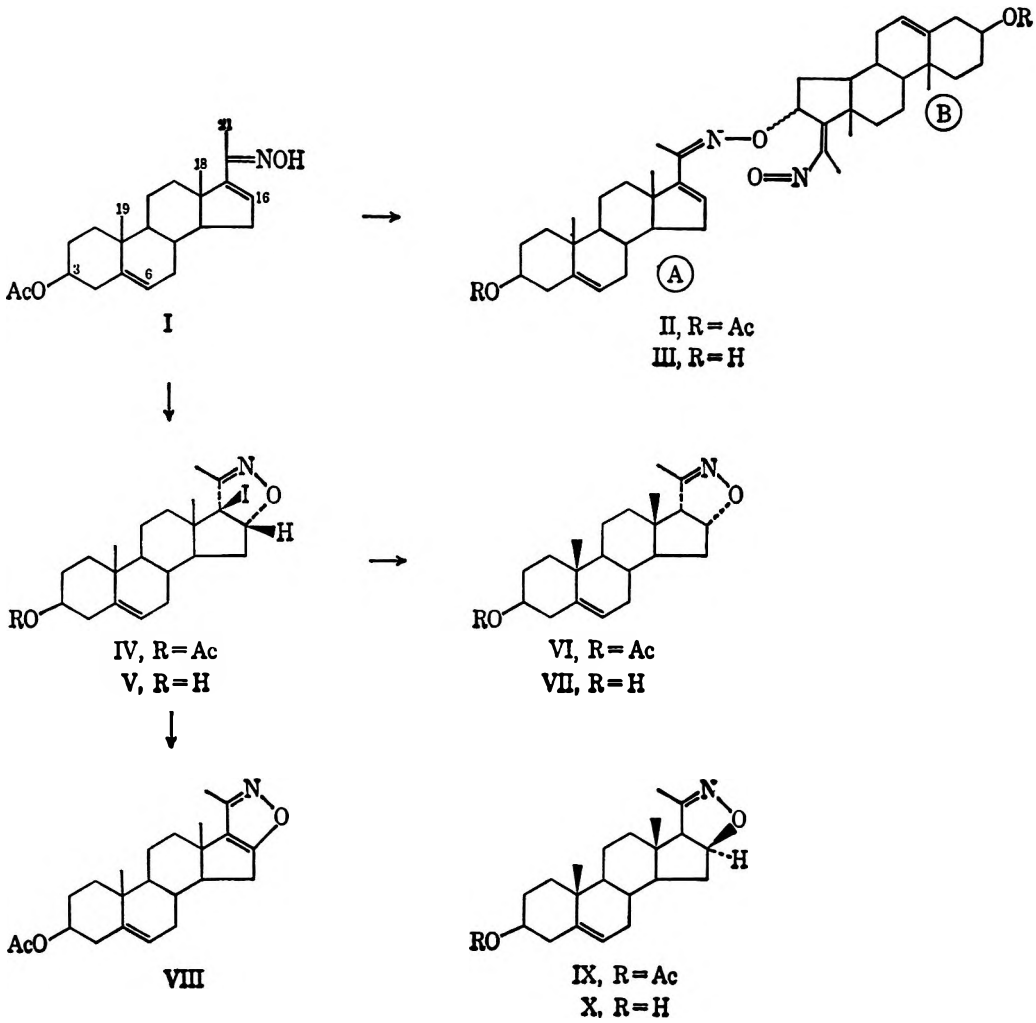
(2) To whom inquiries should be directed.

(3) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(4) A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960); A. Bowers and E. Denot, *J. Amer. Chem. Soc.*, **82**, 4956 (1960); A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(5) K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2161 (1962).

SCHEME I



I − HOAc − 2 H). As expected, a molecular ion (*m/e* 740) could not be detected due to the facile loss of acetic acid, but the presence of the two acetate groups was clearly established, *vide infra*, by nmr.

In addition to these dimeric ions, facile cleavage of the doubly activated O↔C-16 bond (a) provides ion b (*m/e* 370) irrespective of which side carries the charge, a fission which shed further light on the linkage between the two halves of the dimer. Ion b then undergoes further fragmentations, losing a methyl group (*m/e* 355), acetic acid (*m/e* 310), and the combination of the two (*m/e* 295).

The nmr spectrum of II showed two six-proton singlets at 1.03 (19-H) and 2.01 ppm (OAc) and four three-proton singlets at 0.91, 1.01, 1.97 and 1.89 ppm for the 18-H and 21-H of components A and B. The magnetic equivalence of the protons in rings A and B and of the substituents therein (3α-H, C_6-H, 3β-OAc and 19-H) and the nonequivalence of ring-D and side-chain proton resonances (16-H, 18-H and 21-H) confirmed that bonding between the two molecules had taken place in ring D, in the side chain, or in both.

Superimposing the nmr spectrum of I on the spectrum of II confirmed the assignment of the 18-H (0.91 ppm) and 21-H (1.97 ppm and 16-H (6.05 ppm) resonances of component A in structure II. The remaining two three-proton singlets at 1.01 and 1.89 ppm and the doublet at 4.81 ppm (J = 5 cps) may then be assigned to the 18-H, 21-H and 16-H resonances of component B in II, respectively. The low-field position (4.81 ppm) of the 16-H resonance of part B in II is consistent with a proton which is both allylic on a carbon atom bearing oxygen.

The stereochemistry at C-16 was not established but in view of the usual behavior of Δ^{16} steroids attack at C-16 would be expected to occur from the α side.

Formation of dimeric nitroso compounds by lead tetraacetate oxidation of aldoximes has been described previously by Kropf and Lambeck.[6] In the present case we can assume that bonding to C-16 is facilitated by the high reactivity of the Δ^{16} double bond of I.

Whereas the reactions in dry benzene gave compound II as the main product, the oxidation of oxime I with lead tetraacetate and iodine in the presence of small amounts of water led to a product (IV) which according to elemental analysis contained one atom of iodine. The mass spectrum of IV exhibited framgent ions corresponding to the loss of acetic acid (*m/e* 437) and hydrogen iodide (*m/e* 369) from an undetected molecular ion (*m/e* 497). These data suggest an empirical formula of $C_{23}H_{32}O_3NI$ for IV indicating that one hydrogen atom in I has been replaced by iodine. The absence of the vinylic 16-H resonance in the nmr spectrum (6.05 ppm in I) and the appearance of a pair of doublets (J = 6.5 and 1 cps) at 5.18 ppm indicated that cyclization has taken place at C-16.

(6) H. Kropf and R. Lambeck, *Ann.*, **700**, 1, 18 (1966); see also G. Just and K. Dahl, *Tetrahedron*, **24**, 5251 (1968).

The nature of the newly formed ring was established by dehydrohalogenation of IV with silver acetate in acetic acid yielding a known[7] isoxazole derivative VIII whose uv, nmr and mass spectral data were in good agreement with its structural assignment. It follows, therefore, that compound IV is an iodinated isoxazoline derivative. The iodine atom can be readily placed at C-17 in accordance with the chemical shift of the C-16 proton (5.18 ppm).

The assigned stereoconfiguration at positions 16 and 17 was based on the following evidence. Dehalogenation of compound IV with zinc in acetic acid gave rise to an isoxazoline derivative (VI) which was *not* identical with 3β-acetoxy-5-androstene[17ξ,6ξ-*d*]-3′-methylisoxazoline (IX), prepared by Sato and Kaneko,[8] for which the authors proposed the β configuration at C-16 and 17. The corresponding free alcohol (VII), obtained by alkaline hydrolysis of VI, was also different from compound X prepared by Sato and Kaneko.[8] Our isoxazoline VI exhibited a mass spectrum which was almost identical with that of compound IX[9] suggesting stereoisomeric relationship between the two.

The nmr spectrum of VI showed four three-proton singlets as 0.90. 1.03, 1.98 (broad, $J_{17\beta\text{-H},21\text{-H}} = 1$ cps) and 2.02 ppm for the 18-H, 19-H, 21-H, and OAc group, respectively. The 16β-H resonated at 5.05 ppm ($J_{16\beta\text{-H},17\beta\text{-H}} = 9$ cps; $J_{16\beta\text{-H},15\beta\text{-H}} = 4.5$ cps and $J_{16\beta\text{-H},15\alpha\text{-H}} = 0$ cps) and the 17β-H at 3.10 ppm ($J_{17\beta\text{-H},16\beta\text{-H}} = 9$ cps). The differences between the nmr data of compounds VI and IX were particularly noticeable for the chemical shifts or 16-H, 17-H and 18-H. The higher field resonance of the 18-H in IX (0.79 ppm) compared with that of VI (0.90 ppm) is explained by the presence of the adjacent 17β-substituent in IX.

Bis steroid II exhibits a strong positive Cotton effect ($a = +1350$), which corresponds to the summation of two chromophores, *in extenso* the unsaturated azomethine –C=CC=NO– and the –C=CN=O system.[10]

The iodoisoxazoline IV shows an intense positive Cotton effect ($a = +1353$). The 17β-iodine atom affects both the sign and the intensity of the optical properties associated with the isoxazoline VI ($a = -34$). The influence of the iodine on the Cotton effect of IV is in keeping with similar observations made with other chromophores (*e.g.*, carbonyl, etc.), in which cases it is known that an halogen atom situated next to the chromophore can affect its optical properties.

Finally, while the 16α,17α-isoxaline VI presents a weak negative Cotton effect, its β isomer IX exhibits a molecular amplitude which is much more intense ($a = -476$). Moreover, there seems to be a slight bathochromic shift in the position of the optically active transition of the isoxazoline VI, when compared with that of its isomer IX.

On the other hand, the uv spectrum of isoxazole VIII showed a bathochromic shift (λ_{max} 230 mμ) as compared with other steroidal isoxazoles.[11] This is probably due to the strain caused by the fusion of the isoxazole ring to ring D.

Experimental Section[12]

Oxidation of the Oxime of Pregna-5,16-dien-3β-acetoxy-20-one (I) with Lead Tetraacetate.—A solution of 30 g of oxime I and 40 g of lead tetraacetate in 1500 ml of dry benzene was heated under reflux for 5 hr. The reaction mixture was washed first with a concentrated solution of sodium bisulfite and then with water. After separation of the organic layer, the benzene solution was dried with anhydrous sodium sulfate and subsequently the solvent was distilled off to dryness. The dark residue (30 g) was dissolved in benzene and chromatographed on 600 g of aluminium oxide. After separation of less polar impurities, the crystalline fractions were combined and recrystallized from methylene chloride–methanol, whereby 12.5 g of the pure dimeric steroid (II) was obtained: plates; mp 260.5–262.5°; $[\alpha]_D$ +72.7°; λ_{max} 245 mμ ($E^{1\%}_{1cm}$ 265); ν_{max} 1038, 1100, 1132, 1160, 1242, 1378, 1439, 1470 and 1740 cm^{-1}. *Anal.* Calcd for $C_{46}H_{64}O_6N_2$: C, 74.55; H, 8.70; N, 3.77. Found: C, 74.41; H, 9.03; N, 3.95.

The same results are obtained if the reaction is carried out in dry benzene and in the presence of iodine.

Alkaline saponification of II leads to free alcohol III: prisms from methylene chloride; mp 282–283°; $[\alpha]_D$ +75.6°; ν_{max} 244 mμ ($E^{1\%}_{1cm}$ 292). *Anal.* Calcd for $C_{42}H_{60}O_4N_2$: C, 75.90; H, 9.55; N, 4.42. Found: C, 75.99; H, 8.83; N, 4.60.

3β-Acetoxy-17β-iodo-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (IV).—A solution of 10 g of the oxime of pregna-5,16-dien-3β-acetoxy-20-one (I), 10 g of lead tetraacetate and 10 g of iodine in 500 ml of benzene containing 1% water was heated under reflux for 5 hr. After the usual work-up, the dark oily reaction product was chromatographed on 200 g of aluminum oxide in benzene–hexane (1:1). Crystallization of the eluate in methanol yielded 3.5 g of pure 3β-acetoxy-17β-iodo-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (IV): plates; mp 164–166°; $[\alpha]_D$ +282°; λ_{max} 256 mμ ($E^{1\%}_{1cm}$ 75.5); ν_{max} 1020, 1032, 1078, 1138, 1155, 1250, 1365, 1372, 1440 and 1725 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_3NI$: C, 55.55; H, 6.48; N, 2.81; I, 25.51. Found: C, 56.09; H, 6.80; N, 3.41; I, 25.61.

Saponification of IV with potassium bicarbonate led to the free alcohol V: prisms from ethyl acetate; mp 194.5–196.5°; $[\alpha]_D$ +317.5°; λ_{max} 253 mμ ($E^{1\%}_{1cm}$ 75.5). *Anal.* Calcd for $C_{21}H_{30}O_2NI$: C, 55.37; H, 6.63; N, 3.07; I, 27.66. Found: C, 55.18; H, 6.60; H, 3.22; I, 28.00.

3β-Acetoxy-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (VI).—The iodo compound IV (6 g) was dissolved in 100 ml of glacial acetic acid and 10 g of pulverized zinc was added. The mixture was heated under reflux for 1 hr, filtered and then water was added. The reaction product was extracted with ether, washed with water and sodium bicarbonate solution and again with water. After drying with anhydrous sodium sulfate, the ether solution was concentrated until crystallization started. The crystals were harvested and recrystallized from methanol yielding 3.5 g of hexagonal prisms: mp 216–218°; $[\alpha]_D$ –72.90; ν_{max} 1020, 1032, 1136, 1153, 1250, 1320, 1365, 1375, 1440, 1620 and 1725 cm^{-1}. *Anal.* Calcd for $C_{23}H_{33}O_3N$: C, 79.37; H, 8.95; N, 3.76. Found: C, 79.38; H, 9.07; N, 3.90.

3β-Hydroxy-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (VII).—A solution of 2 g of isoxazoline VI in 50 ml of alcohol was treated with a solution of 2 g of potassium hydroxide in 5 ml of water. The mixture was heated under reflux for 1 hr. The reaction product was precipitated in water, filtered and recrystallized from acetone–hexane giving 1.8 g of pure VII: plates; mp 239–242°; $[\alpha]_D$ –78.3°; ν_{max} 1015, 1020, 1044, 1103, 1135, 1153, 1234, 1296, 1324, 1383, 1440, 1622 and 3600 cm^{-1}. *Anal.* Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.66; H, 9.60; N, 4.33.

(7) L. I. Klimova and N. V. Suvorov, *Khim. Prir Soedin.*, **2** (5), 325 (1966).
(8) Y. Sato and H. Kaneko, *Steroids*, **5**, 273 (1965).
(9) We are grateful to Dr. Sato of the National Institutes of Health, Bethesda, Md., for his generous supply of a sample of compounds IX and X.
(10) H. Ripperger, K. Schreiber, and G. Snatzke, *Tetrahedron*, **21**, 1027 (1965); R. Bonnett and T. R. Emerson, *J. Chem. Soc.*, 4508 (1965).
(11) N. J. Doorenbos and L. Milewich, *J. Org. Chem.*, **31**, 3193 (1966).
(12) Melting points were recorded with a Thomas–Hoover melting point apparatus and are corrected. Rotations and infrared spectra were determined in chloroform solution and the ultraviolet spectra in ethanol solution. The nmr spectra were measured in deuteriochloroform solution with tetramethylsilane internal standard on a Varian HA-100 spectrometer and the mass spectra on an Atlas CH-4 mass spectrometer, equipped with a TO-4 ion source, at 70-eV ionizing potential. Microanalyses were performed by A. Bernhardt, Mülheim (Ruhr), Western Germany.

3β-Acetoxy-5-androstene[17,16-*d*]isoxazole (VIII).—The iodo compound IV (5 g) was dissolved in 100 ml of glacial acetic acid and 5 g of silver acetate was added. The mixture was heated under reflux for 1 hr. After separating the insoluble silver salts by filtration, the product was precipitated with water and extracted with ether. The ether solution was washed with water and sodium bicarbonate solution until neutrality and concentrated to dryness. Crystallization of the solid residue from methanol yielded pure VIII (3.2 g): prisms; mp 189–190° [lit.[7] mp 184–186°]; $[\alpha]D$ −47.7°; λ_{max} 230 mμ ($E^{1\%}_{1cm}$ 152); ν_{max} 1015, 1030, 1053, 1086, 1134, 1250, 1310, 1355, 1375, 1418, 1449, 1455, 1470, 1608 and 1725 cm^{-1}; nmr 1.00 (19-H), 1.09 (18-H), 2.02 (OAc) and 2.21 ppm (21-H).

Registry No.—Lead Tetraacetate, 546-67-8; I, 2174-13-2; II, 19471-38-6; III, 19459-14-4; IV, 19459-15-5; V, 19459-16-6; VI, 19459-17-7; VII, 19459-18-8.

Mechanism and Stereochemical Considerations in the Reaction of Some Arylserine Derivatives with Thionyl Chloride

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The reaction of esters of N-acylphenyl- and *p*-nitrophenylserinates with thionyl chloride has been studied by nmr. The *erythro* isomers rapidly cyclize to *trans*-oxazolines which open (more slowly) to *erythro*-β-chloro-β-arylalaninates. *threo*-Phenylserinates give *threo*-β-chloro derivatives without the intervention of oxazolines, while the *threo*-*p*-nitrophenyl analogs slowly form *cis*-oxazolines which do not open under the same conditions. Reasons for the different mechanisms based on both steric and electronic factors are offered. Hydrolytic studies help reconcile present results with some prior reports which, by themselves, seem inconsistent.

Although the reaction of thionyl chloride with vicinal amido alcohols has been known and used both widely and advantageously for more than 45 years,[1] our understanding of it is still far from complete. We wish to describe new studies which clarify and correct some of the considerable ambiguity, uncertainty, and contradiction found in the literature.

A very brief review is in order. Fry,[2] in summarizing the state of knowledge in 1949 pointed out that ". . .in no case has a β-chloro alkylamide been recovered when the reaction mixture is kept cold. . ." Elliott's[3] concurrent work with threonine derivatives supported this view. Not much later, however, Holland, Jenkins, and Nayler[4] synthesized methyl α-acetamido-β-chloro-β-phenylproprionate *via* reaction of the corresponding *threo*-phenylserine derivative with thionyl chloride at 0°.

Bolhofer[5] cited some distincions attributed to stereoisomerism and suggested a generalization: the *erythro*-"β-phenyl-β-hydroxyethylamine" derivatives undergo facile inversion (*via* oxazolines) while the *threo* isomers react with marked difference. Wagner[6] later reported the inversion of ethyl *threo*-N-benzoyl-β-(*p*-nitrophenyl)serinate while the *erythro* isomer was converted into a chloro compound of the same configuration. Some studies of the isomeric 1,2-diaryl-2-acylamido-1-ethanols are also contradictory.[7]

Most recently, experiments with 3-aryl-2-methylserines[8] showed that both *erythro* and *threo* isomers reacted similarly, in accord with the threonine–allothreonine interconversions,[3,9] but contrary to the (desmethyl)arylserine results.

We have examined the reactions of several phenylserine derivatives with thionyl chloride. The starting materials, *erythro* and *threo* pairs of both N-acetyl- and N-benzoylphenylserinates and *p*-nitrophenylserinates, include compounds previously investigated. The reactions were performed initially in an nmr probe, some in deuteriochloroform, others in neat thionyl chloride. Temperatures were adjusted where appropriate in order to "observe" unisolated intermediates, to modify reaction rates, or to minimize secondary reactions. Spectral assignments were verified after isolation and characterization of the products, some of which have been previously reported with or without stereochemical assignments.

The eight starting compounds (Table I), chromatographically free of their diastereomers, were made from the known amino acids by Fischer esterification followed by acylation with benzoyl chloride or acetic anhydride. It was also of interest to apply the oxidation–reduction procedure[8] to phenylserinates *threo* **1** and **2** in order to provide *erythro* **1** and **2** (Scheme I). In connection with the second step of this sequence, we did not experience the stereospecificity which Bolhofer[5,10] reported for the hydrogenation of **5** (ethyl ester). It seems likely to us that the lesser *threo* isomer either escaped his detection or was lost in crystallization mother liquors. Hydrogenation of other very similar

(1) M. Bergmann and E. Brand, *Ber.*, **56**, 1280 (1923).
(2) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).
(3) D. F. Elliott, *J. Chem. Soc.*, 589 (1949).
(4) D. O. Holland, P. A. Jenkins, and J. H. C. Nayler, *ibid.*, 273 (1953).
(5) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **74**, 5459 (1952).
(6) A. F. Wagner, *ibid.*, **79**, 3240 (1957).
(7) T. Ishimaru [*Nippon Kagaku Zasshi*, **81**, 1424 (1960); *Chem. Abstr.*, **56**, 3386 (1962)] claimed inversion of the *threo* isomer in contrast to these reports: J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Amer. Chem., Soc.*, **73**, 1216 (1951); G. G. Lyle and M. L. Durand, *J. Org. Chem.*, **32**, 3295 (1967).
(8) S. H. Pines, S. Karady, M. A. Kozlowski, and M. Sletzinger, *ibid.*, **33**, 1762 (1968).
(9) K. Pfister, 3rd, C. A. Robinson, A. C. Shabica, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 2297 (1948); **71**, 1101 (1949); J. Attenburrow, D. F. Elliott, and G. F. Penny, *J. Chem. Soc.*, 310 (1948); D. F. Elliott, *ibid.*, 62 (1950).
(10) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **75**, 4469 (1963).

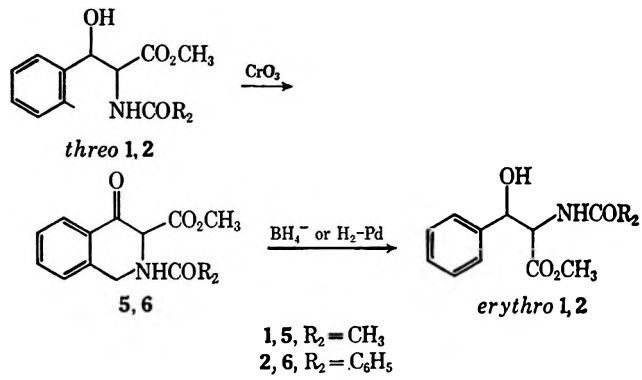
TABLE I
AMIDO ALCOHOLS

Compd	R_1	R_2	X	Mp, °C	Solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
erythro 1	CH_3	CH_3	H	120–122	EA	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	61.09	6.50	5.96
2	CH_3	C_6H_5	H	127–130	EA–H	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.25	5.67	4.77
3	CH_3	CH_3	NO_2	181–184	An	$C_{12}H_{14}N_2O_6$	51.06	5.00	9.93	51.55	5.19	10.10
4	C_2H_5	C_6H_5	NO_2	159–161	E	*b*						
threo 1	CH_3	CH_3	H	180–184	An	*c*						
2	CH_3	C_6H_5	H	110–112	M–Et	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.45	5.80	4.45
3	CH_3	CH_3	NO_2	198–200	M–EA	$C_{12}H_{14}N_2O_6$	51.06	5.00	9.93	51.14	5.01	10.00
4	C_2H_5	C_6H_5	NO_2	140–141	EA	*b*						

[a] Solvent used for recrystallization. EA = ethylacetate, H = hexane, An = acetonitrile, E = ethanol, M = methanol, Et = ether. [b] Reference 6. [c] References 4 and 20.

structures[10,11] have been reported. In many cases single (*erythro*) isomers have been claimed.

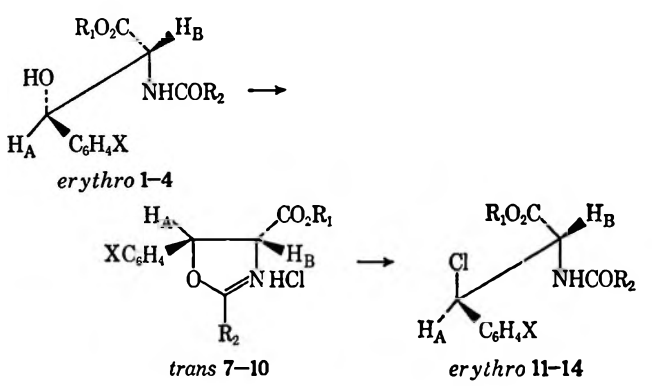
SCHEME I



Results and Discussion

Primary Reactions.—The *erythro* isomers of **1–4** underwent the same[12] basic reaction sequence (Scheme II): at ambient temperature in the nmr, the "instantaneous" products were oxazolines (hydrochloride), *trans* **7–10.** The nmr (Figure 1) showed that the O-alkyl protons of the ester group moved downfield, reflecting the formation of a rigid ring structure in which aromatic shielding was no longer possible. At the same time, the H_A–H_B pattern evolved to a pair of doublets with J_{AB} = 7–8 Hz. Much more slowly, the oxazolines opened to β-chloro compounds of the original stereochemistry, *erythro* **11–14.** The spectral data and specificity of reaction support the stereochemical assignments.

SCHEME II
REACTION OF *erythro* ISOMERS



For the sake of additional substantiation, *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*trans* **8**) was synthesized[13] from *threo*-β-phenylserine methyl ester and benziminoethyl ether hydrochloride and converted into *erythro* **12** in thionyl chloride containing hydrogen chloride. The nmr spectra of this latter sequence were identical with those from the reaction of *erythro* **2** and thionyl chloride.

(11) (a) Y. Chang and W. H. Hartung, *J. Amer. Chem. Soc.*, **75**, 89 (1953); (b) I. Elphimoff-Felkin and H. Felkin, *Compt. Rend.*, **232**, 241 (1951); (c) M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953); (d) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(12) We hesitate to generalize at this stage. See further concerning the *threo* compounds.

(13) By the method of ref 11c.

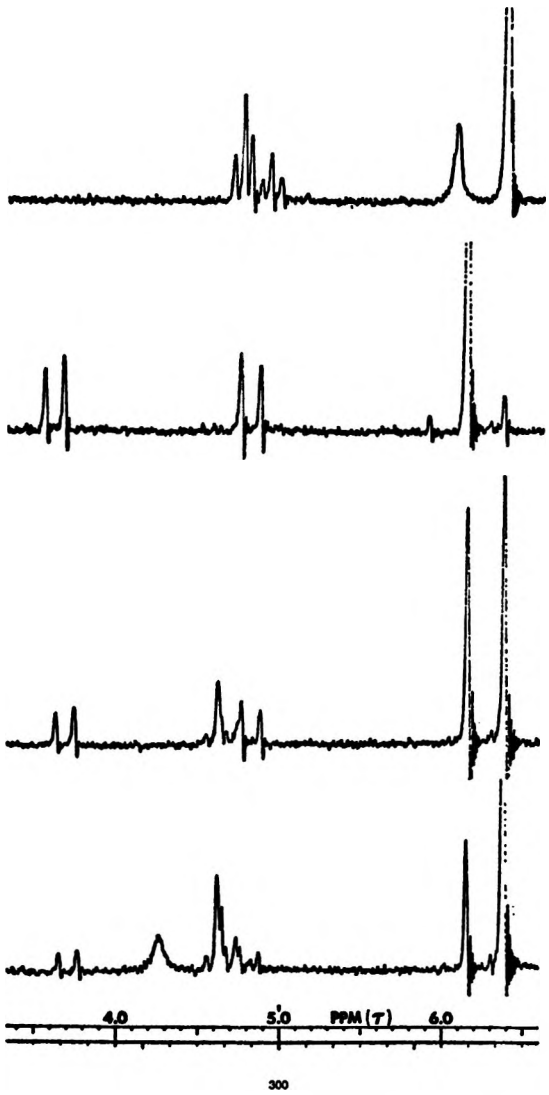
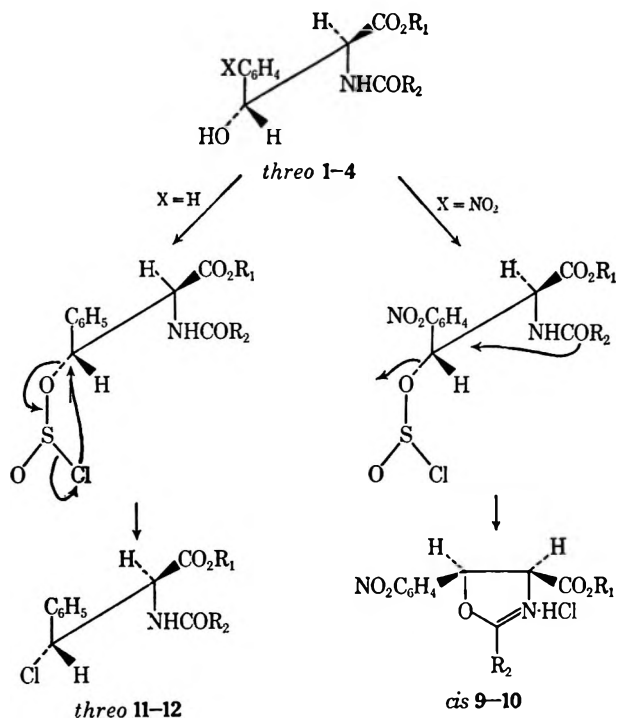


Figure 1.—Main features of typical nmr spectra for the reaction of *erythro* amido esters with thionyl chloride. Top: *erythro*-N-benzoyl-β-phenylserine methyl ester (*erythro* **2**) in $CDCl_3$ (broad resonance at *ca.* 235 cps in OH). Second: one minute after addition of thionyl chloride, *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline hydrochloride (*trans* **8**). Third: one hour; about 50% conversion of *trans* **8** into *erythro*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*erythro* **12**). Bottom: conversion into *erythro* **12** is 75%; broad "mobile" peak at *ca.* 345 cps moves upfield throughout reaction.

To our knowledge, Wagner[6] alone has reported formation of a chloro compound (*erythro* **14**) by reaction of an *erythro*-arylserine derivative with thionyl chloride.[14] He did not observe the oxazoline intermediate and could not verify the reaction mechanism. In our case, the nmr spectra provide compelling evidence for the reaction pathway as described. In one case in which thionyl chloride was added at −20° the chlorosulfite ester was initially evident (H_A shifted downfield) prior to the appearance of the oxazoline spectrum.

threo-Phenylserinates did not react with thionyl chloride like their *erythro* counterparts, nor did the *threo*-*p*-nitro analogs behave like the parent (unsubstituted) compounds. *threo* **1** and **2** underwent rapid SNi (or ion pair)[15] reaction exclusively *via* their chlorosulfite esters to provide chloro compounds *threo* **11** and **12** (Scheme III, X = H). Even at lower temperatures (−20°) where the reaction was reasonably slow, no hint of oxazoline formation could be seen in the nmr. In fact, *cis*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*cis* **8**), synthesized by an alternative route,[13] failed to give a chloro compound [and was, in fact, unchanged (nmr) by anhydrous hydrogen chloride] in over 24 hr at 37°.

SCHEME III
REACTION OF *threo* ISOMERS



The *p*-nitro analogs *threo* **3** and **4**, however, behaved differently. Their chlorosulfite esters (Scheme III, X = NO_2) slowly underwent internal displacement with the formation of oxazolines *cis* **9** and **10** which, over an extended period of time, did not open to chloro compounds.

Two questions arise from the experimental findings. First, why is there a difference in mechanism between the *threo*-phenyl- and -*p*-nitrophenyl compounds (Scheme III)? Second, why are the thermodynamically less stable *cis*-oxazolines resistant to the ring opening observed with the *trans*-oxazolines?

It has long been recognized that increased participation of a neighboring group accompanies the decreased stability of a developing carbonium ion.[16] The destabilizing influence of the *p*-nitro group provides, we believe,[17] the answer to the first question. The

(14) Physical constants reported by E. D. Bergmann, H. Bendas, and W. Taub [*J. Chem. Soc.*, 2673 (1951)] for methyl α-benzamido-β-chloro-β-phenylpropionate and its immediate precursor suggest that these were *erythro* compounds, contrary to implications. The homogeneity of his *threo* starting phenylserine has been questioned before; see also E. D. Bergmann, H. Bendas, and E. Krakauer, *ibid.*, 1064 (1954).

(15) Whether this is an SNi or an ion-pair reaction is not the point. More important, only one reaction pathway was followed to give a sterically pure product.

(16) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).

(17) It could be instructive to examine the reaction with an arylserine containing a ring substituent of the "right" intermediate Hammett σ value. Conceivably, both mechanisms might operate.

recently described radical-anion substitution[18] of *p*-nitrobenzylic substantces does not fit the case. For it to pertain, one would expect both the *erythro* and *threo* isomers to form the same *p*-nitrobenzylic radical (losing steric integrity) and to give, ultimately, the same product.

As for the second question, we suggest that the distinction in reactivity between the *cis*- and *trans*-oxazolines resides in the geometrical requirement of the transition state. It is entirely plausible that the aromatic ring should assume coplanarity[19] with the bond making–bond breaking center in order to assist in charge delocalization. Molecular models show that to do so in the *cis* case creates severe steric interaction with the ester group. No such interference occurs for the *trans* isomer.

Hydrolysis.—At this point, it is important to recognize that many of the prior workers included hydrolytic work-up of their gross reaction mixtures in evaluating the thionyl chloride reaction. In order to reconcile their reports with ours, we must examine the stereochemical consequences of hydrolysis of both the oxazolines and the chloro compounds.

As is well known, mild hydrolysis of a 2-oxazoline occurs without steric change; ring opening proceeds *via* hydration of the C=N linkage. The 2-methyloxazoline hydrochlorides were, in fact, hard to isolate; adventitious moisture frequently converted them into O-acetate amino ester hydrochlorides.

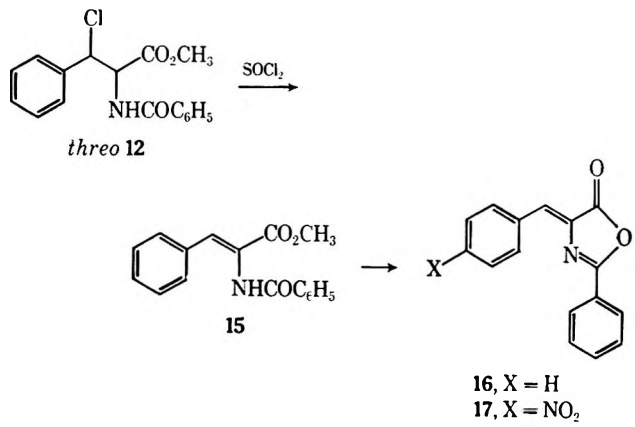
We have shown that acid hydrolysis of *erythro*-β-chloro-β-phenylalaninates occurs with a high degree of inversion to give mostly, but not exclusively, *threo*-β-phenylserine.[20] The *threo*-chloro compounds give rise to a mixture of both *erythro*- and *threo*-phenylserines, the latter predominating.[20]

Thus, it can be seen that with hydrolytic work-up, *erythro* compounds would have given products of net inversion irrespective of whether the *trans*-oxazoline or the *erythro*-chloro compound was the true substrate.

Wagner's[6] inversion of the *threo*-*p*-nitrophenylserinate (*threo* **4**) follows readily from hydrolysis of the *cis*-oxazoline (*cis* **10**) now that its formation has been shown. The inversion of *threo*-N-acetyl-β-phenylserine ethyl ester claimed by Fones[21] was in all probability the consequence of his isolation procedure. We believe that, in fact, he hydrolyzed the *threo*-β-chloro-β-phenylalaninate to a mixture of *erythro*- and *threo*-phenylserines and isolated the former. He also describes a second crop of ". . . 23 g (40%) of material of mp 115–150° which presumably was a mixture. . ."

Finally we have observed a novel decomposition pathway of *threo* **12** (Scheme IV). On extended storage in thionyl chloride, both hydrogen chloride and methyl chloride[22] were eliminated with the formation of the azlactone **16** in good yield. Control experiments showed that methyl 2-(benzoylamido)cinnamate (**15**) was converted into **16** faster than was the starting β-chloro-β-phenylalaninate *threo* **12**. Small amounts of **15** were isolated from 4-day reaction mixtures, along with good yields of **16**. When the reaction of ethyl *erythro*-N-benzoyl-β-(*p*-nitrophenyl)serinate (**4**) was allowed to continue well beyond the formation of the *erythro*-chloroalaninat **14** (1 week, 37°), the azlactone **17** crystallized directly from the thionyl chloride.[23]

SCHEME IV



16, X = H
17, X = NO_2

Experimental Section[25]

Amido Esters. a.—The amino acids were converted into ester hydrochlorides by Fischer esterification. For benzoylation, the ester hydrochloride was treated in ethyl acetate with 2.2 equiv of triethylamine and 1.2 equiv of benzoyl chloride. N-Acetates were prepared by adding 1.1 equiv of acetic anhydride to the free amino esters in ethyl acetate. Acylations were conveniently carried out overnight at ambient temperature. The compounds are listed in Table I.

b.—**Oxidation–Reduction Method.**—*threo* **1** and **2** were oxidized with Jones reagent as previously described[8] to give **methyl α-acetamidobenzoylacetate** (**5**), mp 75–77.5° (ether–hexane). *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.39; H, 5.54; N, 5.87.

Methyl α-Benzamidobenzoylacetate (**6**) was prepared by the

(18) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 725 (1967), and references contained therein.

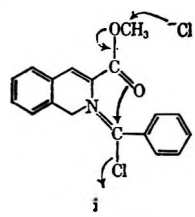
(19) Analogous to the situation discussed by P. D. Bartlett and E. N. Trachtenberg, *ibid.*, **80**, 5808 (1958). In the *cis* compound the aromatic ring occupies a more perpendicular position; *cf.* the shielding effect on the ester alkyl protons (Table IV).

(20) Unpublished observations, estimated from paper chromatograms.

(21) W. S. Fones, *J. Org. Chem.*, **17**, 1534 (1952). Bolhofer[5] simultaneously recorded the same experimental results, but expressed doubt as to whether an actual "oxazoline-type" of inversion had occurred or whether some other series of reactions had taken place. Others[4] reported isolation of a *threo*-β-phenylserine from HCl hydrolysis of *threo* **11**.

(22) This was shown by nmr. CH_3OSOCl is sufficiently stable to have been visible in the spectrum if it had been formed by carbonyl–oxygen cleavage.

(23) We did not look for this reaction in any other case. It is reasonable to suspect that all of the chloro compounds should ultimately eliminate HCl, and that at least the N-benzoylamides should form stable azlactones. Ester cleavage *via* thionyl chloride[24] normally requires more vigorous conditions. For these compounds, however, a mechanism can be written invoking an intermediate imino chloride structure, **i**, that could assist and at the same time provide extended conjugation.



i

(24) M. Green and D. M. Thorp, *J. Chem. Soc., B*, 1067 (1967).

(25) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and associates of these laboratories. Ir spectra were obtained with a Perkin-Elmer Model 137 Infracord, uv with a Perkin-Elmer Model 202 spectrophotometer, and nmr with a Varian A-60A. In the interests of brevity, ir and uv data are not routinely reported. Those physical constants and analyses found in Tables I–III are not repeated in the Experimental Section. Characteristic nmr resonances are found in Table IV for most compounds. Unless otherwise stated, it may be assumed that all organic solutions were dried over sodium sulfate; solvent was removed by vacuum evaporation in a rotating evaporator. Preparative chromatographies were run on silica gel H (E. Merck) with the solvent systems reported parenthetically, unless otherwise specified. Commercially available tlc plates (Analtech or Brinkmann) were used without pretreatment.

TABLE II

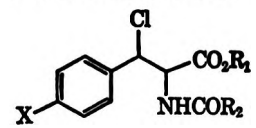
OXAZOLINES

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
trans-4-Carbomethoxy-2-methyl-5-phenyl-2-oxazoline hydrochloride (7)	91–94	$C_{12}H_{14}NO_3Cl$	56.36	5.52	5.48	55.89	6.15	5.42
trans-4-Carbomethoxy-2,5-diphenyl-2-oxazoline (8)	80–85[a]	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.27	5.16	5.21
trans-4-Carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (9)	101–104	$C_{12}H_{13}N_2O_5Cl$	47.93	4.36	9.34	47.89	4.61	9.32
trans-4-Carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (10)	86–88	[b]						
cis 8	142–144	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.68	5.57	5.08
cis 9	140–141	$C_{12}H_{13}N_2O_5Cl$	47.93	4.36	9.34	48.91	4.36	9.42
cis 10	140–141	$C_{18}H_{16}N_2O_5$	63.51	4.74	8.23	63.90	4.49	8.22

[a] Bath temperature at which sample was slowly distilled (short path) *trans* 8 was obtained as an oil. [b] Reference 6.

TABLE III

β-CHLOROALANINATES



Compd	R_1	R_2	X	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
erythro 11	CH_3	CH_3	H	123.5–125.5	$C_{12}H_{14}ClNO_3$	56.36	5.52	5.48	56.53	5.65	5.42
12	CH_3	C_6H_5	H	136–138	$C_{17}H_{16}ClNO_3$	64.26	5.08	4.41	64.56	5.25	4.46
13	CH_3	CH_3	NO_2	99–100	$C_{12}H_{13}ClN_2O_5$	48.00	4.36	9.32	48.03	4.46	9.38
14	C_2H_5	C_6H_5	NO_2	120–121	[a]						
threo 11	CH_3	CH_3	H	128–130	[b]						
12	CH_3	C_6H_5	H	132–133	$C_{17}H_{15}ClNO_3$	64.26	5.08	4.41	64.49	5.02	4.51

[a] Reference 6. [b] Reference 4.

TABLE IV
NMR DATA[a]

Compd	H_A[b]	H_B[b]	J_{AB}	OCH_3
erythro 1	313	299	3.5	221
2	321	311	4	224
3	319	302	4.5	219
4	332	313	3.5	...
threo 1	309	278	3.5	219
2	319	300	3.5	220
3	333	307	3	229
4	331	309	3.5	...
erythro 11	318	306	4.5	220
12	332	323	5	224
13	329	313	4.5	223
14	338	322	4	...
threo 11	333	315	4	227
12	341	327	4	229
cis 8	358	319	11	194
9	406	338	10.5	199
10	363	322	10.5	...
trans 7	383	313	8	235
8	355	291	7.5	231
9	388	312	8	235
10	312	286	7.5	...

[a] All values are in cycles per second downfield from internal TMS = 0. Solutions are in $CDCl_3$ except *erythro and threo* **2**, after dilute DCl exchange; *erythro* and *threo* **3**, in CD_3CO_2D; *threo* **1**, in DMSO-d_6; *erythro* **11** and *trans* **7** *in situ* $CDCl_3$ + $SOCl_2$ + HCl; *cis* and *trans* **9**, *in situ* $SOCl_2$ + HCl. [b] H_A and H_B as shown in Scheme II.

same method, mp 132–134° (ethyl acetate). *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.96; H, 5.12; N, 4.85.

Catalytic hydrogenation of **5** and **6** in either methanol or acetic acid over 5% Pd–C gave *erythro* **1** and **2** which were freed of minor amounts of *threo* isomer by chromatography (*erythro* **1**, benzene–methanol, 9:1 on alumina; *erythro* **2**, chloroform–acetone, 23:2). Reduction *via* sodium borohydride gave very similar results.

Reactions with Thionyl Chloride.—All reactions were initially followed in an nmr tube to determine the appropriate reaction conditions for product isolation.

a. **With *erythro*-N-Acetyl-β-phenylserine Methyl Ester.**—Thionyl chloride (0.2 ml) was added to 150 mg of *erythro* **1** in 3 ml of chloroform. After 2 min, the stirred solution was cooled in ice and crystals separated. After 5 min they were filtered and washed with anhydrous tetrahydrofuran. Because the product, *trans*-4-carbomethoxy-2-methyl-5-phenyl-2-oxazoline hydrochloride (*trans* **7**) was deliquescent, these operations were best accomplished in a dry box.

When a sample of *trans* **7** was dissolved in wet acetone it was rapidly converted into *threo*-O-acetyl-β-phenylserine methyl ester hydrochloride, mp 146.5–148° dec (from acetone–ether). *Anal.* Calcd for $C_{12}H_{16}ClNO_4$: C, 52.65; H, 5.89; N, 5.12. Found: C, 52.30; H, 5.98; N, 5.13. The ir readily differentiated *trans* **7** from the O-acetate.

When the thionyl chloride reaction was continued overnight at room temperature, chromatography of the residue (methylene chloride–ethyl acetate, 5:1) gave *erythro*-N-acetyl-β-chloro-β-phenylalanine methyl ester (*erythro* **11**), crystallized from ethyl acetate–ether.

b. **With *erythro*-N-Benzoyl-β-phenylserine Methyl Ester.**—A solution of 250 mg of *erythro* **2** in 3 ml of chloroform through which nitrogen was bubbled was treated with 0.5 ml of thionyl chloride. After 5 min, the solvent was removed *in vacuo* without heat. Chromatography (chloroform) gave 178 mg of *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*trans* **8**), an oil. When the reaction was allowed to stand overnight, evaporation of the solvent gave crystalline *erythro*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*erythro* **12**) which was recrystallized from tetrahydrofuran–ether for analysis.

c. **With *erythro*-N-Acetyl-β-(*p*-nitrophenyl)serine Methyl Ester.**—After standing 20 min in 5 ml of thionyl chloride, 200 mg of *erythro* **3** was converted into *trans*-4-carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (*trans* **9**). Removal of the solvent and trituration with anhydrous tetrahydrofuran gave analytically pure material. When an identical reaction was allowed to proceed over the weekend, the residue gave (chromatography, ethyl acetate–chloroform–tetrahydrofuran 10:10:2.5) *erythro*-N-acetyl-β-chloro-β-(*p*-nitrophenyl)alanine methyl ester (*erythro* **13**). The analytical sample was recrystallized from methylene chloride–cyclohexane.

d. **With *erythro*-N-Benzoyl-β-(*p*-nitrophenyl)serine Ethyl Ester.**—The residue from reaction of 700 mg of *erythro* **4** in 15 ml of thionyl chloride for 20 min was chromatographed (chloroform) to give both *trans*-4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (*trans* **10**) (crystallized from ether–hexane) and *erythro*-N-benzoyl-β-chloro-β-(*p*-nitrophenyl)alanine ethyl ester (*erythro* **14**) (crystallized from ether).

When a solution of *erythro* **4** in thionyl chloride was stored at 37° for 1 week, there deposited bright yellow crystals, mp 237–240°. Spectral (ir, uv, nmr) and elemental analyses confirmed the structure as 4-*p*-nitrobenzal-2-phenyl-5-oxazolone (**17**).[26]

e. **With *threo*-N-Acetyl-β-phenylserine Methyl Ester.**—Cold (0°) thionyl chloride (5 ml) was added to 500 mg of *threo* **1** and the solution was stored at 0° for 36 hr. Removal of the solvent and crystallization from ethyl acetate gave 380 mg of *threo*-N-acetyl-β-chloro-β-phenylalanine methyl ester (*threo* **11**).

f. **With *threo*-N-Benzoyl-β-phenylserine Methyl Ester.**—Removal of the thionyl chloride with heating after 1 hr of reaction of *threo* **2** at room temperature gave a quantitative yield of crystalline *threo*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*threo* **12**), mp 126–128°. The analytical sample was crystallized from ethyl acetate–hexane.

When a thionyl chloride solution was stored, two new nmr peaks became clearly evident after a day; one, 179 cps, was shown to be due to methyl chloride, and the other, 435 cps, was vinylic. After 4 days at 38°, a reaction was evaporated *in vacuo* without heat, taken up in cold chloroform, and washed quickly with cold salt and bicarbonate solution. The residue crystallized from ethanol to give 1.24 g (50%) of 4-benzal-2-phenyl-5-oxazolone (**16**), mp 158–159°, which exhibited the proper uv[27] absorption. From the mother liquor was deposited 575 mg (17.5%) of *threo* **12**, mp 126–128°. Chromatography (chloroform, then 1% acetone in chloroform) gave an additional 10% **16**, more *threo* **12**, and 370 mg (13%) of a crystalline substance, mp 130–131°, which was identified by its spectral properties[28] as methyl 2-(benzoylamido)cinnamate (**15**).

g. **With *threo*-N-Acetyl-β-(*p*-nitrophenyl)serine Methyl Ester.**—After standing 2 days, a solution of 200 mg of *threo* **3** in 2 ml of thionyl chloride was blown free of solvent with dry nitrogen. Trituration with anhydrous tetrahydrofuran gave *cis*-4-carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (*cis* **9**). Recrystallization of *cis* **9** from water–acetone gave *erythro*-O-acetyl-β-*p*-nitrophenyl)serine methyl ester hydrochloride, mp 188–190° dec. The ir spectrum (Nujol) showed broad ester carbonyl 1760 cm^{-1}; no amide C=O or oxazoline C=N was present. *Anal.* Calcd for $C_{12}H_{15}ClN_2O_6$: C, 45.22; H, 4.74; N, 8.79. Found: C, 45.43; H, 4.92; N, 8.92.

Stirring for 30 min with aqueous bicarbonate converted the product to *erythro* **3** in quantitative yield.

h. **With *threo*-N-Benzoyl-β-(*p*-nitrophenyl)serine Ethyl Ester.**—The reaction run as in g gave a crystalline residue which was dissolved in chloroform and washed with saturated bicarbonated solution. After removal of the chloroform, crystallization from ethyl acetate gave *cis*-4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (*cis* **10**).

***cis*-4-Carbomethoxy-2,5-diphenyl-2-oxazoline** (*cis* **8**).—*erythro*-β-Phenylserine methyl ester was heated on a steam bath [13] with a 20% excess of benziminoethyl ether hydrochloride for 40 min. The melt was dissolved in chloroform, washed with water, dried, and concentrated. The crystalline residue was recrystallized for analysis from tetrahydrofuran–hexane.

***trans*-4-Carbomethoxy-2,5-diphenyl-2-oxazoline** (*trans* **8**) was made as above from *threo*-β-phenylserine methyl ester. The product was indistinguishable from that made *via* the thionyl

(26) A. Pedrazzoli, *Helv. Chim. Acta*, **40**, 80 (1957).
(27) R. E. Buckles, R. Filler, and L. Hilfman, *J. Org. Chem.*, **17**, 223 (1952).
(28) We did not achieve the mp 141–142° reported in ref 26.

chloride reaction b, above. Treatment of *trans* **8** in thionyl chloride with hydrogen chloride opened the oxazoline to give chloro compound *erythro* **12**.

Attempted Opening of *cis* 8 with Hydrogen Chloride.—A cold $CDCl_3$ solution of *cis* **8** in an nmr probe was saturated with hydrogen chloride. The only observable change was a downfield shift of the H_A and H_B doublets (J = 11 cps) as a result of protonation. The spectrum remained essentially unchanged after 24 hr at 37°.

Registry No.—**1** (*erythro*), 19185-82-1; **1** (*threo*), 19185-83-2; **2** (*erythro*), 19185-84-3; **2** (*threo*), 19185-85-4; **3** (*erythro*), 19185-86-5; **3** (*threo*), 19202-70-1; **4** (*erythro*), 19185-38-7; **4** (*threo*), 19185-39-8; **5**, 19185-44-5; **6**, 19185-45-6; **7** (*trans*), 19185-46-7, **8** (*cis*), 19185-47-8; **8** (*trans*), 19185-48-9; **9** (*cis*;) 19185-49-0; **9** (*trans*), 19185-50-3; **10** (*cis*), 19185-51-4; **10** (*trans*), 19185-52-5; **11** (*erythro*), 19185-40-1; **11** (*threo*), 19185-41-2; **12** (*erythro*), 19185-42-3; **12** (*threo*), 19185-43-4; **13** (*erythro*), 19191-01-6; **14** (*erythro*), 19191-02-7; *threo*-O-acetyl-β-phenylserine methyl ester hydrochloride, 19191-04-9; *erythro*-O-acetyl-β-(*p*-nitrophenyl)serine methyl ester hydrochloride, 19191-05-0; thionyl chloride, 7719-09-7.

Acknowledgment.—We wish to express our gratitude to Messrs. R. Zerfing and B. Singleton who followed our reactions in the nmr and provided our spectra.

The Reaction of Arsenic Trihalides with Nucleosides. Halomethylene Dimethylammonium Halide. A New Halogenating Agent for Nucleosides[1]

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The reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro-(bromo)uridine (**7a** and **b**) when carried out in N,N-dimethylformamide (DMF). Arsenic triiodide gave poor results. Specificity for the 5′ position was found in the case of uridine. Two new nucleoside halogenating agents, chloromethylenedimethylammonium chloride (**2a**) and bromomethylenedimethylammonium bromide (**2b**), were found to be the actual halogenating agents. These agents gave excellent halogenation at the 5′ position of both **1** and **6**. Comparison was made of the facility by which these chloro and bromo derivatives cyclized to 5′-O²-cyclo nucleosides **4** and **8**. Attempts at the synthesis of nucleoside 5′-arsenate **5** indicated that these compounds may be too unstable to be isolated.

In attempts at the synthesis of arseno nucleosides we have studied the reactions of arsenic trihalides with nucleosides. In our study it was found that the reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide in anhydrous N,N-dimethylformamide (DMF) gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro(bromo)-uridine (**7a** and **b**) (Scheme I). Arsenic triiodide gave poor results. Surprisingly the reaction of uridine with the arsenic trihalides gave a high degree of specificity for the 5′ position. However when N,N-dimethylacetamide (DMA) was used as the solvent in the reaction of $AsCl_3$ with uridine, 3′-deoxy-3′-chlorouridine (**9**) was formed in addition to **7a**.

Arsenic trihalides have not been known to serve as halogenating agents for alcohols. Instead they have been reported[4,5] to react with alcohols to form dichloroarsenite derivatives. However, DMF has been reported[6-8] to react with inorganic acid halides ($COCl_2$, $POCl_3$, PCl_3, and $SOCl_2$) to form an active intermediate chloromethylenedimethylammonium chloride (**2a**). Initially **2a** found use as a formylating agent for aromatic, heterocyclic, and ethylenic compounds. Nonetheless compound **2a** and its bromide analog (**2b**) have been reported[9] to be highly effective in replacing hydroxyl and related groups with halogen. A mechanism for the formation of **2a** from $SOCl_2$ and DMF has been reported.[10] The applicability of this mechanism to the reaction of arsenic trihalides and DMF has been indicated by the report[11] of the chloromethylation of naphthalene by $AsCl_3$ and paraformaldehyde. Thus it is proposed that arsenic trihalides react with DMF in a manner similar to $SOCl_2$.

On the basis of this information we have synthesized both **2a** and **2b** by the method of Bosshard, *et al.*,[10] and used them for the halogenation of **1** and **6**. In all cases paper chromatography and thin layer chromatography indicated a quantitative conversion into the corresponding 5′-deoxy-5′-halogeno nucleoside. Isolation and purification gave yields in the range of 80–90%. (See Table I.)

In the reactions of **2a** and **2b** with uridine, fast moving (R_f 0.80–0.85, paper chromatography) uv absorbing substances were found when the reaction mixture was not refluxed with NH_4OH. These rather unstable compounds gave a negative *cis*-glycol test,[12]

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(2) Trainee in Cell Biology under Training Grant No. 5TI-GM-317 from the National Institutes of Health. This material is abstracted from the Ph.D. thesis of Dr. R. F. Dods, University of Connecticut, June 1968.

(3) Recipient of Career Award RC 31-63 from the National Cancer Institute, National Institutes of Health.

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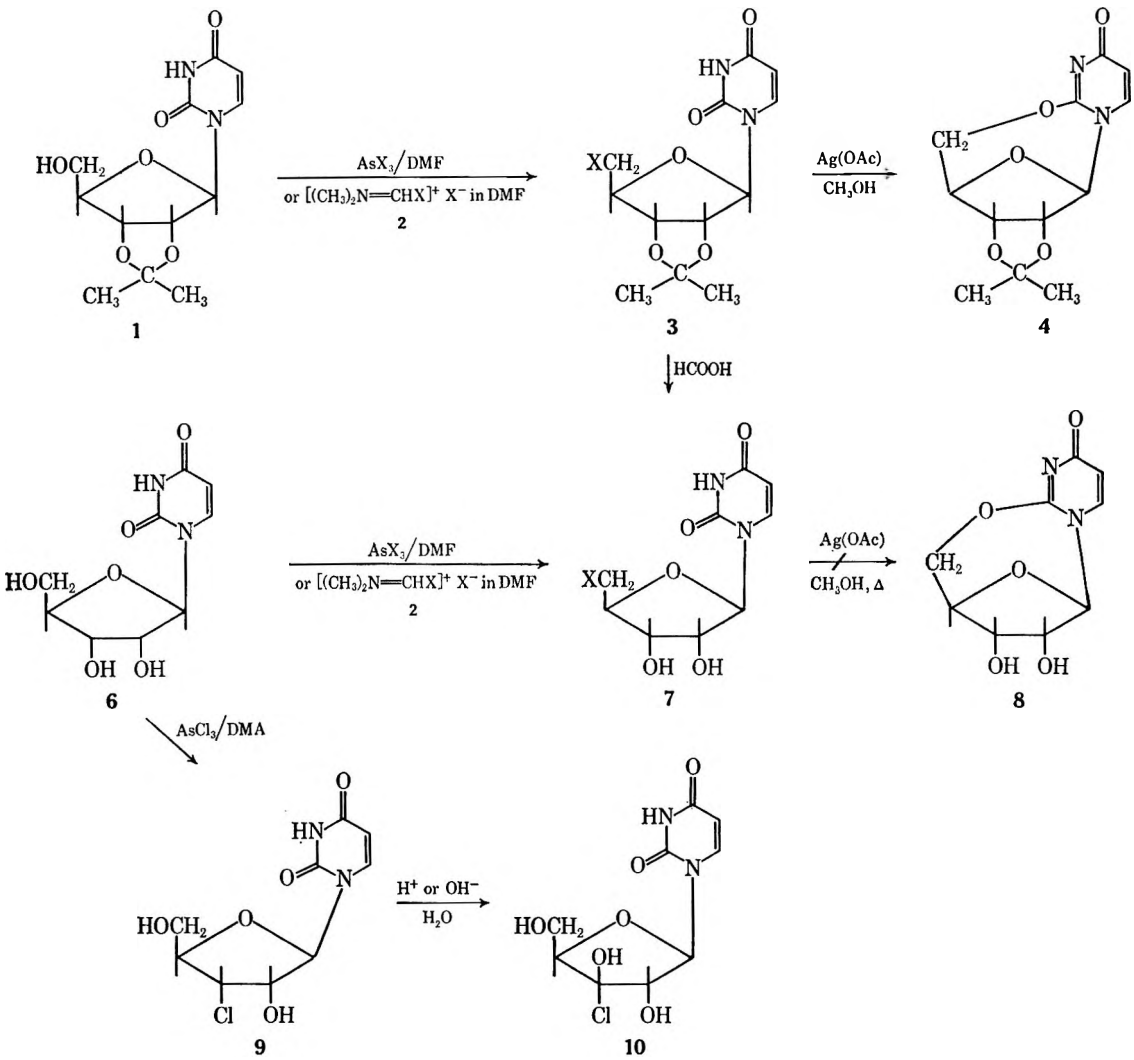
SCHEME I



a, X = chloro
b, X = bromo
c, X = iodo

and a positive ferric hydroxamate test[13] and were rapidly converted on treatment with base into the desired halogenouridine compound. We believe these substances to be the 2′,3′-O-diformate esters of **7a** and **7b**. Compound **2a** has been reported[14] to react with both primary and secondary alcohols to give formates.

It was also interesting to study the ease with which the 5′-deoxy-5′-halogenated derivatives synthesized in this study could be cyclized to the 5′-O^2-cyclo nucleosides. The results of this experiment appear in Table II. Only the bromo and iodo derivatives reacted under the conditions used. It was interesting to note that the product of the cyclization reaction of **7b** was O^2-methyluridine. Nevertheless the formation of O^2-methyluridine must have proceeded *via* a 5′-O^2-cyclo intermediate. This suggests that the difference between **7b** and its 2′,3′-acetonide **3b** in cyclo nucleoside formation lies in the stability of the corresponding cyclo nucleoside. 5′-O^2-cyclouridine is less stable and therefore more reactive with the solvent, methanol, than 2′,3′-O-isopropylidene-5′-O^2-cyclouridine.

Codington, *et al.*,[15] reported 2.5-mμ hypsochromic shifts relative to uridine for their 2′-deoxy-2′-halogenouridine compounds. The shifts were the same regardless of which halogen was present. In the present study 1.0-mμ hypsochromic shifts were found in the 5′-deoxy-5′-halogenouridine series. However the 5′-deoxy-5′-halogeno-2′,3′-O-isopropylideneuridine compunds showed hypsochromic shifts whose magnitude depended on the nature of the halogen present.

Recently reports have appreared which indicate the possible formation of nucleoside arsenates in certain biological systems.[16,17] As indicated earlier the original aim of this study was the chemical synthesis of arsenonucleosides. In the previously described arsenic trihalide reactions in DMF and DMA there were no indications that such a derivative had formed. Reactions of arsenic trihalides with **1** and **6** in solvents other than DMF anf DMA did not produce the desired arseno nucleosides. Since cyclo nucleosides have been

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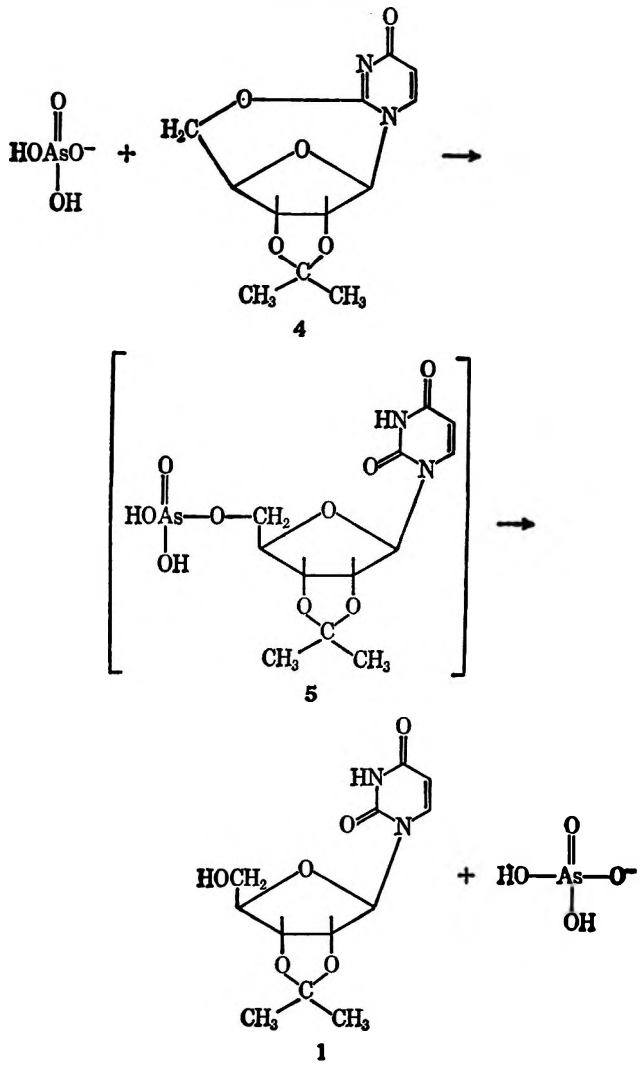
TABLE 1
REACTIONS OF ARSENIC TRIHALIDES AND HALOMETHYLENEDIMETHYLAMMONIUM HALIDES WITH NUCLEOSIDES

Nucleoside, g (mmol)	Halogenating agent, g (mmol)	Solvent DMF, ml	Temp, °C	Time, hr	Product	R_f (paper)	Yield, %	Mp, °C	Formula	Calcd, % C	H	X	N	Found, % C	H	X	N
1, 0.500 (1.76)	$AsCl_3$, 0.360 (2.00)	15	160	0.5	**3a**	0.80	52	174–178	$C_{12}H_{15}ClN_2O_5$	47.60	5.03	11.71	9.58	47.55	4.92	11.71	9.04
1, 0.500 (1.76)	$AsBr_3$, 0.630 (2.00)	15	90	48	**3b**	0.84	62	179–181	$C_{12}H_{15}BrN_2O_5$	41.50	4.32	23.20	8.07	41.62	4.46	23.28	8.07
6, 2.00 (8.20)	$AsCl_3$, 1.73 (9.61)	25	160	4	**7a**	0.42	51	170–172	$C_9H_{11}ClN_2O_5$	41.15	4.22	13.50	10.67	40.96	4.29	13.50	10.75
6, 2.00 (8.20)	$AsBr_3$, 3.01 (9.56)	25	160	2	**7b**	0.47	40	172–175	$C_9H_{11}BrN_2O_5$	35.20	3.64	26.03	9.13	35.25	3.60	26.15	9.13
1, 0.500 (1.75)	**2a**, 0.230 (1.81)	10	90	1.5	**3a**	0.80	90	175–177									
1, 0.50 (1.75)	**2b**, 0.391 (1.80)	10	90	1.5	**3b**	0.84	85	179–181									
6, 2.00 (8.20)	**2a**, 1.04 (8.19)	20	120	8	**7a**	0.42	81	170–172									
6, 2.00 (8.20)	**2b**, 1.78 (8.20)	20	120	8	**7b**	0.47	78	173–175									

SCHEME II



4 5 1

reported[18] to show a high degree of reactivity toward certain nucleophiles including phosphates, an attempt was made at the synthesis of 2′,3′-O-isopropylideneuridine 5′-arsenate (**5**) by reaction of arsenate with cyclo nucleoside **4** (Scheme II). Arseno nucleoside **5** was rapidly hydrolyzed by traces of water during attempts at isolation. The inability to synthesize an arseno nucleoside is consistent with reports of the instability of sugar arsenates.[19]

Experimental Section[20]

Synthesis of 2a and 2b.[10]—Equimolar proportions of dry DMF and $SOCl_2$ or $SOBr_2$ were allowed to react together at room tem-

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(20) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ultraviolet spectra were obtained on a Cary recording spectrophotometer, Model 14. Melting points were measured on a Thomas–Hoover melting point apparatus and were corrected. Paper chromatography was carried out using the descending method on Whatman No. 1 paper and employing butanol saturated with water as solvent. Ultraviolet absorbing compounds were located with the aid of a ultraviolet lamp equipped with a short-wavelength (254 mμ) filter. Thick layer chromatography was performed on 8 × 8 in. glass plates coated with silica gel HF_{254} (1 mm) using butanol saturated with water (ascending method). The arsenic trihalides were obtained from The British Drug Houses, Ltd. Arsenic tribromide (mp 32.8°) was warmed to 40° to convert it into the liquid form for easier handling.

TABLE II

EASE OF CYCLIZATION AND ULTRAVIOLET SPECTRA OF 5′-DEOXY-5′-HALOGENO NUCLEOSIDES

Compound	Cyclization[a]	Ultraviolet spectra, pH 1–7: Max	ϵ_{max}[b]	Min	ϵ_{min}[b]	pH 12: Max	Min
Uridine series							
5′-Deoxy-5′-fluoro-[c]		261		230		262	242
7a	Unchanged	207 261	9.99 10.3	230	2.46	262	242
7b	Forms of O^2-methyluridine	207 261	10.0 10.7	230	2.68	262	242
5′-Deoxy-5′-iodo-[d]	*e*	261		230			
2′-3′-O-Isopropylideneuridine series							
3a	Unchanged	260.5	11.5	230	2.73	260	240
3b	100% conversion into **4** in 40 min	258	11.8	230	6.45	259	240
3c[f]	100% conversion into **4** in 10 min	258		229		258	240

[a] Cyclization of the halo nucleosides to **4** or **8** was carried out by the reaction of 13 μmol of halogeno nucleoside with 56 μmol of silver acetate in 1.20 ml of dry methanol at 67°. The reactions were followed by tlc using butanol saturated with water as solvent and HF_{254} silica gel as the stationary phase. [b] ϵ_{max} and ϵ_{min} (10^{-3}) were determined in water (pH 5). [c] H. M. Kissman, and M. J. Weiss, *J. Amer. Chem. Soc.*, 80, 5559 (1958). [d] D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1967). [e] Forms a compound "too insoluble to permit complete purification." [f] Sample kindly supplied by Dr. B. Otter.

perature for 30 min. The reaction mixture was evaporated to dryness (40°). The residue was washed thoroughly with dry ether and again dried *in vacuo*.

Isolation and Purification of 3a and 3b.—The solution was cooled and then made basic with 1 *N* NH_4OH. The reaction mixture was refluxed 0.5 hr and then evaporated to dryness *in vacuo*. Water (15 ml) was added to the residue and the water suspension was extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, extracted with water, and then dried with Na_2SO_4. After filtration from the drying agent the solution was evaporated to 5 ml. The addition of hexane to a point of slight turbidity resulted in the crystallization of **3a** or **3b**. The solid was recrystallized twice from $CHCl_3$–hexane.

Isolation and Purification of 7a and 7b.—The reaction flask was cooled and its contents were evaporated to a brown oil *in vacuo*. Water (20 ml) was added to the oil and the resulting mixture was made basic with 1 *N* NH_4OH. The solution was refluxed 0.5 hr and then evaporated *in vacuo* to yield a solid which was then dissolved in 100 ml of methanol. Norit A (neutral), 2 g, was added and the mixture stirred at 27° for 3 hr before filtration. The filtrate was evaporated *in vacuo* to 10 ml. The solid deposited at this time was filtered from the solution and did not contain any nucleoside. The liquid was thick layer chromatographed using four plates. Compound **7a** appeared at R_f 0.65 and **7b** at 0.70. The 0.65 band (or 0.70 band) was removed from the plates and the silica gel was then extracted with boiling methanol. The suspension was filtered and the filtrate was then evaporated to 10 ml. The solution was allowed to stand for 3 days at 10° whereupon a white precipitate of product was deposited. The supernatant was evaporated to 5 ml and allowed to stand for 1 day at 10°. An additional yield of product precipitated. The solid was recrystallized twice from acetone.

Synthesis of 3′-Deoxy-3′-chlorouridine (9).—The procedure employed was the same as that used in the reaction of **6** and $AsCl_3$ except that 25 ml of dry DMA was used and the reaction was carried out at 127° for 12 hr. Thick layer chromatography gave four uv absorbing bands at R_f 0.20, 0.43, 0.54 and 0.80. Paper chromatography of the same methanol solution gave the following uv absorbing bands: 0.26 (10%), 0.36–0.42 (60%), 0.52 (5%), and 0.76 (25%). Each tlc band was removed and compared by paper chromatography and uv absorption spectrum to a pure sample of possible reaction components. As anticipated the tlc band at 0.20 was found to be 6. The band at 0.43 resolved, upon paper chromatography, into two uv absorbing spots, 0.36 and 0.42, uracil and **7a**, respectively. The band at 0.52 was probably 1-β-D-xylofuranosyluracil (**10**) as indicated by its uv spectrum, a negative *cis*-glycol test and its electrophoretic mobility.[21] The band at 0.80 was removed and extracted with 100 ml of boiling methanol. The mixture was filtered and the filtrate was evaporated to dryness. An analytical sample of this rather unstable product was obtained by recrystallization from methanol. A yield of 430 mg (20%) was obtained, mp 177–179°, R_f (paper) 0.78. Compound **9** gave a negative *cis*-glycol test and could be converted into **10** by 6 *N* HCl or 6 *N* NaOH on standing at 25° for 24 hr: uv spectrum, $\lambda_{max}^{CH_3OH}$ 258 (ε 7400), $\lambda_{min}^{CH_3OH}$ 229.

Anal. Calcd for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.67. Found: C, 41.25; H, 4.30; Cl, 13.70; N, 9.70.

Attempts at the Synthesis of Arseno Nucleosides. A. The Reaction of Monopyridinium Arsenate with 5′-O^2-Cyclo-2′,3′-O-isopropylideneuridine (4).—Arsenic acid (1.10 ml of a 4.16 mg/ml aqueous solution) was evaporated to dryness *in vacuo* and then further dried by evaporation thrice with 2 ml of dry pyridine. Dry DMA (2 ml) was added and the mixture evaporated to 0.2 ml. In a second test tube, 4 mg (0.0150 mmol) of **4** was dried by evaporation with dry pyridine thrice. Under a stream of N_2 0.20 ml of dry DMA was added to the nucleoside. The flask was then evacuated, filled with N_2 and immediately sealed. The solution was maintained at 25° for 3 hr. A sample removed for paper chromatography showed that **4** was completely converted into **1**. In a control experiment the above steps were followed exactly as described except that water (1 ml) was used instead of arsenic acid. Paper chromatography showed that there had been no conversion of **4** into **1**.

B. The Reaction of Morpholine-N,N′-dicyclohexylcarboxamidinium Arsenate with 4.—Equimolar quantities (0.0134 mmol) of morpholine-N,N′-dicyclohexylcarboxamidinium arsenate and **4** were allowed to react in 0.20 ml of dry DMA at 25° for 3 hr. A control solution containing morpholine-N,N′-dicyclohexylcarboxamidine,[22] **4**, and DMA but no arsenate was also allowed to stand at 25° for 3 hr. Paper chromatography of the two reaction solutions showed conversion of **4** into **1** only in the reaction containing arsenate.

Registry No.—**3a**, 19556-51-5; **3b**, 19556-52-6; **3c**, 14671-65-9; **7a**, 19556-54-8; **7b**, 19556-55-9; **9**, 18810-36-1.

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Formation of Oligomers on N Acylation of Tripeptides. Proton Magnetic Resonance Spectra of the Peptides[1]

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Received August 12, 1968

The peptides L-Phe-Gly-L-Leu, L-Leu-L-Phe-L-Ala, and L-Ala-L-Phe-Gly-L-Leu were prepared *via* controlled acylation by amino acid N-carboxyanhydrides. Acylation of the tripeptides by benzyloxycarbonyl chloride resulted in extensive formation of tripeptide oligomers, indicating that the carboxylate anion of a free peptide competes favorably with the terminal amino group as a nucleophile. The proton magnetic resonance spectra of L-Leu-L-Phe-L-Ala and its oligomers and of L-Ala-L-Phe-Gly-L-Leu are reported and briefly discussed.

Unblocked peptide fragments are potentially available, with speed and convenience, and in quantity, using the method of controlled acylation of amino acids and peptides by amino acid N-carboxyanhydrides.[3-5]

In exploring this method in our laboratory we readily prepared two free tripeptides and a tetrapeptide, and for subsequent use subjected the tripeptides to standard conditions for N acylation by benzyloxycarbonyl chloride. Extensive oligomerization of the tripeptides occurred in the acylation process. This observation, together with the high-resolution proton magnetic resonance spectra of the oligomers, is described and discussed below. The reactions reported are summarized in Figure 1.

Experimental Section[6]

General Nmr Spectra.—Proton magnetic resonance spectra were measured using Varian A-60, HA-60 and HA 100 spectrometers with occasional assistance of a Varian C-1024 time averaging computer. We are grateful to the Department of Chemistry, University of Chicago, for the use of the HA-100 instrument. Assignment of resonances was made on the basis of chemical shifts and homonuclear spin-decoupling experiments. Spectra were measured on solutions in trifluoroacetic acid, trifluoroacetic acid-*d*, dimethyl sulfoxide-d_6 and D_2O, and referred to internal tetramethylsilane, or, for aqueous solutions, to internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate.

Controlled Acylation by Amino Acid N-Carboxyanhydrides (NCA).—A Waring Model 1002 Commercial Blendor with a 1-qt clover-shaped Pyrex jar was used. The tightly fitting plastic cap provided for the jar had a 2-in. central opening with a removable plug. This opening was used for addition of the solid anhydrides to the cooled and stirred reaction mixture. The outer part of the cap was bored with two holes in one corner to support and pass the leads of a single-turn cooling coil of $\frac{3}{16}$-in. stainless steel tubing. The turn of the coil was placed below the stirrer blades of the jar and the leads were brought up along one corner of the jar, carefully placed to avoid interference with the blades. Additional holes were bored in the other corners of the cap, one to support an alcohol thermometer, and one to support a combination pH electrode; the active part of each of these was placed so as to be bathed in the stirred mixture. Though the remaining hole passed a piece of Teflon tubing through which alkali was added from a syringe to maintain constant pH during the reaction.

Through the cooling coil was passed a water–glycol cooling mixture, pumped from a reservoir chilled by solid carbon dioxide. Coolant was pumped at a rate and temperature so that the *stirred* reaction mixture could be held at 0° or slightly below; with sufficient cooling for the stirred condition, the unstirred reaction mixture would freeze.

L-Phe-Gly-L-Leu (I).—A solution of 0.94 g (0.005 mol) of glycyl-L-leucine (Mann Research Laboratories) in 50 ml of trimethylammonium chloride buffer (0.42 *M* amine, 0.25 *N* hydrochloric acid) was adjusted, *at* 0°, to pH 10.4 by addition of 1.2 ml of 4 *N* sodium hydroxide. This solution was agitated at 0° in the Blendor fitted as described above, at its maximum speed, and to it was added all at once 1.05 g (0.0055 mol) of solid L-phenylalanine N-carboxyanhydride.[7] The pH of the reacting mixture was maintained at 10.4 by continuous addition of 4 *N* sodium hydroxide. Consumption of alkali ceased after several minutes; 1.20 ml of base was consumed. After 10 min the pH was adjusted to 6, using concentrated sulfuric acid. The solution was filtered and concentrated to dryness at reduced pressure. The residue was washed with a small amount of water, and the water-insoluble part, 1.7 g, was crystallized from glacial acetic acid–ether to yield 1.57 g (94%) of tripeptide, mp 233–234° dec. This product was chromatographically homogeneous in a system known to separate it from the starting dipeptide and the three amino acids involved—Eastman silica chromagram sheet, 1-butanol–acetic acid–water 7:1:2 (7:1:2 BAW). Upon hydrolysis with 4 *N* hydrochloric acid, it yielded a chromatogram with three spots corresponding to its amino acid components. An analytical sample was dried at 100° at 0.05-mm pressure.

Anal. Calcd for $C_{17}H_{25}O_4N_3$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.48; H, 7.70; N, 12.38.

This experiment was repeated in the same apparatus at ten times the scale (0.005 mol) with no loss in yield.

L-Ala-L-Phe-Gly-L-Leu (II).—A procedure analogous to that described above was used. L-Phe-Gly-L-Leu (I) (12.0 g, 0.036 mol), prepared as above, and L-alanine N-carboxyanhydride[8] (4.6 g, 0.04 mol) were the reactants. The crude product obtained from the reaction mixture, after acidification, evaporation to dryness, and washing with a small amount of water, contained four components; in order of decreasing R_f in 7:1:2 BAW they were initial tripeptide, tetrapeptide, unknown (possibly alanylanine), and alanine. The major component, tetrapeptide, crystallized first from acetic acid–ether; 7.3 g (50% was obtained.[9] Separation of tri- and tetrapeptide could also be achieved making use of the fact that the tripeptide is insoluble but the tetrapeptide soluble in 1-butanol or 1-pentanol.

A chromatographically pure analytical sample, mp 191–192° dec, was obtained from acetic acid–ether, but although dried at 100° and 0.05 mm for 24 hr, it appeared to retain 1 mol of water.

Anal. Calcd for $C_{20}H_{30}O_5N_4 \cdot H_2O$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.97; H, 7.30; N, 13.08.

L-Leu-L-Phe-L-Ala (V).—A solution of 1.78 g (0.02 mol) of

(1) Work supported by research grants from the National Science Foundation (GB 4514) and the U. S. Public Health Service, National Institute of General Medical Sciences (GM 14069).

(2) Faculty of Science, Kanazawa University, Kanazawa, Japan; on leave 1966–1967.

(3) R. G. Denkewalter, *et al.*, *J. Amer. Chem. Soc.*, **88**, 3163 (1966).

(4) R. Hirschmann, *et al.*, *J. Org. Chem.*, **32**, 3415 (1967).

(5) D. F. Veber, K. Pfister, and R. Hirschmann, *J. Med. Chem.*, **10**, 986 (1967).

(6) Elemental analyses performed by Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected.

(7) M. Sela and A. Berger, *J. Amer. Chem. Soc.*, **77**, 1893 (1955).

(8) J. L. Bailey, *J. Chem. Soc.*, 3461 (1950); A. Elliott, *Proc. Roy. Soc.* (London), **A211**, 104 (1954).

(9) Reaction on this scale overloaded our apparatus; mixing and cooling were not optimal. On an 0.005-mol scale the yield was 60%.

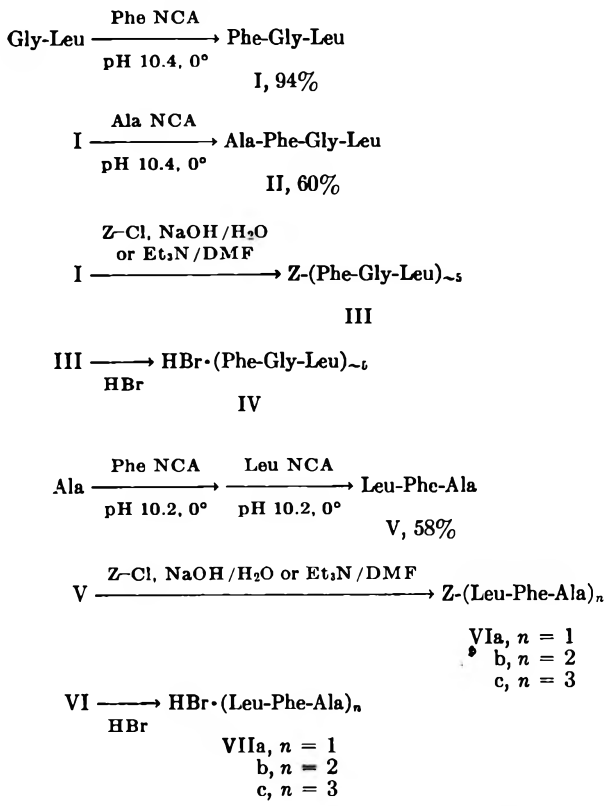


Figure 1.—Peptide couplings and oligomerizations discussed in this report. Abbreviations: NCA, N-carboxyanhydride; Z benzyloxycarbonyl; DMF, dimethylformamide. All dissymmetric amino acid residues are L series. Yields shown are of isolated, homogeneous products.

L-alanine in 100 ml of trimethylammonium chloride buffer (0.42 *M* amine, 0.25 *M* hydrochloric acid) was adjusted at 0° to pH 10.2 (2.6 ml of 4 *N* sodium hydroxide) and agitated in the Blendor at 0°. To this solution was added, all at once, 4.05 g (0.021 mol) of L-phenylalanine N-carboxyanhydride and the pH was held at 10.10–10.25 by continuous addition of 4 *N* sodium hydroxide (8.1 ml). After 10 min, 18 *N* sulfuric acid (3.3 ml) was added to bring the pH to 3.0, and 5 min later 7.2 ml of 4 *N* sodium hydroxide was used to readjust the pH to 10.15 *at* 0°.

To the chilled and agitated reaction mixture was now added all at once 3.46 g (0.021 mol) of L-leucine N-carboxyanhydride[10] and pH was maintained at 10.10–10.25 by continuous addition of 4 *N* sodium hydroxide (7.1 ml). At the completion of reaction, pH was adjusted first to 3.0 and then to 6.

The reaction mixture was filtered to remove a small amount of insoluble (polymeric?) material. On thin layer chromatography the soluble material was resolved into L-Leu-L-Phe-L-Ala (V), the predominant product, and L-Phe-L-Ala; it appeared to contain very little else. Concentration under reduced pressure to a volume of 10–15 ml caused precipitation of crystalline tripeptide, most of the dipeptide remaining in the mother liquors. The crystalline product was washed with alcohol and recrystallized from glacial acetic acid–ether to yield 4.0 g (58%) of tripeptide. This product was chromatographically single and free of dipeptide and amino acids.

An analytical sample was crystallized from water–dioxane and ethanol–dioxane and dried at 0.05 mm and 100° for 24 hr. It decomposed above 220° without melting. Thin layer chromatography of a hydrolysate (4 *N* hydrochloric acid) showed the constituent three amino acids.

Anal. Calcd for $C_{18}H_{21}O_4N_3 \cdot 0.5H_2O$: C, 60.31; H, 7.87; N, 11.72. Found: C, 60.22, 60.14; H, 7.79, 7.83; N, 11.40, 11.42.

Benzyloxycarbonylation of L-Phe-Gly-L-Leu. A. In Water.—To a vigorously stirred solution of 0.84 g (0.0025 mol) of L-Phe-Gly-L-Leu (I) in 1.25 ml of 2 *N* sodium hydroxide were added, in alternating portions of one-half, 0.51 g (0.003 mol) of benzyloxycarbonyl chloride and 1.5 ml of 2 *N* sodium hydroxide. The addition required about 30 min and was conducted at 0°. After 30 min of further stirring, the reaction mixture was acidified to pH 4 using 4 *N* hydrochloric acid; then the precipitated product was collected by filtration and washed with alcohol and petroleum ether (bp 30–60°); it weighed 0.83 g After reprecipitation from acetic acid solution by addition of ether, the product had mp 285–288° dec.

B. In Dimethylformamide.—To a stirred solution of 0.84 g (0.0025 mol) of L-Phe-Gly-L-Leu (I) in 30 ml of dimethylformamide cooled in an ice bath were added, first, 0.73 ml (0.0052 mol) of triethylamine and, second, 0.47 g (0.0028 mol) of benzyloxycarbonyl chloride, drop by drop. After 1 hr of stirring at ice bath temperature, 1.25 ml of 2 *N* hydrochloric acid was added, the mixture was filtered free of precipitated triethylammonium chloride, and the filtrate was concentrated to dryness at reduced pressure. The dried residue was triturated with petroleum ether and then with water, to yield 0.8 g of solid, mp 276–280° dec. This was purified by precipitation from dimethylformamide solution on addition of ether, with almost quantitative recovery, mp 285–288° dec.

Anal. Calcd for pentamer III, $C_{93}H_{123}O_{18}N_{15}$: C, 64.23; H, 7.13; N, 12.08. Found: C, 63.36; H, 7.03; N, 12.10.

Benzyloxycarbonylation of L-Leu-L-Phe-L-Ala. A. In Water.—To a vigorously stirred solution of 0.87 g (0.0025 mol) of L-Leu-L-Phe-L-Ala in 2.5 ml of *N* sodium hydroxide at 0° were added, in alternating portions of about one-half, 0.51 g (0.003 mol) of benzyloxycarbonyl chloride and 1.5 ml of 2 *N* sodium hydroxide. Addition required about 30 min and stirring was continued 30 min at 0° and 30 min more without cooling.

The reaction mixture, which contained a precipitate, was acidified to pH 4, using 4 *N* hydrochloric acid, and vigorously shaken with 30 ml of ethyl acetate. An insoluble product was collected by filtration and purified by repeated precipitation induced by adding ether to a dimethylformamide solution. This substance, mp 310–313° dec, was obtained in 13% yield (0.12 g). It was assigned the structure of N-benzyloxycarbonyl nonapeptide (trimer VIc).

Anal. Calcd for $C_{62}H_{63}O_{12}N_9$: C, 64.96; H, 7.30; N, 11.00. Found: C, 65.07; H, 7.38; N, 10.73.

The ethyl acetate phase was dried over magnesium sulfate and concentrated to dryness at reduced pressure. The residue was taken up in methanol, and after the solution had been filtered, a small amount of water was added to induce crystallization of a second product. This product was recrystallized from methanol–water to yield 0.15 g (15%) of what proved to be the benzyloxycarbonyl hexapeptide (dimer VIb), mp 228–231° dec.

Anal. Calcd for $C_{44}H_{58}O_9N_6$: C, 64.84; H, 7.17; N, 10.31. Found: C, 64.55; H, 7.16; N, 10.08.

From the methanolic mother liquors of the hexapeptide an oil was thrown down by further addition of water. This was triturated with water until it solidified, and then recrystallized several times from ethyl acetate–petroleum ether to afford 0.40 g (33%) of benzyloxycarbonyl tripeptide, VIa, mp 142–144°.

Anal. Calcd for $C_{26}H_{33}O_6N_3$: C, 64.58; H, 6.88; N, 8.69. Found: C, 64.84; H, 6.99; N, 8.75.

Repetition of the above experiment resulted in isolated yields of monomer, dimer and trimer of 21, 25, and 21% respectively. From an experiment using 2 equiv of benzyloxycarbonyl chloride and an appropriate amount of base were isolated 17, 13, and 23% respectively, of the three peptides.

B. In Dimethylformamide.—To a stirred solution of 0.87 g (0.0025 mol) of L-Leu-L-Phe-L-Ala (V) in 30 ml of dimethylformamide cooled in an ice bath were added, first, 0.73 ml (0.0052 mol) of triethylamine and, second, 0.47 g (0.0028 mol) of benzyloxycarbonyl chloride. After 30 min 1.25 ml of 2 *N* hydrochloric acid was added. The reaction mixture was filtered to remove precipitated triethylammonium chloride. The filtrate was evaporated to dryness under reduced pressure and the resultant was triturated with petroleum ether and then water to yield 0.6 g of a solid. This was extracted with ethyl acetate. The ethyl acetate insoluble material, 0.4 g, was trimer VIc, mp 310–312° dec.

The ethyl acetate solution, on evaporation, yielded 0.2 g of dimer, VIb, mp 226–230° dec. No benzyloxycarbonyl tripeptide was obtained.

Hydrogen Bromide Cleavage of Z-L-Leu-L-Phe-L-Ala (VIa) and Its Dimer (VIb).—The benzyloxycarbonyl peptides, 0.15 g,

(10) D. Coleman, *J. Chem. Soc.*, 3222 (1950); J. L. Bailey, *ibid.*, 3461 (1950); A. C. Farthing and R. J. W. Reynolds, *Nature*, **165**, 647 (1950).

were dissolved in 5 ml of 30% hydrogen bromide in acetic acid, and the solutions were allowed to remain at room temperature for 1 hr. Anhydrous ether was then added to precipitate apparently crystalline solids, which were collected on a glass frit funnel and washed copiously with ether.

The cleavage product from the tripeptide derivative was recrystallized from absolute ethanol–ether to give 0.15 g of tripeptide hydrobromide VIIa, mp 218–220° dec.

Anal. Calcd for $C_{18}H_{28}O_4N_3Br$: C, 50.23; H, 6.56; N, 9.76; Br, 18.57. Found: C, 50.83; H, 6.73; N, 9.76; Br, 18.12.

The cleavage product from the hexapeptide derivative was purified by precipitation from dimethylformamide by the addition of ether to yield 0.15 g of hydrobromide, mp 290–300° dec.

Anal. Calcd for $C_{36}H_{53}O_7N_6Br$: Br, 10.49. Found: Br, 9.58.

Hydrogen Bromide Cleavage of Z-(L-Leu-L-Phe-L-Ala)$_3$ (VIc) and Z-(L-Phe-Gly-L-Leu)$_n$ (III).—The benzyloxycarbonyl peptides, 0.11 g, were dissolved in 3 ml of trifluoroacetic acid and to these solutions were added 0.5-ml portions of 30% hydrogen bromide in acetic acid. After 1 hr at room temperature dry ether was added to precipitate solid products, which were collected on a glass frit funnel and washed copiously with ether.

The cleavage product of VIc was purified by precipitation from trifluoroacetic acid solution on addition of dry ether; 0.1 g of product VIIc was obtained.

Anal. Calcd for $C_{54}H_{78}O_{10}N_9Br$: N, 11.53; Br, 7.31. Found: N, 11.33; Br, 7.73.

The cleavage product (IV) of III was also purified by precipitation from trifluoroacetic acid–ether; 0.1 g was obtained.

Anal. Calcd for pentamer, $C_{85}H_{118}N_{15}O_{16}Br$: C, 60.55; H, 7.06; N, 12.46; Br, 4.74. Found: C, 60.40; H, 7.00; N, 12.09; Br, 4.42.

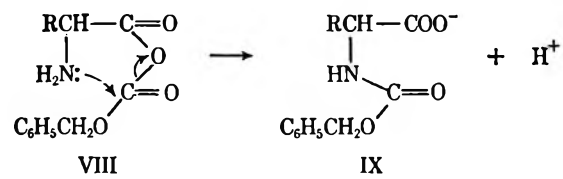
Discussion

Synthesis.—In preparing peptides I, II and V (Figure 1) *via* the N-carboxyanhydride method, we followed the procedure described by the Merck group,[3-5] with the exception that, rather than the original borate buffer, we used a trimethylamine–trimethylammonium system, 0.4 *M* in total amine concentration. We chose trimethylamine because its pK_A at 0°, 10.7,[11] is closer to the required pH for minimization of side reactions (10.2–10.4),[3,4] and therefore at a given concentration it could be expected to provide greater buffer capacity than borate (pK_A at 0°, 9.5[12]). It was nonetheless necessary to control pH by addition of concentrated alkali during acylation.

Oligomerization.—When the tripeptide Phe-Gly-Leu was subjected to Schotten–Baumann conditions for N acylation by benzyloxycarbonyl chloride,[13,14] there was obtained, almost quantitatively, a peptide of solubility characteristics different from those expected for the benzyloxycarbonyl tripeptide. The integral of the proton magnetic resonance spectrum of this product (trifluoroacetic acid solution) indicated a ratio of one benzyloxycarbonyl methylene (5.1 ppm) to four or five phenylalanyl methylenes. Treatment with hydrogen bromide in trifluoroacetic acid afforded in high yield a peptide hydrobromide with bromine content consistent with the hydrobromide of tripeptide pentamer. A similar oligomeric product was obtained, also in excellent yield, when the acylation was carried out in dimethylformamide solution, using triethylamine as base.

With the tripeptide Leu-Phe-Ala (V), treatment with benzyloxycarbonyl chloride in aqueous base resulted in a mixture of three discrete compounds: the N-benzyloxycarbonyl derivatives of the tripeptide (VIa), of its dimer (VIb) and of its trimer (VIc). The yield of VIa was not increased by use of 2 equiv of acylating agent. When acylation was carried out in dimethylformamide solution (triethylamine as base) only the trimeric (VIc) and dimeric (VIb) derivatives were isolated.

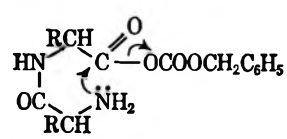
Reaction of an acyl halide with an amino acid anion, or with the anion of an unblocked peptide, can occur at either of the two nucleophilic centers, amino and carboxylate. Benzyloxycarbonylation of amino acids in aqueous base consistently affords the N-benzyloxycarbonyl derivatives in good yield,[13] and would do probably so regardless of the initial site of reaction. Reaction at the carboxylate group leads to the mixed anhydride VIII, which can readily undergo intramolecular acyl transfer to the stable N-acyl derivative IX. An indication that some C acylation occurs,



VIII IX

however, is given by the observation that reaction of glycine in bicarbonate buffer affords benzyloxycarbonylglycylglycine as a contaminant (10%) of the desired benzyloxycarbonylglycine.[15]

Carboxyl acylation of a dipeptide anion would be expected to result in formation of a diketopiperazine, *via* the six-membered intermediate state shown as X,



X

by analogy with the facile cyclization of even unactivated dipeptide esters. In our laboratory we have, in other work, successfully benzyloxycarbonylated glycylglycine and glycyltyrosine under Schotten–Baumann conditions, indicating that in these peptides containing N-terminal glycine at least, acylation occurs predominantly on nitrogen.

In case of a tripeptide, a mixed anhydride formed by acylation at the C terminus cannot readily undergo intramolecular reaction with the terminal amino group; with one exception,[16] attempts at cyclization of tripeptides have failed.[17] Carboxylate acylation should therefore be unproductive (hydrolysis of the anhydride) or should lead to oligomerization, that is, peptide bond formation by intermolecular reaction of amino groups

(11) Measured pH at half-neutralization of 0.47 *M* solution at 0°.

(12) "Handbook of Chemistry and Physics," 46th ed, Chemical Rubber Co., Cleveland, Ohio, 1965, p D-80.

(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, N. Y., 1961, pp 887–901.

(14) M. Rothe, H. Brunig and G. Eppert, *J. Prakt. Chem.*, [4] **8**, 323 (1959).

(15) T. Ito, reported at the 2nd Symposium on Peptide Synthesis, Osaka, Japan, 1963. The bicarbonate buffer method of Greenstein and Winitz, p 895 of ref 13, was used.

(16) M. Roth and K. D. Steffen, *Angew. Chem.*, **77**, 347 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 356 (1965).

(17) E. Schroeder and K. Lubke, "The Peptides," Vol. I, E. Gross, Translator, Academic Press, New York, N. Y., 1965, p 271 ff.

with the mixed anhydride, in the usual manner for carbonic–carboxylic anhydrides.[18]

The tripeptide glycyclglycylglycine can be N acylated with benzyloxycarbonyl chloride in aqueous alkali; a 65% yield of N-acyltripeptide has reported.[14] We have repeated this acylation without detecting higher polyglycine derivatives chromatographically.[19] Thus it appears that N acylation is favored for glycylglycylglycine, but, considering the extent of oligomerization described above, tripeptides L-Phe-Gly-L-Leu and L-Leu-L-Phe-L-Ala must undergo predominant carboxyl acylation.

The evidence just cited is admittedly scanty, since N acylation of free peptides is not a common piece of synthetic strategy, but it does appear that the intrinsic reactivities toward an acyl halide of amino and carboxylate groups in peptides are quite similar. The difference between the course of reaction of triglycine, on the one hand, and that of the two tripeptides discussed here, on the other, is very likely the result of steric inhibition by the side chain of the N-terminal residue.

Nmr Spectra.—Chemical shift data are given in Table I for the aliphatic protons of Z-Leu-Phe-Ala

TABLE I

ALIPHATIC PROTON RESONANCES OF L-LEU-L-PHE-L-ALA DERIVATIVES AT 31° [a]

	Proton	VIa (DMSO)[b]	VIIa (TFA)[b]
Leu	α	3.98	4.44
	α, int.[c]	~4.2	~4.7
	δ[e]	0.81	1.04
Phe	α	4.58	5.02
	β[d]	2.95	3.19
Ala	α	4.24	4.64
	α, int.[c]	~4.2	~4.7
	β	1.29	1.52[f]
	β, int.[c]	1.20	1.41

[a] Peptide concentration 30–50 mg/ml. Chemical shifts are in parts per million and refer to internal tetramethylsilane [b] Abbreviations: DMSO, dimethyl sulfoxide-d_6; TFA, trifluoroacetic acid. [c] Internal residues in oligomers. [d] See Discussion. [e] Overlapping 6-Hz doublets, $\Delta\nu$ = 0.02–0.06 ppm. [f] In oligomers 1.56.

(VIa) in dimethyl sulfoxide, and for the corresponding unblocked peptide (VIIa) in trifluoroacetic acid. Except for differences between internal and terminal residues, noted in the table, the chemical-shift values for protons of the dimeric and trimeric analogs (VIb and c and VIIb and c) do not differ significantly from those given for VIa and VIIa. In the spectrum of the carbobenzyloxy trimer (VIc), however, the resonance lines are unusually broad. In VIc the alanyl methyl lines appear only as a broad unresolved peak, while in other cases they are two (internal and C terminal) cleanly resolved 7-Hz doublets, spaced about 0.1 ppm between centers. This increase in line width for VIc suggests that in VIc (in dimethyl sulfoxide) there may be some rigid tertiary structure. (The 0.4–0.5-ppm upfield shift of a α-proton resonances that is apparently associated with helix formation in amino acid homopolymers[20] is not observed in comparing VIb and VIc.)

(18) T. Wieland and D. Stimming, *Ann.*, **579**, 97 (1953); J. R. Vaughan and R. L. Osato, *J. Amer. Chem. Soc.*, **74**, 676 (1952).

(19) Studies by Miss Anita Go.

(20) See, for example, E. N. Bradbury, C. Crane-Robinson, H. Goldman, and H. W. E. Rattle, *Nature*, **217**, 812 (1968).

TABLE II

ALIPHATIC PROTON RESONANCES OF L-ALA-L-PHE-GLY-L-LEU AT 31° [a]

	Proton	D_2O, pH 2	D_2O, pH 6–8	D_2O, pH 12	DMSO[b]	TFA[b]
Ala	α	4.03	4.01	3.45	3.75	4.80
	β[c]	1.43	1.38	1.16	1.23[h]	1.71
Phe	α	4.60	4.58	4.61	4.40	5.00
	β[g]	3.11	3.10	3.13	3.00	3.22
Gly	α[g]	3.85[d]	3.82[e]	3.90[d]	3.72[e]	4.21[d]
Leu	α	4.47	4.28	4.25	4.20	4.49
	δ[f]	0.89	0.88	0.93	0.87	1.03

[a] Peptide concentration 30–50 mg/ml; chemical shifts (in parts per million) refer to internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate in water and to tetramethylsilane in organic solvents. [b] Abbreviations: DMSO, dimethyl sulfoxide-d_6; TFA, trifluoroacetic acid. [c] Doublet, J = 7 Hz. [d] Singlet. [e] AB pattern, $\Delta\nu$ = 0.16 ppm, J_{AB} = 17 Hz. [f] Overlapping 6-Hz doublets, $\Delta\nu$ = 0.04 ppm. [g] See Discussion. [h] Concentration dependent: 1.23 at 12.5 mg/ml, 1.32 at 150 mg/ml.

Table II reports chemical-shift values for protons of Ala-Phe-Gly-Leu in water under acidic, neutral and basic conditions, as well as in dimethyl sulfoxide and trifluoroacetic acid. In the aqueous solutions, the chemical shifts of the terminal alanyl and leucyl residues change with state of ionization in the manner and to the extent already observed in dipeptides.[21] The internal glycyl residue has apparently identical α protons in aqueous acid, aqueous base and trifluoroacetic acid, but in neutral aqueous solution and in dimethyl sulfoxide these protons differ in chemical shift (0.16 ppm). Nonequivalence of glycine α protons is frequently observed in dipeptides, and, as in the present case, depends on the state of ionization of the peptide, being most common in the dipolar form.[22–24] Whereas in zwitterionic dipeptides the chemical shift difference might possibly result from the stereochemical nonidentity of the two protons, not averaged by free rotation, and the presence of a strong electric field gradient,[24] this explanation is less likely for tetrapeptide II. In II the glycyl residue is internal, removed from the charged terminii of the dipolar form, and the electric field gradient will be weaker; yet the chemical-shift difference in II is not smaller than that in the dipeptides. It is more reasonable to ascribe the observed α-proton nonequivalence to conformational preferences that are more pronounced in the dipolar form than in the charged forms.

For both II and VIa the phenylalanyl β protons are sufficiently nonequivalent in dimethyl sulfoxide (0.2 ppm) and in water (0.08 ppm) to permit analysis of their spin–spin splitting patterns. The geminal coupling constant is 14 Hz, but the significant observation is that in each case the α proton is coupled to the higher field β proton by about 10 Hz, and to the lower field β proton by about 4 Hz. These α–β couplings indicate that the favored α–β rotamer for this residue is one with a *trans* arrangement of vicinal protons. One such conformation, XI, has been established for phenylalanyl side chains in the crystal structures of L-threonyl-L-

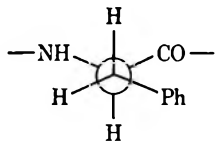
(21) M. Sheinblatt, *J. Amer. Chem. Soc.*, **88**, 2845 (1966).

(22) O. Jardetzky and A. Nakamura, *Proc. Natl. Acad. Sci. U. S.*, **58**, 2212 (1967).

(23) J. W. Westley and B. Weinstein, *Chem. Commun.*, 1232 (1967).

(24) V. J. Morlino and R. B. Martin, *J. Amer. Chem. Soc.*, **89**, 3107 (1967).

phenylalanyl nitrobenzyl ester and glycyclphenylalanylglycine.[25]



XI

(25) A. V. Lakshminarayanan, V. Sasisekharan, and G. M. Ramachandran in "Conformation of Biopolymers," Vol. 1, G. N. Ramachandran, Ed., Academic Press, New York, N. Y., p 61.

In the higher analogs of VI, which contain more than one phenylalanyl residue, overlapping of the β-proton patterns precludes analysis of the β-proton spectra. For trifluoroacetic acid solutions of all of the peptides, the phenylalanyl β protons appear as a doublet in the pmr spectra.

Registry No.—I, 19459-22-4; II, 19459-23-5; III, 19471-37-5; IV, 19459-24-6; V, 6514-26-7; VIa, 7625-14-1; VIb, 19459-27-9; VIc, 19459-28-0; VIIa, 19459-29-1; VIIb, 19459-30-4; VIIc, 19459-31-5.

Heterocyclic Amino Sugar Derivatives. I. Derivatives of 2-Amino-2-deoxy-D-allopyranose[1]

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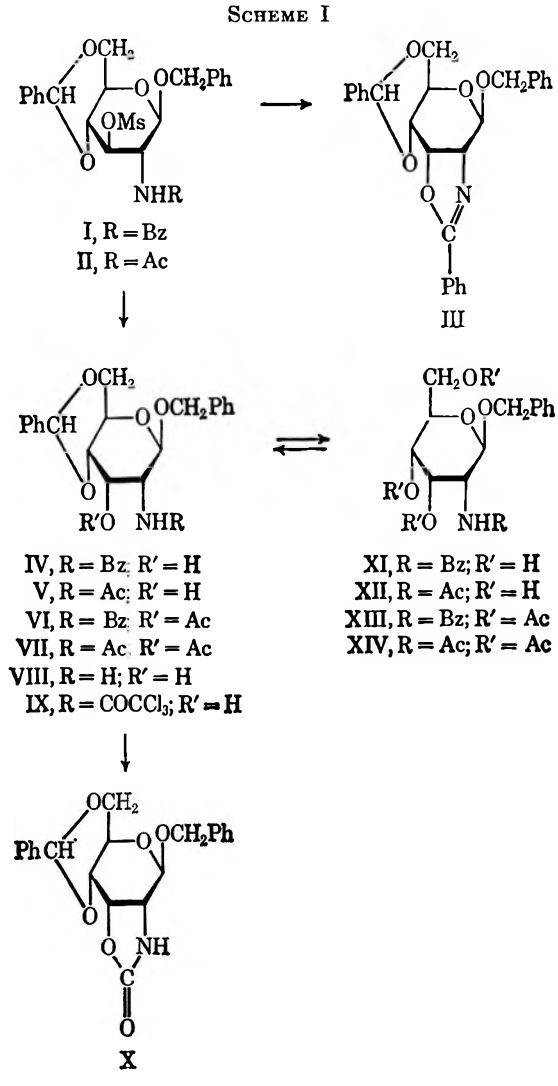
Received September 6, 1968

A facile synthetic route from D-glucosamine to benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII) was developed. A number of D-allosamine derivatives were prepared for characterization. Reaction of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII) with phosgene, diphenylcarbonate, *N*,*N*′-carbonyldiimidazole, or hexachloroacetone gave benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X) in excellent yield. A new method developed in this investigation is the utilization of hexachloroacetone to prepare a *N*-trichloroacetamido compound which is subsequently cyclized to give 2-oxazolidone X.

2-Amino-2-deoxy-D-allose (D-allosamine), an amino sugar not as yet found in nature, and some of its derivatives have been previously synthesized.[3-7] In view of the possible use of this amino sugar for the synthesis of antibiotics and nucleosides,[3] two derivatives which should be useful intermediates, benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII), and the cyclic carbamate benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X) have been synthesized (Scheme I). Compound VIII would provide for a variety of anomerically pure, *N*-substituted derivatives, in analogy to corresponding derivatives of D-glucosamine prepared by Gross and Jeanloz,[8] and compound X would provide for an excellent acid-stable, alkali-labile protective group for positions 2 and 3.

It was found that sulfonate can be eliminated with the 2-methoxyethanol–sodium acetate reagent[4] from benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (II) to give benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (V) in excellent yield without any laborious purification process. This approach seems to be superior to other known methods in large-scale preparations. However, we could not convert by this method the α anomer of II into the α anomer of V. Similarly, Rhoads and Gross[9] observed that eliminations of the sulfonate from benzyl 2-benzyloxycarbonylamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-D-glucopyranosides proceeded only with the β anomer.

SCHEME I



(1) A preliminary communication was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, by K. Miyai and P. H. Gross, Abstracts C-017. Taken from the doctoral thesis of K. Miyai, University of the Pacific, 1968. This work was partially supported by Grant No. GP-4587 of the U. S. National Science Foundation.

(2) To whom inquiries should be directed.

(3) E. J. McEvoy, M. J. Weiss, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 205 (1960).

(4) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

(5) W. Meyer zu Reckendorf and W. A. Bonner, *Chem. Ber.*, **95**, 1917 (1967).

(6) P. H. Gross, K. Brendel, and H. K. Zimmerman, *Ann.*, **683**, 175 (1965).

(7) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057, 1063 (1964).

(8) P. H. Gross and R. W. Jeanloz, *ibid.*, **32**, 2759 (1967).

(9) W. D. Rhoads, Dissertation, University of the Pacific, 1968.

The elimination of sulfonate from benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (I) gave a mixture of benzyl 4,6-*O*-benzylidene-β-D-allopyranosido-(2′-phenyl)-[2,3:4′,5′]-2′-oxazoline (III) and benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (IV). The cyclic intermediate of the reaction (I → IV), the very stable oxazoline (III), was obtained in high yield, predominating over the formation of the desired compound (IV). The result is in agreement with earlier observations that a stable oxazoline is formed with the N-benzoyl neighboring group.[10] For good yields, it was necessary to prepare IV from the previously known benzyl 2-benzamido-2-deoxy-β-D-allopyranoside (XI)[6] with benzaldehyde–$ZnCl_2$. Formation of a 3,4-*O*-benzylidene compound was not observed in this reaction. Removal of the benzylidene group of IV and V with aqueous acid gave compounds XI and XII. Acetylation into compounds VI, VII, XIII, and XIV posed no special problems, when done at 0° in fairly dilute solutions.

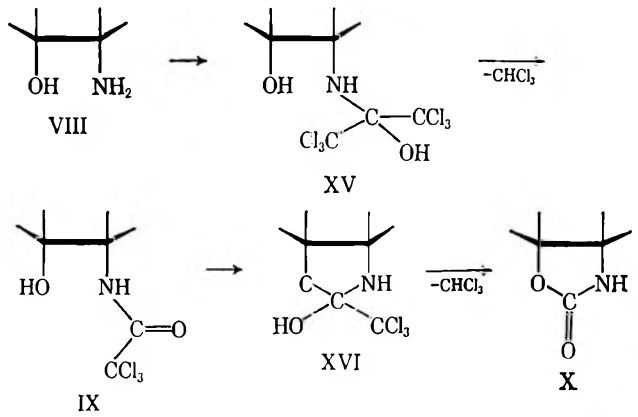
Alkaline hydrolysis of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (V) and of the corresponding *N*-benzoyl compound (IV) gave benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII), unblocked at positions 2 and 3.

When VIII was treated with phosgene in toluene or with diphenyl carbonate, it gave the desired cyclic compound, benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X), in excellent yield. The structure of compound X was supported by its independent synthesis,[9] and by examination of its ir spectrum (amide I at 1750 cm^{-1}, amide II absorption absent).[11,12]

We found only one literature report[13] in which a 2-oxazolidone compound was obtained from a β-amino alcohol with *N*,*N*′-carbonyldiimidazole. When this reagent was used, compound X was obtained quantitatively from VIII.

A new method developed in this investigation is the utilization of hexachloroacetone to prepare a *N*-trichloroacetamido compound which is then cyclized to give a 2-oxazolidone compound. It was observed that hexachloroacetone and amino alcohol VIII initially form a hexachloroacetone–amine adduct. This loses a molecule of chloroform to give the *N*-trichloroacetamido compound. Thus, benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX) was obtained in good yield under mild conditions. The *N*-trichloroacetamido compound, IX, was also prepared with trichloroacetyl chloride to confirm the structure of the product obtained with hexachloroacetone. Base-catalyzed cyclization reaction of benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX) yielded benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X). As a possible interpretation of the observed results, a double haloform cleavage mechanism is proposed (Scheme II). The initially formed addition product (XV), which can be isolated, eliminates successively two molecules of chloroform to yield oxazolidone X.

SCHEME II



Experimental Section

Melting points were taken in a Thomas–Hoover melting point apparatus, Model 6404H. All the melting points reported herein are uncorrected. Optical rotations were measured with a O. C. Rudolph and Sons, Inc., Model No. 956 polarimeter. Infrared spectra were recorded with Perkin-Elmer spectrophotometers (Models 137 and 337) using the KBr pellet technique. The homogeneity of the compounds synthesized was determined by thin layer chromatography using silica gel G (Merck) and silica gel GF (Merck). The plates were developed with chloroform containing a sufficient portion of ethanol or *n*-hexane to produce R_f values between 0.2 and 0.7. The compounds were detected with ultraviolet light and also by subsequent spraying with 10–15% sulfuric acid–methanol and heating about 15 min at 120°. All the compounds reported herein are chromatographically homogeneous. The microanalyses were performed by Alfred Bernhardt of Mikroanalytisches Laboratorium im Max-Plank-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

Benzyl 4,6-*O*-Benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-phenyl-2′-oxazoline (III).—A solution of benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (I, 1 g, 0.0018 mol)[14] and sodium acetate trihydrate (1 g) in 2-methoxyethanol (60 ml) containing water (3 ml) was refluxed for 33 hr. The solvent was evaporated *in vacuo*, water was added and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from methanol to give 536 mg (67.1%): mp 160.5–161°, $[\alpha]^{23}D$ +31.8° (*c* 2.17, pyridine).

Anal. Calcd for $C_{27}H_{25}NO_5$ (443.5): C, 73.12; H, 5.69; N, 3.16; O, 18.02. Found: C, 73.59; H, 5.74; N, 3.18; O, 17.76.

From the mother liquor of the crystallization, 7% IV could be isolated by fractional crystallization from absolute ethanol–ether.

Benzyl 2-Benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (IV). A.—Intensively dried compound XI (10.5 g, 0.0281 mol) was shaken 25 hr in a solution of freshly prepared anhydrous zinc chloride (4 g) in distilled benzaldehyde (65 ml). Diethyl ether was added and the mixture was kept several hours at 0°. The precipitate was filtered off and washed with cold diethyl ether. The filtrate was treated with water to obtain additional crude product. The combined product was recrystallized from absolute dioxane, then from absolute ethanol to give 11.3 g (86.8%): mp 240–240.5°; $[\alpha]^{30}D$ −169.5° (*c* 1.0, pyridine).

Anal. Calcd for $C_{27}H_{27}NO_6$ (461.5): C, 70.26; H, 5.90; N, 3.04; O, 20.55. Found: C, 70.10, H, 5.97; N, 3.58; O, 20.55.

B.—The compound was also prepared from III by following a procedure similar to that described for the preparation of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII). Fractional crystallization from absolute ethanol–diethyl ether gave IV in 12% yield plus a 70% recovery of the starting material.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyran-

(10) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967).
(11) M. E. Dyen and D. Swern, *Chem. Rev.* **67**, 197 (1967).
(12) S. Pinchas and D. Ben-Ishai, *J. Amer. Chem. Soc.*, **79**, 4099 (1957).
(13) W. B. Wright, *J. Heterocycl. Chem.*, **2**, 41 (1965).
(14) K. Miyai, P. H. Gross, and H. K. Zimmerman, *Ann.*, in press.

oside (V).—A solution of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (II, 28 g, 0.058 mol)[8] and sodium acetate trihydrate (28 g) in 2-methoxyethanol (750 ml) containing water (28 ml) was refluxed 50 hr. The solvent was evaporated *in vacuo*. Water was added to the remaining syrup and the mixture was kept at 0°.

The precipitate was filtered off, dried, and recrystallized from absolute ethanol to give 19.8g (85%): mp 260–260.5°; $[\alpha]^{24}D$ −115 6° (*c* 1.27, chloroform).

Anal. Calcd for $C_{22}H_{25}NO_6$ (399.5): C, 66.14; H, 6.31; N, 3.51; O, 24.03. Found: C, 66.29; H, 6.40; N, 4.05; O, 23.77.

Benzyl 3-*O*-Acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VI).—Compound IV (3 g, 0.0065 mol) in absolute pyridine (50 ml) was acetylated at 0° with acetic anhydride (6 ml) for 24 hr. The mixture was poured into ice–water and kept at 0°. The precipitate was filtered off, washed with water, and recrystallized from dioxane–diisopropyl ether, then from absolute ethanol to give 2.8 g (87.5%): mp 247–248°; $[\alpha]^{21}D$ −125.6° (*c* 1.04, pyridine).

Anal. Calcd for $C_{29}H_{29}NO_7$ (503.6): C, 69.17; H, 5.80; N, 2.78; O, 22.24. Found: C, 69.29; H, 5.78; N, 2.89; O, 22.53.

Benzyl 2-Acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VII).—Compound V (2 g, 0.005 mol) was dissolved in absolute pyridine (40 ml) at 50–60°. The solution was cooled rapidly to 0° and acetic anhydride (6 ml) was dropped in with stirring. Stirring was continued for 1 additional hr at 0–5° and 4 days at room temperature. The mixture was concentrated *in vacuo* to 20 ml and poured into ice–water. The precipitate was filtered off, washed with water, dried, and recrystallized from absolute ethanol–diethyl ether–*n*-hexane to give 2.0 g (90.9%): mp 171–171.5°; $[\alpha]^{22}D$ −137.9° (*c* 1.03, pyridine).

Anal. Calcd for $C_{24}H_{27}NO_7$ (441.5): C, 65.29; H, 6.17; N, 3.18; O, 25.37. Found: C, 65.49; H, 6.08; N, 3.53; O, 24.93.

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII). A.—A solution of V (16 g, 0.040 mol) in a hot mixture of potassium hydroxide (60 g, 86.7% assay) and 95% ethanol (200 ml) was refluxed for 9–10 hr at 87°. The mixture was diluted with 400 ml of hot water, allowed to cool to room temperature, and kept at 0°. The precipitate was filtered off, washed with water, and dried *in vacuo* at room temperature. Recrystallization from absolute ethanol gave 12.5 g (87.5%): mp 141–142°; $[\alpha]^{25}D$ −77.3° (*c* 1.01, pyridine).

Anal. Calcd for $C_{20}H_{23}NO_5$ (357.4): C, 67.20; H, 6.49; N, 3.92; O, 22.39. Found: C, 66.87; H, 6.55; N, 4.01; O, 22.55.

B.—Starting from X, a 95% yield of VIII was obtained. Compound IV was completely de-N-benzoylated only after 27 hr at 87° to give VIII (67%).

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX). A.—Compound VIII (1 g, 0.0027 mol) was refluxed with hexachloroacetone (5 g) and dimethylmesidine (1.5 ml) in absolute chloroform (100 ml). Precipitation of the initial hexachloroacetone adduct occurred after 10–15 min refluxing. Refluxing was continued for 6 hr and after addition of 1.5 ml of hexachloroacetone for 8 hr. The solvent was evaporated *in vacuo* and the remaining syrup was dissolved in ethanol which was again evaporated. Hot ethanol (5 ml) was added, followed by addition of warm water. The mixture was kept at 0° and the precipitate filtered off. Careful recrystallization from absolute ethanol gave 1.1 g (78.5%): mp 173–175° (sintering at 170°); $[\alpha]^{23}D$ −89.0° (*c* 1.09, pyridine).

Anal. Calcd for $C_{22}H_{22}NO_6Cl_3$ (502.8): C, 52.55; H, 4.41; N, 2.78; O, 19.10; Cl, 21.16. Found: C, 52.42; H, 4.52; N, 2.78; O, 19.26; Cl, 21.01.

B.—This compound was also prepared by treating compound VIII with trichloroacetyl chloride in pyridine under normal acylation conditions (yield 42%).

Benzyl 4,6-*O*-Benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X). A.—To a solution of VIII (3.57 g, 0.01 mol) in absolute pyridine (50 ml) was added dropwise a solution of phosgene (2.1 g) in dry toluene (20 ml). The mixture was stirred at room temperature for 5 hr, poured into ice water–petroleum ether (bp 30–60°), and kept at 0°. The precipitate was filtered off, washed with cold water, dried, and recrystallized from absolute ethanol to give 3.37 g (88%): mp 208.5–209.5°; $[\alpha]^{27}D$ +17.2° (*c* 1.04, pyridine).

Anal. Calcd for $C_{21}H_{21}NO_6$ (383.4): C, 65.78; H, 5.52; N, 3.66; O, 25.04. Found: C, 65.55; H, 5.83; N, 3.66; O, 24.97.

B.—Compound VIII (0.357 g, 0.001 mol) was heated in *N,N*-dimethylformamide (7 ml) with diphenyl carbonate (0.25 g) and sodium phenoxide (0.03 g) for 15 hr at 110°, and the mixture poured into excess ice–water. The precipitate was recrystallized by decolorization with charcoal from absolute ethanol to give 0.271 g (76%).

C.—Compound IX (0.5 g, 0.001 mol) was heated in *N,N*-dimethylformamide (10 ml) with 1,5-diazabicyclo[4.3.0]-5-nonene (0.25 g) for 15 hr at 110–115° and worked up as above to give 0.35 g (91%). Sodium methoxide or sodium phenoxide can also be used as the base catalyst in the reaction.

D.—Compound VIII (1.78 g, 0.0049 mol) in absolute tetrahydrofuran (40 ml) was mixed with a solution of *N,N′*-carbonyldiimidazole (1.62 g) in absolute tetrahydrofuran (40 ml) with exclusion of moisture, and the solution was stirred at room temperature for 15 hr. The solvent was evaporated *in vacuo*, excess water was added and the mixture kept at 0°. The precipitate was filtered off, dried, and recrystallized from absolute ethanol to give 1.80 g (96%).

Benzyl 2-Acetamido-2-deoxy-β-D-allopyranoside (XII).—A solution of compound V (4 g, 0.01 mol) in glacial acetic acid (120 ml) was heated to 90° and water (80 ml) was added dropwise over a period of 30 min. The mixture was stirred 70 min at 80–85°. The solvent was evaporated *in vacuo*, followed by repeated coevaporation with water and finally with toluene. Petroleum ether (bp 30–60°) was added to the remaining syrup and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from methylene chloride and ethanol–petroleum ether to give 2.6 g (85%): mp 156–158°; $[\alpha]^{25}D$ −114° (*c* 1.4, pyridine).

Anal. Calcd for $C_{15}H_{21}NO_6$ (311.3): C, 57.88; H, 6.80; N, 4.50; O, 30.84. Found: C, 57.79; H, 6.80; N, 4.07; O, 31.49.

Benzyl 3,4,6-Tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-allopyranoside (XIII).—Compound XI (1 g, 0.0026 mol) in absolute pyridine (15 ml) was treated with acetic anhydride (3 ml). The mixture was kept at room temperature overnight, poured into ice–water, and kept at 0°. The precipitate was filtered off, dried, and recrystallized from pyridine–water to give long needles, melting at 149.5–151°, which may be a hydrate. This product was recrystallized again from dry toluene–petroleum ether to give 1.2 g (92.3%): mp 165.5–166°; $[\alpha]^{25}D$ −27.9° (*c* 0.6, pyridine).

Anal. Calcd for $C_{26}H_{29}NO_9$ (499.5): C, 62.51; H, 5.85; N, 2.80; O, 28.82. Found: C, 62.47; H, 5.79; N, 3.05; O, 28.70.

Benzyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-allopyranoside (XIV).—Compound XII (0.62 g, 0.002 mol) in absolute pyridine (8 ml) was treated with acetic anhydride (1.5 ml). The mixture was kept at room temperature overnight and poured into ice–water. The product was extracted with chloroform which was then evaporated *in vacuo*. *n*-Heptane was added to the remaining syrup and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from chloroform–petroleum ether to give 0.61 g (70%): mp 106–108°; $[\alpha]^{25}D$ −54.4° (*c* 1.0, pyridine).

Anal. Calcd for $C_{21}H_{27}NO_9$ (437.4): C, 57.66; H, 6.22; N, 3.21; O, 32.92. Found: C, 57.58; H, 6.35; N, 3.40; O, 32.76.

Registry No.—III, 19398-20-0; IV, 19374-63-1; V, 19374-64-2; VI, 19374-65-3; VII, 19374-66-4; VIII, 19374-67-5; IX, 19374-68-6; X, 19374-69-7; XII, 19374-70-0; XIII, 19374-71-1; XIV, 19374-72-2.

Heterocyclic Amino Sugar Derivatives. II. Preparation of D-Glucopyranosido[2,3:4′,5′]-2′-oxazolidinones[1]

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Received September 12, 1968

trans-Fused oxazolidinone derivatives of glucosamine (benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside-2,3-carbamates) could be obtained in three ways. A synthesis utilizing *N*,*N*′-carbonyldiimidazole gave the best results. The compounds prepared demonstrate the usefulness of *trans*-fused 2,3-carbamates as a novel protective group for amino sugars.

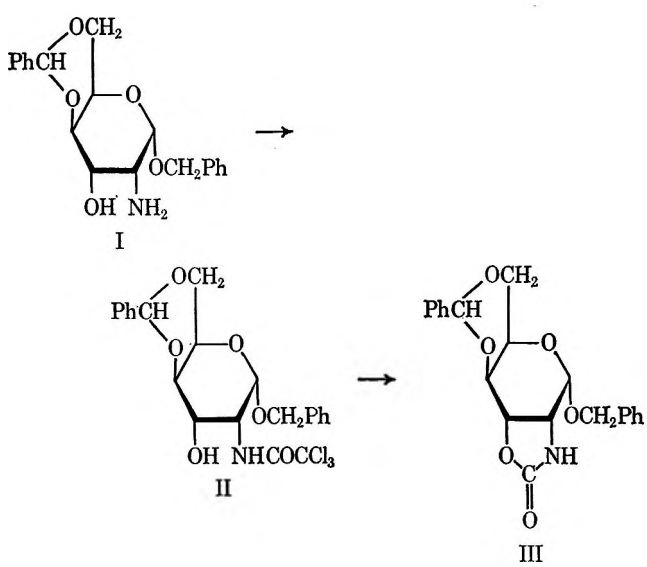
Many natural products contain amino sugars in biologically important 1,4-linked oligosaccharides. Synthesis of model substances having this type of linkage requires protection groups at C-2 and C-3 of 2-amino-2-deoxy-D-hexopyranoses that do not participate in and/or sterically hinder reactions at C-1 and C-4.

Heterocyclic derivatives, bridging C-2 and C-3 of 2-amino-2-deoxy-D-hexopyranoses, would be useful as blocking groups in the preparation of such oligosaccharides. Specifically, 2-oxazolidinone compounds of D-gulosamine and D-glucosamine were of interest. In the preceding paper,[2] new methods for the preparation of a cyclic carbamate (oxazolidinone) of D-allosamine were investigated. One method utilized hexachloroacetone for the generation of this protective group.

We demonstrated the general usefulness of this reaction for the synthesis of *cis*-fused cyclic carbamates when benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-α-D-gulopyranoside (II) and subsequently benzyl 4,6-*O*-benzylidene-α-D-gulopyranosido-[2,3:4′,5′]-2′-oxazolidinone (III) were prepared with hexachloroacetone from benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-gulopyranoside (I) (Scheme I). However, the two most frequently occuring amino sugars, 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-galactose, have the amino group and the hydroxyl group of C-3 in a *trans* configuration. In these amino sugars, the *C1* conformation of the pyranose ring has a 2,3-*trans*-diequatorial arrangement and, if a five-membered ring should be fused to positions C-2 and C-3 of the pyranose ring, is a steric requirement. The 2,3-*trans*-diequatorial arrangement in D-glucosamine can be maintained by forming the 4,6-*O*-benzylidene derivative.

Stable heterocyclic rings fused *trans*-diequatorial to C-2 and C-3 of the 2-amino sugars have been unknown until 1963 when Carroll[3] obtained muramolactams in attempts to acetylate muramic acid. In these lactams the six-membered heterocyclic derivative, morpholinone, is fused *trans* diequatorial to C-2 and C-3 of the 2-amino-2-deoxy-D-glucopyranose ring. Gross and Jeanloz[4] synthesized stereospecifically such morpholinones from the anomeric benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides. There is no example in which a five-membered ring is fused *trans* diequatorial

SCHEME I



to an amino sugar. However, considering work on nitrogen-free sugars, such compounds should be possible.

In 1961 and 1962, Angyal and coworkers[5,6] have reported the preparation of *trans*-ketal derivatives of cyclitols. These preparations have demonstrated that five-membered rings can be fused to *trans*-diequatorial positions of carbohydrates. Similar work was reported by Bissett and coworkers[7] in 1967. Later, Evans, Parrish, and Long[8] have reported successful preparation of *trans*-ketal compounds of methyl D-glucopyranoside and methyl D-galactopyranoside. Very recently, cyclic thiocarbonate and carbonate fused *trans* diequatorially to C-2 and C-3 of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside were reported by Stout, Doane, Shasha, Russell, and Rist.[9,10] Their synthetic method was improved by application of the method of Bokadia, *et al.*,[11] who had prepared carbonates of a flavan *trans*-3,4-diol The similar compound with galactose configuration was reported by Sibral and Schmid.[12] Brimacombe and coworkers[13] in 1967 and Marvel and

(1) A preliminary communication was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, by K. Miyai and P. H. Gross, Abstracts C-017. Taken from the doctoral thesis of K. Miyai, University of the Pacific, 1968. This work was partially supported by Grant No. GP-4587 of the U. S. National Science Foundation.

(2) K. Miyai, H. K. Zimmerman, and P. H. Gross, *J. Org. Chem.*, **34**, 1635 (1969).

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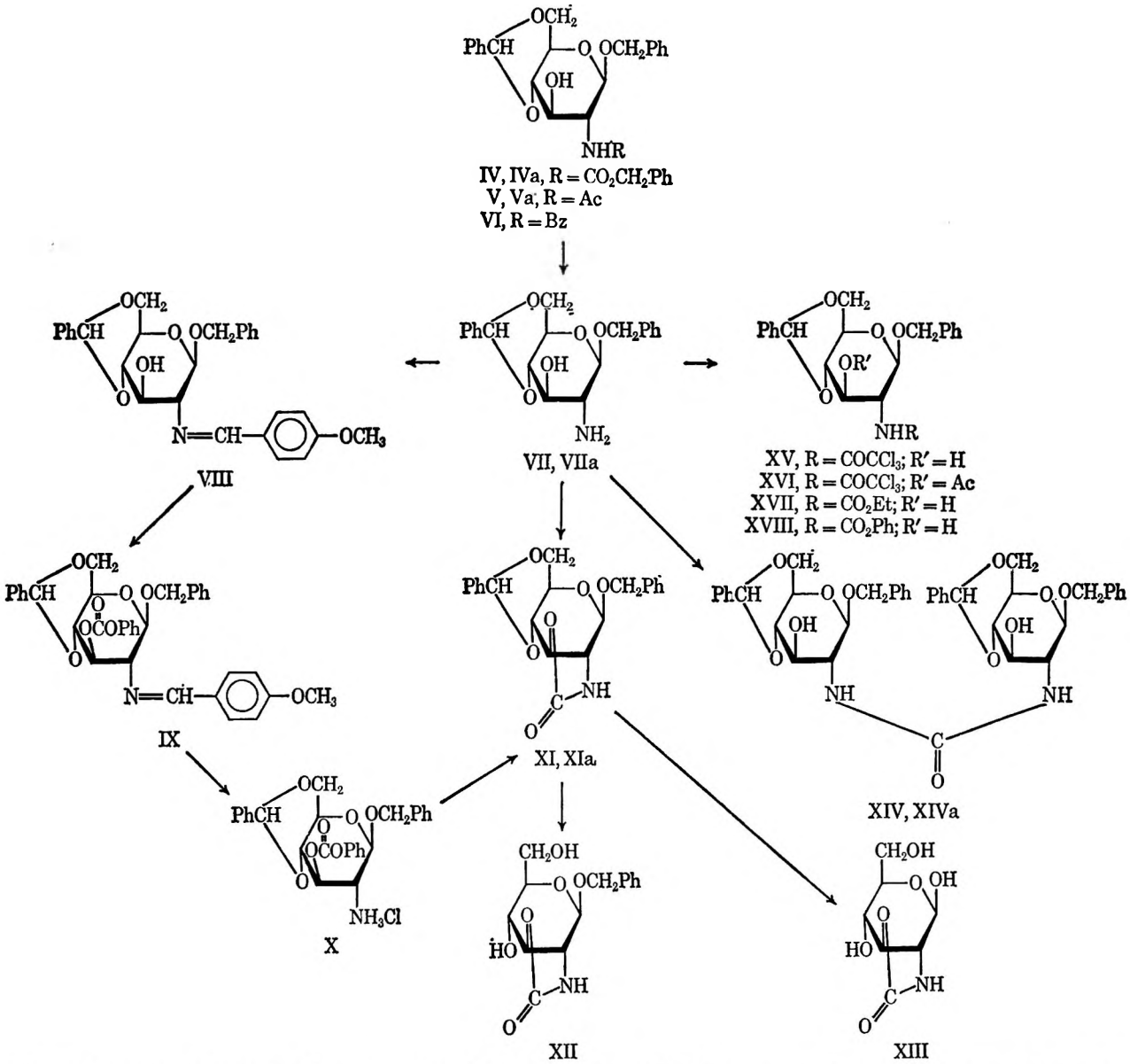
SCHEME II[a]



[a] All reactions were carried out with β-glycosides. Where noted (*e.g.*, IVa) the corresponding α anomers were also prepared.

coworkers[14] in 1968 reported different cyclic acetals of methyl 4,6-*O*-benzylidene-D-glucopyranoside and the corresponding D-galactopyranoside. The ease of the ring-opening reaction of the *trans*-carbonate was utilized by Doane, Shasha, Stout, Russell, and Rist[15,16] to incorporate glucose units into starch with a carbonate linkage. This last work cited is the only one that reports in detail the chemical properties of these *trans*-fused bicyclic carbohydrate derivatives. It seems, however, that none of them possesses value as a protection group since they are sensitive to the conditions needed to give the compounds that are unprotected at C-1, C-4, and C-6.

In order to synthesize cyclic carbamates (oxazolidindones) fused *trans* diequatorial to glucosamine, benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides, VIIa and VII, seemed to be a suitable starting material (Scheme II). Both anomers were first prepared by Gross and Jeanloz.[17] We reinvestigated the synthesis of these compounds by alkaline hydrolysis of *N*-benzoyl, *N*-acetyl, and *N*-benzyloxycarbonyl compounds. Hydrolysis was fastest with *N*-benzyloxycarbonyl compounds IVa and IV and slowest with the *N*-benzoyl compound VI. Orientation of the aglycon seems to play no role in the hydrolysis of *N*-acyl compounds. It was found, however, that *N*-acyl-D-glucosamine derivatives hydrolyze faster than their corresponding D-allosamine derivatives.[2] Stability of the benzyl glycosides under severe alkaline conditions of hydrolysis seems to be a general feature.

Starting from an amino alcohol, it has been shown that phosgene, diphenylcarbonate, hexachloroacetone, and *N*,*N*'-carbonyldiimidazole are suitable reagents to prepare 2,3-*cis*-oxazolidinones.[2] The methods suitable for the preparation of model 2,3-*cis*-oxazolidinones were applied in the preparation of *trans*-oxazolidinones. The

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(15) W. M. Doane, E. I. Stout, B. S. Shasha, C. R. Russell, and C. E. Rist, *ibid.*, **5**, 366 (1967).

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(17) P. H. Gross and R. W. Jeanloz, *J. Org. Chem.*, **32**, 2759 (1967).

use of hexachloroacetone which was so successful in the preparation of *cis*-oxazolidinone gave benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (XV) as anticipated. This compound, however, failed to cyclize to give a *trans*-fused bicyclic compound. Reactions of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII) with diethyl carbonate or diphenyl carbonate gave the *N*-carbethoxy compound, XVII, and the *N*-carbophenoxy compound, XVIII, respectively. XVII and XVIII also failed to cyclize to give the *trans*-oxazolidinone compound.

Reaction of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII) with phosgene gave a *trans*-fused bicyclic compound. The product obtained was difficult to purify but it confirmed that 2-oxazolidinones of anomeric benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides could be prepared. The reaction conditions were improved by the use of triethylamine with the result of better yields, but the difficulties in purification persisted. At present, the only way to work-up these products is the application of preparative thin layer chromatography or column chromatography. This purification problem was overcome when *N*,*N*′-carbonyldiimidazole was used as a reagent to prepare 2,3-*trans*-oxazolidinones. Formation of a urea, XIV, bridging two glucosamine units was observed as a side reaction. The urea, because of its low solubility, is separated easily from the desired product. Both the α and β anomer of benzyl 4,6-*O*-benzylidene-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XI) were obtained in good yield.

The structure of the 2,3-*trans*-oxazolidone is supported by the infrared spectrum, by elemental analysis, and by the easy alkaline hydrolytic regeneration of the starting material, VIIa and VII.

As an alternative synthetic approach, the preparation of the same 2,3-*trans*-oxazolidinone (XI) by cyclization from a C-3 substituent to a free amine group at C-2 has been carried out. Although benzyl 4,6-*O*-benzylidene-2-deoxy-2-(phenyloxycarbonyl)amino-β-D-glucopyranoside (XVIII) failed to cyclize to yield a *trans*-fused bicyclic compound, we have anticipated that benzyl 2-amino-4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-β-D-glucopyranoside (free base of X) would. Therefore, benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII) was treated with anisaldehyde to give the *N*-(*p*-methoxybenzylidene) compound VIII.[17] The *O* carbophenoxylation of VIII in absolute pyridine gave a 93% yield of benzyl 4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-2-[(*p*-methoxybenzyliden)imino]-β-D-glucopyranoside (IX). When IX was treated with hydrochloric acid (0.25 *N*) in acetone, benzyl 2-amino-4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-β-D-glucopyranoside hydrochloride (X) was obtained quantitatively in very pure form. Cyclization of X yielded benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XI) which was identical with the sample prepared from benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII) with phosgene or *N*,*N*′-carbonyldiimidazole.

It has been shown that the 2,3-*cis*-oxazolidinone derived from D-gulosamine is very stable toward acid.[18] Rhoads and Gross[19] have shown that the 2,3-*cis*-oxazolidinone derived from D-allosamine is stable under the conditions needed to remove a benzylidene group. However, this could not be said *a priori* for the oxazolidone with the D-*gluco* configuration. It was found, fortunately, that it is at least stable enough to withstand the conditions needed to remove the benzylidene group. Treatment of benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XI) with aqueous acetic acid at 70° for 70 min removed the benzylidene group but did not affect the oxazolidinone group. Thus, benzyl β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XII) was obtained in fair yield.

Hydrogenation of benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido[2,3:4′5′]-2′-oxazolidinone (XI) gave a compound which showed a characteristic carbonyl absorption band at 1750 cm^{-1} and a positive Benedict test. This compound is believed to be β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XIII) but needs to be characterized further. The test, however, showed that hydrogenation did not affect the oxazolidone blocking group.

Experimental Section

Melting points were taken in a Thomas–Hoover melting point apparatus, Model No. 64C4H. All the melting points reported herein are uncorrected. Optical rotations were measured at the sodium D line with a O. C. Rudolph and Sons, Inc., Model No. 956 polarimeter. Infrared spectra were recorded with Perkin-Elmer spectrophotographs (Models 137 and 337) using the KBr pellet technique. The homogeneity of the compounds synthesized was determined by thin layer chromatography using silica gel G (Merck) and silica gel GF (Merck). The plates were developed with chloroform containing a sufficient portion of ethanol or *n*-hexane to produce R_f values between 0.2 and 0.7. The compounds were detected with ultraviolet light and also by subsequent spraying with 10–15% sulfuric acid–methanol and heating about 15 min at 120°. All the compounds reported herein are chromatographically homogeneous. The microanalyses were performed by Alfred Bernhardt of Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-α-D-gulopyranoside (II).—Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-gulopyranoside (I, 2 g, 0.0056 mol)[20] was refluxed with hexachloroacetone (10.3 g) and dimethylmesidine (3 ml) in absolute chloroform (200 ml) for 6 hr. Additional hexachloroacetone (3 ml) was added and refluxing was continued for 1 more hr. The solvent was evaporated *in vacuo* to a syrup, which was dissolved in hot ethanol. The product was precipitated by addition of petroleum ether (bp 30–60°). The mixture was kept at 0° to complete precipitation and the precipitate collected by filtration. Recrystallization from absolute ethanol gave 2.5 g (0.0049 mol, 99.3% yield) of II melting at 199–201°, $[\alpha]^{27}D$ +111.4° (*c* 1.15, pyridine).

Anal. Calcd for $C_{22}H_{22}NO_6Cl_3$ (502.8): C, 52.55; H, 4.41; N, 2.78; O, 19.10; Cl, 21.16. Found: C, 52.43; H, 4.84; N, 2.83; O, 19.13; Cl, 20.98.

Benzyl 4,6-*O*-Benzylidene-α-D-gulopyranosido[2,3:4′,5′]-2′-oxazolidinone (III). A.—Benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-α-D-gulopyranoside (II, 0.5 g, 0.001 mol) was heated in *N*,*N*-dimethylformamide (10 ml) with 1,5-diazabicyclo-[4.3.0]-5-nonene (0.25 g) for 15 hr at 110–115°. The product was precipitated by addition of excess ice–water. After several hours at 0° the precipitate was collected by filtration and recrystallized with decolorization by charcoal from absolute ethanol. This gave 0.36 g (0.00095 mol, 95% yield) of III melting at 216.5–217°, $[\alpha]^{25}D$ −9.2° (*c* 1.0, pyridine). Noorzad and Gross[20] reported melting point 210–211°, $[\alpha]^{30}D$ −9° (*c* 1, pyridine).

B.—Sodium phenoxide or sodium methoxide can also be used

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(19) W. D. Rhoads and P. H. Gross, Abstracts of Papers, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, C-019.

as the base catalyst in the cyclization reaction of benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-α-D-gulopyranoside.

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII).—Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII) was prepared from benzyl 4,6-*O*-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (IV), benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (V), and benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VI) in the manner described previously by Gross and Jeanloz.[17] The results were the following: reaction conditions—15 g of KOH (86.7% assay) and 0.01 mol of amino sugar in 50 ml of 95% ethanol; reaction temperature inside vessel—83–87°; reaction time required in hours (yield after recrystallization from methanol)—N-Cbz compound IV, 4.5–5.5 (80–85%), N-Ac compound V, 6–7 (80–85%), N-Bz compound VI, 19–31 (65–75%); mp 145–146°; $[\alpha]^{25}D$ −131° (*c* 1, pyridine).

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (VIIa).—Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (VIIa)[17] was prepared by a procedure identical with that used for the preparation of the β anomer. Alkaline hydrolysis of benzyl 4,6-*O*-benzylidene-2-deoxy-2-benzyloxycarbonylamido-α-D-glucopyranoside (IVa) of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (Va) yielded VIIa: mp 173–174°; $[\alpha]^{25}D$ +90° (*c* 1.0, pyridine).

Benzyl 4,6-*O*-benzylidene-2-deoxy-2-[(*p*-methoxybenzylidene)imino]-β-D-glucopyranoside (VIII) was prepared in the manner described by Gross and Jeanloz:[17] mp 178–179°; $[\alpha]^{25}D$ −119° (*c* 1, pyridine).

Benzyl 4,6-*O*-Benzylidene-3-*O*-carbophenoxy-2-deoxy-2-[(*p*-methoxybenzyliden)imino]-β-D-glucopyranoside (IX).—Benzyl 4,6-*O*-benzylidene-2-deoxy-2-[(*p*-methoxybenzyliden)imino]-β-D-glucopyranoside (VIII, 2.375 g, 0.005 mol) in absolute pyridine (10 ml) was treated with phenyl chloroformate (1.2 g) at −5° for 24 hr. The mixture was then poured into ice–water and kept at 0° to complete precipitation. The product was collected by filtration, dried, and recrystallized from dichloromethane–diethyl ether–*n*-hexane to give 2.73 g (0.00465 mol, 93% yield) of IX melting at 153.5–154°, $[\alpha]^{25}D$ −119.2° (*c* 1.2, pyridine).

Anal. Calcd for $C_{35}H_{35}NO_8$ (595.6): C, 70.58; H, 5.58; N, 2.35; O, 21.50. Found: C, 69.80; H, 5.85; N, 2.73; O, 21.79.

Benzyl 2-Amino-4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-β-D-glucopyranoside Hydrochloride (X).—A solution of benzyl 4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-2-[(*p*-methoxybenzyliden)imino]-β-D-glucopyranoside (IX, 1.7 g, 0.003 mol) in acetone (60 ml) was cooled to 0° and 0.25 *N* hydrochloric acid (24 ml) was slowly added at 0°. After being kept with stirring for 3 hr at 0°, the product was collected by filtration, washed several times with acetone, and dried to give 1.435 g (0.0028 mol, 93% yield) of X melting at 250–250.5°. No suitable solvent was found for a measurement of optical rotation.

Anal. Calcd for $C_{27}H_{28}NO_7Cl$ (514): C, 63.09; H, 5.49; N, 2.73; O, 21.79; Cl, 6.90. Found: C, 63.33; H, 5.29; N, 2.55; O, 22.02; Cl, 6.91.

Benzyl 4,6-*O*-Benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XI). A.—A solution of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII, 3.57 g, 0.01 mol) in absolute tetrahydrofuran (150 ml) was added dropwise to a solution of *N,N′*-carbonyldiimidazole (3.24 g) in 150 ml of absolute tetrahydrofuran with stirring at room temperature (25–30°) for 24 hr. The mixture was filtered to remove the urea compound, XIV, which was insoluble in tetrahydrofuran. The filtrate was evaporated *in vacuo*. To the remaining residue, water was added and the mixture kept under refrigeration to complete precipitation. The product was collected by filtration, dried, and recrystallized from 2-propanol to give 3.33 g (0.0087 mol, 87% yield) of XI melting at 232–234°, $[\alpha]^{22}D$ −102.6° (*c* 1.67, pyridine).

Anal. Calcd for $C_{21}H_{21}NO_6$ (383.4): C, 65.78; H, 5.52; N, 3.66; O, 25.04. Found: C, 65.40; H, 5.74; N, 3.31; O, 25.44.

B.—To a solution of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII, 3.57 g, 0.01 mol), and triethylamine (1 g) in absolute pyridine (50 ml) was added dropwise a solution of phosgene (2.1 g) in dry toluene (20 ml) and the reaction mixture was stirred at room temperature for 12 hr. The mixture was then poured into ice–water–petroleum ether and kept under refrigeration to complete precipitation. The product was collected by filtration, washed with cold water, and dried to give 3.3 g (0.0087 mol, 87% yield) of crude product which was best purified by column chromatography on silica gel (Davison) with 2% ethanol in chloroform.

C.—Benzyl 2-amino-4,6-*O*-benzylidene-3-*O*-carbophenoxy-2-deoxy-β-D-glucopyranoside hydrochloride (X, 0.514 g, 0.001 mol) was heated in *N,N*-dimethylformamide (10 ml) with sodium phenoxide (0.30 g) for 10 hr at 95–100°. After neutralization with carbon dioxide, the product was precipitated by addition of excess ice–water. The mixture was kept at 0° for several hours to complete precipitation. The product was collected by filtration, dried, and recrystallized from tetrahydrofuran–petroleum ether and from 2-propanol to give 0.256 g (0.00067 mol, 67% yield) of XI.

Benzyl 4,6-*O*-benzylidene-α-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XIa) was prepared by procedure A identical with that used for the preparation of the β anomer XI: yield 67%; mp 214–215°; $[\alpha]^{22}D$ +59.3° (*c* 1.2, pyridine).

Anal. Calcd for $C_{21}H_{21}NO_6$ (383.4): C, 65.78; H, 5.52; N, 3.66; O, 25.04. Found: C, 65.44; H, 5.69; N, 2.97; O, 25.76.

Benzyl β-D-Glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XII).—Benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XI, 0.58 g, 0.0015 mol) was dissolved in glacial acetic acid (15 ml). The solution was heated to 70–71° and water (10 ml) was added dropwise over a period of 10 min. After the addition of water the reaction mixture was stirred for 60 min at 65–70°. The cooled solution was evaporated *in vacuo*, followed by repeated coevaporation with water and finally with toluene. Petroleum ether (bp 30–60°) was added to the remaining syrup and the mixture was kept at 0° to complete precipitation. The product was collected by filtration, dried, and recrystallized from diisopropyl ether–diethyl ether–petroleum ether–2-propanol to give 0.295 g (0.0010 mol, 68% yield) of XII melting at 159.5–160.5°, $[\alpha]^{29}D$ −38.8° (*c* 1.3, pyridine).

Anal. Calcd for $C_{14}H_{17}NO_6$ (295.3): C, 56.94; H, 5.80; N, 4.75; O, 32.51. Found: C, 57.32; H, 5.21; N, 4.29; O, 33.32.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosido)carbamide (XIV).—The precipitate (side-reaction product) of the preparation of benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidone (XI) with *N,N′*-carbonyldiimidazole was collected by filtration and dried. Recrystallization from dimethyl sulfoxide–tetrahydrofuran gave XIV melting at 291–293°, mol wt 740.8.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)carbamide (XIVa) was prepared by a procedure identical with that used for the preparation of the β anomer. Recrystallization from dimethyl sulfoxide–tetrahydrofuran–2-propanol gave XIVa melting at 304–305°, mol wt 740.8.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (XV). A.—Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VIIb, 2 g, 0.0056 mol) was refluxed with hexachloroacetone (12 g) and dimethylmesidine (2 ml) in absolute chloroform (225 ml). Precipitation of the initial hexachloroacetone adduct occurred after 10–15 min refluxing. Refluxing was continued for 7 hr and after addition of hexachloroacetone (7 ml) for 8 more hr. The solvent was removed by evaporation *in vacuo*. The remaining syrup was dissolved in ethanol which was then evaporated. The product was precipitated by addition of *n*-heptane and collected by filtration after several hours at 0°. Recrystallization from absolute ethanol gave 2.1 g (0.0041 mol, 75% yield) of XV melting at 215–216°, $[\alpha]^{27}D$ −55.1° (*c* 1.3, pyridine).

Anal. Calcd for $C_{22}H_{22}NO_6Cl_3$ (502.8): C, 52.55; H, 4.41; N, 2.78; O, 19.10; Cl, 21.16. Found: C, 52.54; H, 4.81; N, 2.78; O, 18.94; Cl, 20.95.

B.—This compound was also prepared by treating benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VIIb) with trichloroacetyl chloride in pyridine at −5°, yield 47%.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (XVI).—Benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (XV, 1.5 g, 0.0029 mol) in absolute pyridine (15 ml) was acetylated with acetic anhydride (2 ml) by stirring at room temperature for 36 hr. The mixture was then poured into ice–water and kept at 0° to complete precipitation. The product was collected by filtration and recrystallized from absolute ethanol to give 1.3 g (0.0023 mol, 82.8% yield) of XVI melting at 236–236.5°, $[\alpha]^{27}D$ −72.8° (*c* 1.42, pyridine).

Anal. Calcd for $C_{24}H_{24}NO_7Cl_3$ (544.8): C, 52.91; H, 4.44;

(20) H. M. Noorzad and P. H. Gross, Abstracts of Papers, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, C-018.

N, 2.57; O, 20.56; Cl, 19.53. Found: C, 52.88; H, 4.51; N, 2.66; O, 20.57; Cl, 19.32.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethoxycarbonyl)amino-β-D-glucopyranoside (XVII).—Ethyl chloroformate (0.33 g) was added dropwise with stirring to a solution of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII, 1 g, 0.0027 mol) in 20 ml of absolute pyridine. The resulting mixture was stirred for 1 hr, kept overnight at 0°, and poured into ice–water. After 3 hr at 0° the precipitate was collected by filtration, washed with cold water, and recrystallized from absolute methanol to give 1.02 g (0.0026 mol, 96.2% yield) of XVII melting at 233–233.5°, $[\alpha]^{23}D$ −87° (*c* 1.26, pyridine).

Anal. Calcd for $C_{23}H_{27}NO_7$ (429.4): C, 64.33; H, 6.34; N, 3.27; O, 26.08. Found: C, 64.25; H, 6.57; N, 3.37; O, 26.33.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-phenoxycarbonylamino-β-D-glucopyranoside (XVIII).—Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (VII, 1.07 g, 0.003 mol) in absolute pyridine (40 ml) was cooled to −5°, and phenyl chloroformate (0.52 g) was added dropwise with exclusion of moisture. The mixture was stirred 1 day at −5°. Pyridine was then removed by evaporation *in vacuo* until the volume was 15 ml and the mixture was poured into ice–water. The precipitate was collected by filtration, washed with cold water, and dried. Two recrystallizations from dioxane–hexane and absolute methanol gave 1.2 g (0.0025 mol, 87.5% yield) of XVIII melting at 247–247.5°, $[\alpha]^{27}D$ −84.5° (*c* 1.28, pyridine).

Anal. Calcd for $C_{27}H_{27}NO_7$ (477.5): C, 67.91; H, 5.70; N, 2.93; O, 23.46. Found: C, 67.46; H, 5.77; N, 3.28; O, 23.54.

Treatment of Benzyl 4,6-*O*-Benzylidene-D-glucopyranosido-[2,3:4′,5′]-2′-oxazolidinones (XIa and XI) with Alcoholic Potassium Hydroxide. Regeneration of Starting Compounds VIIa and VII.—A solution of benzyl 4,6-*O*-benzylidene-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (XIa or XI, 0.5 g, 0.00133 mol) in a hot mixture of potassium hydroxide (1 g) and 95% ethanol (60 ml) was refluxed for 5 hr at 85°. The mixture was then diluted with hot water (150 ml), allowed to cool, and kept at 0° to complete precipitation. The product was collected by filtration, washed with cold water, and dried. Recrystallization from absolute methanol gave 0.499 g (0.00126 mol, 95% yield) of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (VIIa or VII).

Catalytic Hydrogenation of *trans*-Oxazolidinone XI.—Palladium black (1 g) was suspended in ethyl acetate (125 ml) in a hydrogenation flask. Benzyl 4,6-*O*-benzylidene-β-D-glucopyranosido-[2,3:4′5′]-2′-oxazolidinone (XI, 0.8138 g, 0.0021 mol) was then introduced, followed by hydrogen at atmospheric pressure. The hydrogen uptake started immediately and the hydrogenation was stopped after 30 min. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The remaining syrup was taken up in dioxane–acetone–petroleum ether and the mixture was kept at 0° for 2 weeks. Compound XIII, giving a characteristic carbonyl absorption at 1750 cm^{-1} and a positive test with Benedict reagent, was obtained.

Registry No.—II, 19358-93-1; III, 19358-94-2; IX, 19358-95-3; X, 19358-96-4; XI, 19358-97-5; XIa, 19358-98-6; XII, 19358-99-7; XIV, 19359-00-3; XIVa, 19359-01-4; XV, 19359-02-5; XVI, 19359-03-6; XVII, 19359-04-7; XVII, 13347-81-4.

Reactions of Chlorine with Some Thiocarbonyl Sugar Derivatives[1a]

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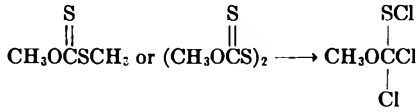
The reactions between chlorine and some thiocarbonyl sugar derivatives were investigated. In each reaction the major product(s) was (were) isolated and identified. Both bis(1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonyl-α-D-glueofuranose) disulfide (**1**) and bis[methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-thiocarbonyl-α-D-glucopyranoside] disulfide (**3**) added four chlorine atoms (two chlorine atoms to each carbon–sulfur double bond) to yield corresponding chloromethylsulfenyl chloride derivatives **2** and **4**. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-D-glucofuranose (**5**) reacted in a similar fashion to give **6**. On further reaction with chlorine, **6** lost the methylthio group and gave a dichloromethanesulfenyl chloride derivative (**7**). 1,2-*O*-Isopropylidene-α-D-glucofuranose 5,6-thionocarbonate (**8**), methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-thionocarbonate (**10**), and 3-*O*-ethoxythiocarbonyl-1,2:5,6-di-*O*-isopropylidene-α-n-glucofuranose (**12**) yielded the corresponding carbonates **9**, **11**, and **13**. Conversion of **8** → **9** in the presence of $H_2{}^{18}O$ established the origin of the carbonyl oxygen atom. A dithiocarbonate derivative (**17**) was obtained from 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose 5,6-trithiocarbonate (**16**). Two major reaction products from methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-[(1-piperidyl)thiocarbonyl]-α-D-glucopyranoside (**14**) were identified as the corresponding carbonyl compound **15** and the cyclic carbonate **11**.

The formation of sulfenyl chlorides by reaction of chlorine with certain organic disulfides and dithio esters has been reported.[2] Douglas and Osborne[3] studied the action of anhydrous chlorine at low temperature on some simple thio esters. Such dithio esters as the methyl ester of methyl xanthate undergo chlorinolysis with removal of the methylthio group as methylsulfur trichloride and with formation of methoxydichloromethanesulfenyl chloride. This product is also formed during chlorinolysis of bis(methoxythiocarbonyl) disulfide. Although this reaction has been conducted with a number of organic sulfur derivatives,



no information is available on such a reaction with similar sulfur derivatives of carbohydrates. We have now extended our studies[4] on the preparation and reactions of thiocarbonyl derivatives of carbohydrates to the reaction of these derivatives with chlorine. We examined the behavior of carbohydrate bis(*O*-thiocarbonyl)disulfides, (alkylthio)dithiocarbonates, cyclic

(1) (a) Presented before the Division of Carbohydrate Chemistry, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968. (b) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article is not copyrighted.

(2) I. B. Douglass in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, pp 350–360.

(3) I. B. Douglass and C. E. Osborne, *J. Amer. Chem. Soc.*, **75**, 4582 (1953).

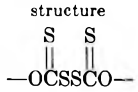
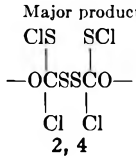
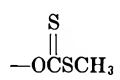
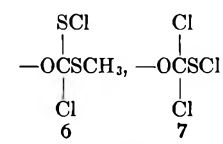
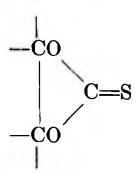
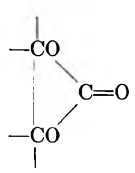
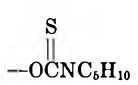
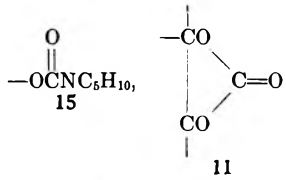
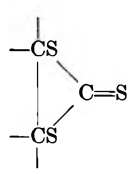
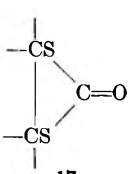
(4) W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, **30**, 3071 (1965); **32**, 1080 (1967); references cited therein.

and acyclic thionocarbonates, thiocarbamates, and trithiocarbonates upon treatment with chlorine at room temperature and without special precautions to exclude moisture.

Bis(*O*-thiocarbonyl) disulfide and (methylthio)-thiocarbonyl derivatives chlorinate readily under these conditions, the initial reaction being addition of chlorine to the carbon–sulfur double bond. Bis(1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonyl-α-D-glucofuranose) disulfide (**1**) and bis[methyl 4,6-*O*-benzylidene-2 (and 3-) *O*-thiocarbonyl-α-D-glucopyranoside] disulfide (**3**) each added four atoms of chlorine and gave bis[3-*O*-(chloromethylsulfenyl chloride)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose] disulfide (**2**) and bis[methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-(chloromethylsulfenyl chloride)-α-D-glucopyranoside] disulfide (**4**) (Table I).

TABLE I

PRODUCTS OF REACTION OF CARBOHYDRATE THIOCARBONYL DERIVATIVES WITH CHLORINE

Compd	Thiocarbonyl structure	Major product(s)
1, 3		 **2, 4**
5		 **6** **7**
8, 10, 12		 **9, 11, 13**
14		 **15** **11**
16		 **17**

Compound **2** was isolated as a white crystalline product in nearly quantitative yield.

The proposed structure of **2** was consistent with its elemental analysis, ir spectrum, and mass spectrum. While the mass spectrum did not reveal a molecular ion peak at 810, it did exhibit a peak at M − 15 which is characteristic[5] for *O*-isopropylidene derivatives. In addition the five mass peaks present in the spectrum at 795, 797, 799, 801, and 803 were in the proper ratios expected for the presence of four chlorine atoms in the molecule.

Product **4** was recovered as a white partly crystalline compound in about 30% yield. Analyses of **4** were consistent with the proposed structure.

Sulfenyl chloride **2** was stable during storage at room temperature for several weeks Under similar storage conditions, sulfenyl chloride **4** gradually decomposed and evolved acidic vapors. Instability of **4** is largely attributed to the presence of the hydroxyl group in the molecule. Sulfenyl chlorides react with alcohols and form hydrogen chloride and carbonyl-containing compounds along with other products.[2] Such a reaction might also explain the lower yield for **4** compared with that of **2** since the residue remaining after removal of **4** showed strong carbonyl absorption in the 5.6–5.9-μ region.

When bis(methoxythiocarbonyl) disulfide was treated with chlorine under our conditions, the tetrachloro derivative was obtained as a syrup in a quantitative yield.

We also examined bis(*O*-thiocarbonyl) disulfide derivatives of starch (starch xanthide) and 6-*O*-tritylstarch (*O*-tritylstarch xanthide). Powdered starch xanthide rapidly consumed gaseous chlorine with the evolution of heat. Exposure of the xanthide to chlorine gas for 10 min or for several hours gave essentially the same product based on sulfur and chlorine content. The ratio of chlorine to sulfur in the product was about 2:1 and not 1:1 as it would if chlorine were added to the carbon–sulfur double bond. Treatment of *O*-tritylstarch xanthide with chlorine caused detritylation and gave a chlorinated product with a chlorine–sulfur ratio of 0.6:1. Both the product from starch xanthide and from *O*-tritylstarch xanthide had strong carbonyl absorptions near 5.7 μ. Upon storage, both products lost much of their sulfur and chlorine.

Addition of chlorine to the carbon–sulfur double bond appeared also to be the initial reaction when 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-D-glucofuranose (**5**) was treated with chlorine. Careful addition of a solution of chlorine in ether to **5**, while the progress of the reaction was monitored spectroscopically, permitted the isolation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-[(methylthio)chloromethanesulfenyl chloride]-α-D-glucofuranose (**6**) as a yellow unstable syrup, which gave off acidic vapors upon standing. Sulfur and chlorine values and nmr data acquired soon after isolation of **6** were consistent with the proposed structure.

When the addition of chlorine to **5** was continued beyond that required for formation of **6**, the major compound formed was 3-*O*-(dichloromethylsulfenyl chloride)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**). This product also decomposed on standing.

Compounds that possess thiocarbonyl groups flanked on either side by oxygen gave no isolable sulfenyl chloride derivative. 1,2-*O*-Isopropylidene-α-D- glucofuranose 5,6-thionocarbonate (**8**), methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-thionocarbonate (**10**), and 3-*O*-ethoxythiocarbonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**) reacted with chlorine and gave their respective carbonate derivatives 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate (**9**), methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-

(5) D. C. DeJongh and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 67 (1964).

carbonate (**11**), and 3-*O*-ethoxycarbonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**). Each reaction was followed by observing the disappearance of the absorption maxima for the thiocarbonyl group near 230–238 mμ. Yields of carbonate ranged from 50 to 70% when the reaction was conducted in the presence of aqueous sodium carbonate or when the reaction mixtures were treated with aqueous sodium carbonate upon completion of the chlorine treatment. Omission of the sodium carbonate permitted hydrolysis of the isopropylidene group in compounds **8** and **12** and the benzylidene group in compound **10** and resulted in lower yields of **9**, **11**, and **13**. Thionocarbonate has been oxidized to carbonate with other reagents, such as silver nitrate, silver carbonate, and lead tetraacetate.[4]

The thiocarbonyl sulfur atom in thiocarbamates and trithiocarbonates is likewise replaced by oxygen upon treatment with chlorine. Methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-[(1-piperidyl)thiocarbonyl]-α-D-glucopyranoside (**14**) gave two major chlorinolysis products in almost equal amounts as shown by tlc. Separation and isolation of the two components by preparative tlc gave the cyclic carbonate **11** and methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-[(1-piperidyl)carbonyl]-α-D-glucopyranoside (**15**). Cyclic carbonate **11** was obtained in somewhat higher amount than **15**. The mechanism for the formation of **11** is not clear. That **15** is not intermediate was demonstrated when reaction of **15** under the conditions used for **14** gave none of the cyclic product.

Chlorine treatment of 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose 5,6-trithiocarbonate (**16**) afforded a 47% yield of crystalline 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose 5,6-dithiocarbonate (**17**). Compound **17** was prepared independently from **16** upon oxidation with potassium permanganate.

The precise mechanism involved in replacement of the thiocarbonyl sulfur atom in **8**, **10**, **12**, **14**, and **16** by oxygen is not clear. The reaction might proceed *via* addition of a molecule of chlorine to form a chlorosulfenyl chloride intermediate, which is then hydrolyzed by water. Although water was not intentionally added to some of the reaction solutions, the solvents used were not dried and the reactions were often conducted in open flasks.

That the carbonyl oxygen atom is indeed provided by water was shown when the conversion **8** → **9** was performed in the presence of a small amount of water which contained 5% $H_2{}^{18}O$. The mass spectrum of **9** prepared in the presence of $H_2{}^{18}O$-enriched water showed 4.54% more ^{18}O than the spectrum of **9** prepared without added $H_2{}^{18}O$. The calculation was made from the intensities of the mass peaks at 233 mass units which correspond to M − 15 plus two mass units for the ^{18}O isotope.

Experimental Section

Melting points were determined with a Fisher-Johns[6] apparatus and are uncorrected. Optical rotations were measured in a 1-dm tube with a Rudolph polarimeter. Ultraviolet and infrared spectra were recorded by Perkin-Elmer Models 202 and 137 spectrophotometers, respectively. Nmr spectra were recorded in deuterated chloroform by a Varian A-60 nmr spectrometer with tetramethylsilane as internal reference. Tlc was performed with silica gel as the adsorbent in the solvents indicated. Components were detected by sulfuric acid. Mass spectra were obtained with a Nuclide 12-90-G mass spectrometer equipped with a probe inlet. Water enriched (5%) with $H_2{}^{18}O$ was a product of Yeda Research and Development Co., Rehovoth, Israel.

Reaction of Bis(*O*-thiocarbonyl) Disulfides with Chlorine. A.—A solution of bis(1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonyl-α-D-glucofuranose) disulfide[7] (**1**, 1.0 g) in ether (50 ml) was treated with a slow stream of chlorine. Within a few minutes white crystals deposited from the solution and the chlorine stream was stopped. The contents of the flask were kept at 5° for 1 hr and then filtered. The solid material was washed with ether and dried. The yield of product characterized as bis[3-*O*-(chloromethylsulfenyl chloride)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose] disulfide (**2**) was nearly quantitative, mp 168–169° (recrystallized from ether–hexane), $[\alpha]^{23}D$ +52° (*c* 1, chloroform). Comparison of the infrared spectra (films) of **1** and **2** revealed that the characteristic absorption[7] for the bis(*O*-thiocarbonyl) disulfide group near 8.0 and 9.7 μ was lacking in compound **2** and instead there was strong absorption at 9.0 and 13.8 μ (C–Cl). Mass spectrum showed peaks at 795, 797, 799, 801, and 803 mass units, which correspond to M − 15 for the various distributions of ^{35}Cl and ^{37}Cl. Intensities of the five peaks were in the ratios expected for the presence of four chlorine atoms.

Anal. Calcd for $C_{26}H_{38}Cl_4O_{12}S_4$: C, 38.4; H, 4.7; Cl, 17.5; S, 15.8. Found: C, 38.7; H, 5.0; Cl, 17.4; S, 15.6.

B.—Bis[methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-thiocarbonyl-α-D-glucopyranoside] disulfide[8] (**3**, 1.0 g) was treated with ether (5 ml) that contained excess chlorine. Yellow solid **3** readily dissolved and within several seconds a white precipitate was deposited from the solution. The liquid layer was decanted and the precipitate was washed three times with ether (3 ml each) and dried. Yield of the white solid, which was characterized as bis[methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-(chloromethylsulfenyl chloride)-α-D-glucopyranoside] disulfide (**4**), was 350 mg: mp 108–112°; infrared spectrum (Nujol), 2.86 (OH), 9.1, 13.3 (phenyl), 13.8 (C–Cl), and 14.3 μ (phenyl).

Anal. Calcd for $C_{30}H_{34}Cl_4O_{12}S_4$: C, 42.1; H, 4.0; Cl, 16.6; S, 15.0. Found: C, 41.8; H, 4.3; Cl, 16.5; S, 14.9.

C.—Bis(methoxythiocarbonyl) disulfide (0.5 g) in ether (20 ml) was treated with a slow stream of chlorine for 5 min and then the ether and excess chlorine were removed under reduced pressure. The syrup, which remained, weighed 0.8 g: infrared spectrum (film), 8.4, 9.0, 10.6, 12.0, and 13.9 μ. A spectrum (film) of the starting material showed 8.0, 8.6, 9.7, and 10.8 μ.

Anal. Calcd for $C_4H_6Cl_4O_2S_4$: Cl, 40.0; S, 36.0. Found: Cl, 39.4; S, 35.6.

D.—Starch, sodium hydroxide, and carbon disulfide (1:1:1 molar ratio) were mixed in a reactor as described previously.[9] A 2% aqueous dispersion of this starch xanthate was adjusted to pH 6, and aqueous iodine was added to convert the xanthate into xanthide. The insoluble xanthide was washed with water, ethanol, and ether and then air equilibrated for several hours. Sulfur content of the product was 14.7%. A portion (200 mg) of the product was placed in a 50-ml flask and the flask was then filled with chlorine gas. The xanthide was agitated for 10 min by means of a magnetic stirring bar. After excess chlorine was removed by evacuation, benzene (20 ml) was added to the flask and distilled off at 40° under reduced pressure. Extraction with benzene was repeated until the distillate was neutral to pH test paper. The starch product was then washed with ether and carbon disulfide and dried to constant weight. Sulfur and chlorine contents of the product were 5.5 and 13.6%, respectively. Analyses were similar for a product (200 mg) kept 16 hr in a flask (500 ml) filled with chlorine. Infrared spectrum (KBr) revealed carbonyl absorption near 5.7–5.8 μ.

E.—6-*O*-Tritylstarch xanthide was prepared as previously described[8] for the corresponding amylose derivative. Sulfur in the product amounted to 15.7%. After reaction of the air dried

(6) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(7) W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, **30**, 162 (1965).

(8) E. I. Stout, W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, **3**, 354 (1967).

(9) C. L. Swanson, T. R. Naffziger, C. R. Russell, B. T. Hofreiter, and C. E. Rist, *Ind. Eng. Chem., Prod. Res. Dev.*, **3**, 22 (1964).

and pulverized product with chlorine for several minutes, the product had only 2% chlorine. When the reaction was repeated with freshly prepared, undried xanthide suspended in ether, a chlorine content of 8.8% was realized. Sulfur content of the chlorinated product was 13% and its infrared spectrum (KBr) showed carbonyl absorption near 5.7 μ but no phenyl absorption near 6.1 μ. That detritylation had occurred during chlorination was confirmed when no precipitate formed when the product was dissolved in concentrated sulfuric acid and diluted with water.

Reaction of (Alkylthio)dithiocarbonate with Chlorine.—A solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-[(methylthio)thiocarbonyl]-α-D-glucofuranose (**5**, 0.5 g) in ether (25 ml) was stirred while a solution of chlorine in ether was added dropwise. The progress of the reaction was followed by observing the decrease in the absorption maximum at 285 mμ for the starting material. Upon disappearance of the maximum at 285 mμ, the ether was removed under reduced pressure to yield a yellow syrup. Sulfur and chlorine analyses (14.9 and 16.8%, respectively) and nmr spectrum (signal at τ 7.36 for S–CH_3) were consistent with the proposed structure of 1,2:5,6-di-*O*-isopropylidene-3-*O*-[(methylthio)chloromethanesulfenyl chloride]-α-D-glucofuranose (**6**). When the addition of chlorine was continued after the 285-mμ maximum had disappeared, a different product was formed. Removal of the ether left a yellow syrup, which gave correct sulfur and chlorine analyses (7.8 and 26.3%, respectively) for 3-*O*-(dichloromethanesulfenyl chloride)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**). An nmr spectrum had no S–CH_3 signal.

Both chlorinated products **6** and **7** were unstable and decomposed when kept for several hours. The products were not amenable to tlc since chromatograms varied in the number of spots depending upon the length of time that elapsed between application of the components and immersion in the solvent.

Reaction of Thionocarbonates with Chlorine. A.—1,2-*O*-Isopropylidene-α-D-glucofuranose 5,6-thionocarbonate[7] (**8**, 260 mg) in tetrahydrofuran (15 ml) was treated with a solution of chlorine in ether by dropwise addition. The progress of the reaction was followed spectrometrically by observance of the decrease in thionocarbonate absorption near 235 mμ of periodically withdrawn samples. Addition of chlorine was stopped when there was no maximum at 235 mμ. Upon completion of the reaction a white compound crystallized from the solution. Yield of the product, identified as 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate (**9**), was 200 mg, mp 230–231°, infrared spectrum (Nujol) identical with an authentic sample.

The experiment was repeated but with addition of 1 drop of water, which was enriched (5%) with $H_2{}^{18}O$, to the tetrahydrofuran solution. The product was isolated and gave the same melting point and infrared spectrum as **9**. Mass spectrum of the product had a M − 15 peak at 231 mass units. The intensity of the peak at 233 mass units (two units higher than the M − 15 peak due to the ^{18}O isotope) showed that there was 4.54% more ^{18}O in **9** isolated from the $H_2{}^{18}O$ treatment than in **9** prepared without such treatment.

B.—Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-thionocarbonate[8] (**10**, 300 mg) in chloroform (20 ml, spectroscopic grade) was stirred and sodium carbonate (2 g) in water (30 ml) was added. A solution of chlorine in chloroform was added slowly while progress of the reaction was monitored as in part A. Upon complete disappearance of the absorption maximum near 238 mμ for **10**, the mixture was stirred an additional 30 min. After the chloroform layer was separated and dried, the chloroform was removed under reduced pressure. Tlc (carbon disulfide–ethyl acetate 7:3) revealed a major component of R_f 0.3 and a minor spot at the origin. Separation of the major component from a preparative tlc plate afforded 132 mg of a crystalline product identified as methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-carbonate (**11**). Infrared spectrum and melting point of this product were identical with those of authentic[8] **11**.

C.—3-*O*-Ethoxythiocarbonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**, 300 mg) was treated with chlorine by the procedure used in part B. Infrared spectrum (film) of the product was identical with a spectrum of 3-*O*-ethoxycarbonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**). Separation of the major product by preparative tlc (ethyl acetate–carbon disulfide 1:9) from a minor contaminant gave the known ethoxycarbonyl derivative, 195 mg, mp 71–73°.

Reaction of Thiocarbamates with Chlorine.—A mixture of methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-[(1-piperidyl)thiocarbonyl]-α-D-glucopyranosides (**14**) was prepared by reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-thionocarbonate (**10**) with piperidine.[10] The mixture of 2- and 3-*O* isomers was used for reaction with chlorine. A solution of the thiocarbamates (180 mg) in ether (100 ml) was stirred while chlorine in ether was added dropwise. The addition of chlorine, which was accompanied by precipitation of piperidine hydrochloride, was continued until no more precipitate formed. The mass was then shaken with water (100 ml) that contained sodium carbonate (2 g). The ether layer was separated and evaporated to a syrup. Tlc (chloroform–acetone 9.5:0.5) revealed two spots. Separation of the components on a preparative tlc plate and isolation therefrom gave methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-carbonate (**11**, 68 mg) and methyl 4,6-*O*-benzylidene-2- (and 3-) *O*-(1-piperidyl)carbonyl-α-D-glucopyranoside[11] (**15**, 50 mg). These products were identified by comparison with authentic samples.

Reaction of Trithiocarbonate with Chlorine.—1,2-*O*-Isopropylidene-5,6-dithio-β-L-idofuranose 5,6-trithiocarbonate[4] (**16**, 500 mg) in chloroform (50 ml of spectroscopic grade) was treated with chlorine by a procedure similar to that used for **10** except that the absorption maximum near 315 mμ was monitored. Tlc (chloroform–acetone 4:1) showed one major spot with R_f 0.5 and two minor spots with R_f 0.1 and 0.9. The major component was separated by preparative tlc and extracted from the plate with acetone. Evaporation of the acetone gave 220 mg of a crystalline compound (mp 144–146°) which upon recrystallization from chloroform–hexane had mp 152–154°, $[\alpha]^{23}D$ +48° (*c* 1, chloroform). The product was identified as 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose 5,6-dithiocarbonate (**17**) by infrared (film) at 5.7 and 6.1 μ (carbonyl), by elemental analyses, and by independent synthesis from **10** (see following section).

Anal. Calcd for $C_{10}H_{14}O_6S_2$: C, 43.2; H, 5.0; S, 23.0. Found: C, 42.9; H, 5.2; S, 23.4.

When a chloroform solution of **16** was treated with a stream of chlorine gas at 25° or lower until the yellow solution became colorless, a major component of R_f 0.9 was observed by tlc. Evaporation of the reaction mixture to constant weight gave a syrup which, from several preparations, analyzed for 20–25% of chlorine.

Preparation of 1,2-*O*-Isopropylidene-5,6-dithio-β-L-idofuranose 5,6-Dithiocarbonate (17).—Potassium permanganate (4.0 g) in water (5 ml) and acetone (100 ml) was mixed with **16** (400 mg). After the mixture was refluxed for 45 min, ethanol (50 ml) was added and reflux was continued for another 15 min. Manganese dioxide thus formed was filtered off and the colorless filtrate was evaporated to dryness to yield 320 mg of a crystalline product, mp 142–146°, which was washed with water and recrystallized, mp 148–150° (chloroform–hexane) or 150–152° (acetone–hexane). Tlc of the product showed only one spot with an identical R_f as **17** and the infrared spectrum of the product was superimposable with **17**.

Registry No.—**1**, 2946-03-4; **2**, 19461-97-3; bis(methyl 4,6-*O*-benzylidene-2-*O*-thiocarbonyl-α-D-glucopyranoside) disulfide, 14419-71-7; bis(methyl 4,6-*O*-benzylidene-3-*O*-thiocarbonyl-α-D-glucopyranoside) disulfide, 19426-90-5; **5**, 16667-96-2; **8**, 2816-87-7 **10**, 14419-72-8; **12**, 19189-59-4; methyl 4,6-*O*-benzylidene-2-*O*-[(1-piperidyl)thiocarbonyl]-α-D-glucopyranoside, 19407-33-1; **16**, 19426-91-6; **17**, 19407-34-2; chlorine, 7782505; methyl 4,6-*O*-benzylidene-3-*O*-[(1-piperidyl)thiocarbonyl]-α-D-glucopyranoside, 19407-35-3.

Acknowledgment.—We thank C. E. McGrew and B. R. Heaton for microanalysis, D. Weisleder for nmr spectra, and W. K. Rohwedder for mass spectra.

(10) Unpublished work.

(11) E. I. Stout, W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *Tetrahedron Lett.*, 4481 (1967).

The Stereospecific Synthesis of *trans*- and *cis*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (Dihydrotoxol). Dihydrobenzofuran Derivatives in Which $J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$[1]

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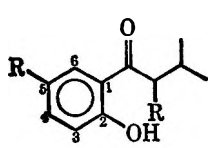
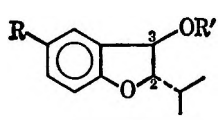
2'-Hydroxy-2,5'-dibromo-3-methylbutyrophenone (II) has been converted into *trans*-2-isopropyl-2-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII) by successive treatment with sodium borohydride in aqueous ethanolic potassium hydroxide, butyllithium, then carbon dioxide and finally methyllithium. When II was reduced with sodium borohydride and the product then treated with potassium hydroxide, *cis*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X) was obtained, which was converted by an identical sequence of reactions into *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (racemic dihydrotoxol, IX). The sodium borohydride reduction of II in alkaline medium is believed to lead first to cyclization to 2-isopropyl-5-bromocoumaran-3-one (XIV) followed by reduction to give the thermodynamically more stable *trans* isomer (III), while in the absence of alkali II is first reduced to give the *erythro* isomer (steric approach control) which then leads to the *cis* isomer (X) by backside displacement of the α-bromo atom by the phenolic OH group. The unexpected observation that $J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$ in the two families of 2,3-dihydrobenzofurans is believed to arise from a stereochemical dependence of the electronegativity effect of the hydroxyl groups in the *cis* series as observed by Booth[10] for six-membered rings.

Rayless goldenrod (*Aplopappus heterophyllus*), a toxic plant indigenous to the Southwestern United States, has been found to contain four benzofuran derivatives: toxol[3] [(2*S*)-isopropenyl-(3*S*)-hydroxy-5-acetyl-2,3-dihydrobenzofuran], dehydrotremetone[3] (2-isopropenyl-5-acetylbenzofuran), tremetone[4] [(2*S*)-isopropenyl-5-acetyl-2,3-dihydrobenzofuran] and 2,5-diacetylbenzofuran.[5] We wish to record here the stereospecific synthesis of racemic dihydrotoxol and its *trans* isomer and to comment on certain unexpected aspects of the nmr spectra of these compounds and their synthetic precursors.

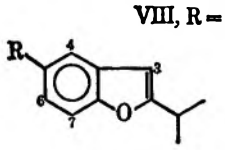
Treatment of phenol with isovaleryl chloride gave phenyl isovalerate, which in turn gave *o*-hydroxyisovalerophenone, I, by the Fries rearrangement. On treatment with bromine in acetic acid, *o*-hydroxyisovalerophenone afforded 2'-hydroxy-2,5'-dibromo-3-methylbutyrophenone, II. Introduction of a bromine atom at C-5 was particularly advantageous since it made possible the later introduction of an acetyl group at this position under nonacidic conditions. Attachment of bromine α to the carbonyl group and at position C-5 was apparent from the nmr spectrum of II. Thus the α proton appeared as a downfield doublet centered at δ 4.83 while the aromatic protons gave a typical ABC pattern expected of a trisubstituted aromatic system such as II with $J_{3,4} = 9$ Hz and $J_{4,6} = 2.5$ Hz.



I, R = H
II, R = Br



III, R = Br; R' = H
IV, R = Br; R' = $COCH_3$
VII, R = CO_2H; R' = H
VIII, R = $COCH_3$; R' = H



V, R = Br
VI, R = H

Reduction of II with sodium borohydride in an aqueous ethanolic solution of potassium hydroxide gave *trans*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III) in 54% yield. The infrared and nmr spectra of III showed it to be a dihydrobenzofuran derivative but the assignment of a *trans* relationship at C-2 and C-3 was not apparent until the *cis* isomer was prepared and the latter correlated with dihydrotremetone as described below. The infrared spectrum showed a strong hydroxyl band at 3340 cm^{-1} and the OH proton appeared as a doublet (J = 6 Hz) in the nmr spectrum centered at δ 4.37; the latter signal disappeared on addition of D_2O. The C-3 proton, which appeared as a triplet, in the nmr spectrum, in the absence of D_2O, gave a clean doublet (J = 6 Hz) in CD_3COCD_3 in the presence of D_2O, while the C-2 proton gave a quartet (J = 6 and 10 Hz) centered at δ 3.99. The aromatic protons and isopropyl group appeared as expected in the nmr spectrum for structure III.

Distillation of the mother liquor remaining after removal of crystalline III gave 2-isopropyl-5-bromobenzofuran (V) as an unstable liquid which rapidly decomposed. The nmr spectrum of V showed the characteristic C-3 proton as a sharp doublet (J = 1 Hz) centered at δ 6.15. The previously reported[6] 2-isopropylbenzofuran (VI) was found to show infrared and nmr spectra similar to that observed for V. Protons at

(1) Presented at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1-3, 1967. A portion of this material has appeared in preliminary form: L. H. Zalkow and M. Ghosal, *Chem. Commun.*, 922 (1967).

(2) Postdoctoral Fellow, Jan 1965-Sept 1966.

(3) L. H. Zalkow, N. Burke, G. Cabat, and E. A. Grula, *J. Med. Chem.*, **5**, 1342 (1962).

(4) Unpublished work M. Ghosal and L. H. Zalkow, Georgia Institute of Technology.

(5) C. T. Ramming, Masters Thesis, Oklahoma State University, Stillwater, Okla., 1965.

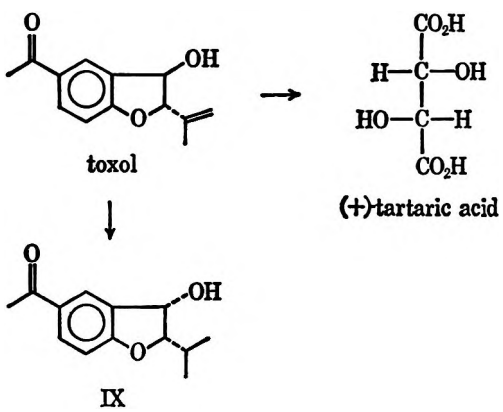
(6) J. I. DeGraw, Jr., and W. A. Bonner, *Tetrahedron*, **18**, 1311 (1962).

C-6 and C-7 in V were found to have the same chemical shift when the nmr spectrum was measured in carbon tetrachloride. On refluxing in benzene in the presence of a crystal of iodine III also gave V. The formation of V lends further support to the assignment of a dihydrobenzofuran structure to III. On treatment with acetic anhydride in pyridine III gave IV. Again the infrared and nmr spectra were consistent with the assigned structure. Of particular significance was the observed coupling of 6 Hz for the C-2 and C-3 protons in the nmr spectrum of IV.

Treatment of *trans*-2-isopropyl-3-hydroxyl-5-bromo-2,3-dihydrobenzofuran with butyllithium followed by carbon dioxide led to 2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (VII). The latter acid was converted into racemic *trans*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII) upon treatment with methyllithium.

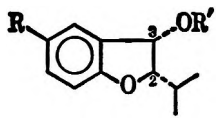
The nmr spectrum of VIII showed a coupling constant of $J = 6$ Hz for the C-2 and C-3 protons and VIII was found to differ in infrared and nmr spectra from dihydrotoxol (IX) prepared by hydrogenation of toxol.[7] Ozonolysis of toxol has been shown to yield (+)-tartaric acid.[7] This established the configuration of toxol and therefore dihydrotoxol at C-2 and C-3 as indicated in Scheme I. The alternative explanation

SCHEME I



that toxol, and therefore dihydrotoxol, possess a *trans* relationship at C-2 and C-3 and epimerization occurs at C-2 during ozonolysis is seen to be invalid since the configuration at C-2 in toxol has been established by independent correlation with (+)-dihydrocoumarilic acid and with rotenone.[7] Thus a *trans* relationship can be assigned to VIII and the cyclic precursors leading to VIII. However, a slight variation in the experimental conditions lead to dihydrotoxol as described below.

When the reduction of 2′-hydroxy-2,5′-dibromo-3-methylbutyrophenone (II) with sodium borohydride was conducted in ethanol in the absence of potassium hydroxide, and then the crude product treated with ethanolic potassium hydroxide, *cis*-2-isopropyl-3-hydroxyl-5-bromo-2,3-dihydrobenzofuran (X) was obtained in good yield. Alcohol X differed in the fingerprint region of its infrared spectrum from isomer III and the nmr spectra of the two isomers were different. Thus the isopropyl methyl groups in X were magnetically equivalent and appeared at higher field (δ 0.88) than those of III (δ 1.09 and 1.15). Likewise, the isopropyl proton in X (δ 1.68) appeared at higher field than the corresponding proton in III (δ 2.2) but of even greater significance was the observation that the coupling constant for the C-2 and C-3 protons in X was only 4 Hz as compared to 6 Hz in III. Likewise, the coupling constant of the C-2 and isopropyl protons in X (6 Hz) was less than that in III (10 Hz). In X the C-3 proton (δ 4.71) was more highly shielded than the corresponding proton in III (δ 5.08).

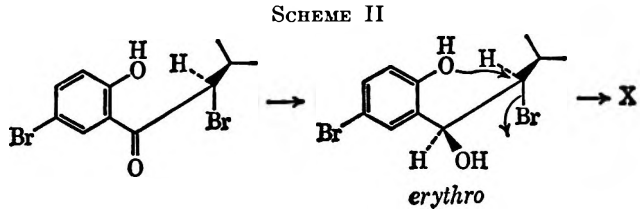


IX, R = $COCH_3$; R′ = H
X, R = Br; R = H
XI, R = Br; R′ = $COCH_3$
XII, R = CO_2H; R′ = H
XIII, R = $COCH_3$; R′ = $COCH_3$

As previously described, X was converted into acetate XI, the nmr spectrum of which again showed the isopropyl groups (δ 0.92, 0.97) at higher field than in the isomeric acetate IV (δ 0.97, 1.15). The couplings of the C-2 and C-3 protons ($J = 3.5$ Hz) and the C-2 proton and isopropyl proton ($J = 6$ Hz) were also less than that observed for IV ($J = 6$ and 9.5 Hz, respectively). Acetate XI was converted into *cis*-2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (XII) by the action of butyllithium followed by treatment with solid carbon dioxide. On treatment with methyllithium, XII gave after distillation racemic dihydrotoxol (IX) identical in every way, except for optical rotation, with active dihydrotoxol prepared by hydrogenation of natural toxol.[7] In addition to IX, a dehydrated product, presumably 5-acetylbenzofuran was obtained in the above distillation. Dihydrotoxol acetate (XIII) was obtained when IX was treated with acetic anhydride and pyridine and the synthetic sample was again identical with the naturally derived material on infrared and nmr spectral comparisons. As observed in X and XI, the C-2 and C-3 proton coupling in IX, XII and XIII was 4 Hz while the C-2, isopropyl proton coupling was 6 Hz.

The slight change in experimental conditions, which allowed preparation of either *trans*- (VIII) or *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX) can be explained as follows. In the two-step conversion of II into X, the carbonyl group is reduced in the first step and ring closure occurs in the second step. By application of Cram's rule,[8] using Dreiding models, one would expect to get predominantly the *erythro* alcohol; backside displacement of the bromine atom by the phenolic OH group would then lead to the *cis* isomer, as illustrated in Scheme II. In the one step,

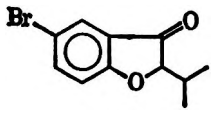
SCHEME II



(7) W. A. Bonner, N. I. Burke, W. E. Fleck, R. K. Hill, J. A. Joule, B. Sjoberg, and L. H. Zalkow, *Tetrahedron*, **20**, 1419 (1964).

(8) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

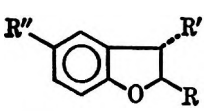
conversion of II into III, ring closure apparently occurs first to give XIV, which is then reduced under these



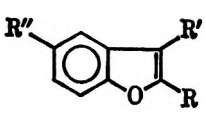
XIV

conditions to give the thermodynamically more stable *trans* product III (product-development control). In support of the latter postulation is the observation that XIV prepared by treatment of II with diethylamine gave only III on reduction with sodium borohydride in aqueous ethanolic potassium hydroxide.

During earlier attempts to synthesize dihydrotoxol, some interesting observations were made.[9] Thus reaction of *trans*-3-hydroxy- (XV) or 3-acetoxy-2-isopropyl-2,3-dihydrobenzofuran (XVI) with acetic anhydride and trifluoracetic acid or stannic chloride lead to 2-isopropyl-5-acetylbenzofuran (XVII), while similar conditions failed to lead to acetylation at C-5 in the case of 3-acetoxy-2-isopropylbenzofuran (XVIII). As previously reported,[7] reduction of toxol (*cis*-2-isopropenyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran) with 5% rhodium-on-alumina catalyst gave dihydrotoxol; under similar conditions, however, 2-carbethoxy-3-acetylbenzofuran (XIX) gave 2-carbethoxy-2,3-dihydrobenzofuran (XX). An attempt to oxidize (5′-acetyl-2′-dihydrobenzofuryl)-2-propyl acetate at C-3 with chromium trioxide in acetic anhydride at 0° led



XV, R = isopropyl; R′ = OH; R″ = H
XVI, R = isopropyl; R′ = acetoxy; R″ = H
XX, R = carbethoxy; R′ = R″ = H
XXI, R = 2-(2-acetoxy)propyl; R′ = H; R″ = acetyl
XXIV, R = isopropyl; R′ = H; R″ = Br or OH



VII, R = isopropyl; R′ = H; R″ = acetyl
XVIII, R = isopropyl; R′ = acetoxy; R″ = H
XIX, R = carbethoxy; R′ = acetoxy; R″ = H
XXII, R = isopropyl; R′ = H; R″ = acetyl
XXIII, R = 2-(2-hydroxy)propyl; R′ = R″ = H

instead to 5-acetylsalicyclic acid. Attempts to functionalize the C-3 position of dihydrotremetone *via* the ketal by reaction with N-bromosuccinimide gave, after hydrolysis, 2-isopropyl-5-acetylbenzofuran (XXII). The later substance, in the form of its ketal, when treated with lead tetraacetate, gave, after hydrolysis, 2-(5′-acetyl-2′-benzofuryl)-2-propanol (XXIII). An attempt to hydroborate 2-isopropylbenzofuran did not meet with success while treatment of 2-isopropyl-2,3-dihydrobenzofuran (XXIV, R″ = H) with N-bromosuccinimide or Fenton reagent lead to attack in the aromatic ring (XXIV, R″ = Br or OH).

(9) For details of these experimental conditions, see N. Burke, Ph.D. Dissertation, Oklahoma State University, Stillwater, Okla., 1965.

A comparison of the nmr spectra of the two series of benzofuran derivatives provides some unexpected information. Thus the coupling constants for the C-2 and C-3 protons in the *cis* series (IX, X, XI, XII, XIII) are always smaller (J = 3–4 Hz) than in the *trans* (III, IV, VII, VIII) series (J = 5–6 Hz). The observed low value for $J_{2,3}$ in the *cis* isomers may be due to the stereochemical dependence of the electronegativity effect pointed out by Booth[10] for six-membered rings. Thus, in the *cis* isomers, as the C-2 and C-3 substituents bend away from each other to remove steric compression, the angle between the C-3 hydroxyl group and the C-2 proton approaches 180°, the angle of maximum electronegativity effect and minimum $J_{2,3}$. In the case of 2-alkyl-3-methyl-2,3-dihydrobenzofurans, Tarbell, *et al.*,[11] have observed that $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$ as expected. However, an isomer of 2-phenyl-3-hydroxyl-2,3-dihydrobenzofuran in which $J_{2,3}$ = 6 Hz has been assigned as *cis* relationship of the C-2 and C-3 groups.[12] Since only one isomer was obtained in the later case it is not worthwhile commenting further on this example at this time; however, it is clear that assignment of stereochemistry in systems such as 2,3-dihydrobenzofurans solely on the basis of the size of coupling constants can be misleading.

Experimental Section

Melting points were taken on a Kofler block and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., or by Dr. A. Bernhardt, Mülheim, Germany. Infrared spectra were recorded with a Perkin-Elmer Model 237B Infracord spectrophotometer and nmr spectra were recorded with a Varian A-60 spectrometer, using TMS as an internal standard (δ 0).

Preparation of 2′-Hydroxy-2,5′-dibromo-3-methylbutyrophenone (II).—*o*-Hydroxyisovalerophenone was prepared following the procedure previously described[13] for the preparation of *o*-hydroxypropiophenone. Isovalerylchloride (150 g) was added slowly to 117 g of phenol and after the evolution of hydrogen chloride ceased, the reaction mixture was heated on the steam bath for 12 hr. The crude phenyl isovalerate thus obtained was slowly added to a well-stirred suspension of aluminum chloride (184.2 g) in carbon disulfide (201 ml). After refluxing on the steam bath for 3 hr, the carbon disulfide was removed by distillation and the residue was heated with an oil bath at 170–180° for 1 hr. The solid mass was then hydrolyzed with dilute hydrochloric acid (360 ml, 1:1 concentrated HCl–water) by warming on the steam bath, then diluted with water (300 ml) and steam distilled. The steam distillate was extracted with ether; the ether extract was washed with water, dried over anhydrous $MgSO_4$, and finally concentrated. Distillation of the residue gave 162 g of *o*-hydroxyisovalerophenone (I) [bp 73° (0.4 mm); ν_{max}^{film} 3500–2900 (OH), 1637 (C=O), 1370–1170 (five strong bands, C–O stretch), 750 cm^{-1}; nmr (CCl_4) δ 0.96 (d, 6, J = 6 Hz), 2.26 (septet, 1, J = 6), 2.76 (d, 2, J = 6), 6.67–8.35 (complex pattern, integrating for four protons, identical with that observed for the four aromatic protons in *o*-hydroxyacetophenone)] which was brominated without further purification.

A typical procedure for the preparation of 2′-hydroxy-2,5′-dibromo-3-methylbutyrophenone (II) was as follows. A solution of bromine (3.1 ml) in acetic acid (40 ml) was added over a period of 1 hr with stirring to a solution of *o*-hydroxyisovalerophenone (4.9 g) in acetic acid (100 ml) cooled in ice

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water. After this stood at room temperature for 1 hr most of the acetic acid was removed by distillation at reduced pressure and the residue was poured into ice water. The solid which crystallized was collected by filtration, washed with water, dried and recrystallized from petroleum ether (bp 60–90°) to give 7.3 g of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II), mp 85–86°. Repeated recrystallization from petroleum ether (bp 30–60°) gave the analytical sample: mp 88.5–90°, ν_{max}^{Nujol} 1634, 1370–1150 (six bands), 750, 695 cm^{-1}; nmr (CCl_4) δ 1.05 (d, 3, J = 6 Hz), 1.25 (d, 3, J = 6), 4.83 (d, 1, J = 9), 6.93 (d, 1, J = 9), 7.59 (q, 1, J = 9, 2.5), 7.90 (d, 1, J = 2.5).

Anal. Calcd for $C_{11}H_{12}O_2Br_2$: C, 39.29; H, 3.57. Found: C, 39.13; H, 3.48.

The above procedure was not found to be efficient for the bromination of more than 5 g of the ketone and the following modification was used for larger quantities. To a stirred solution of *o*-hydroxyisovalerophenone (20 g) in 400 ml of acetic acid was added approximately one-half of a solution prepared by the addition of 12.4 ml of bromine to 100 ml of acetic acid over a period of 7 min. After the reddish color of bromine disappeared (about 20 min), the remainder of the bromine solution was added over a period of 15 min; the solution was allowed to stand at room temperature for 15 min, then heated for 20 min at 100°, when the initial rapid evolution of hydrogen bromide ceased. The solution was concentrated to about 300 ml under reduced pressure, then diluted with water until 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone(23.5 g) crystallized. After washing with water it gave mp 81.5–83°.

Preparation of *trans*-2-Isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III).—A solution of potassium hydroxide (4 g) in water (30 ml) was added to a suspension of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II, 10 g) in ethanol (100 ml). Sodium borohydride (1.5 g) was added to the clear solution thus obtained and the resulting solution was stirred at room temperature for 24 hr. The pale yellow solution was filtered and the filtrate was acidified with acetic acid (5 ml), then concentrated under reduced pressure and diluted with water to give shiny white crystals of *trans*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III). Recrystallization from ethanol–water gave 3.5 g, mp 106–108°. Concentration of the mother liquid gave an additional 1 g of III, which after recrystallization from ethanol–water gave 0.6 g, mp 106–108°. The analytical sample, prepared by further recrystallization from ethanol–water, gave mp 112–113°; ν_{max}^{KBr} 3340, 1605, 1475, 1245, 1185, 1062, 988, 952, 825 cm^{-1}; nmr (CD_3COCD_3) δ 1.09 (d, 3, J = 6 Hz), 1.15 (d, 3, J = 6), 3.99 (q, 1, J = 6, 10), 4.37 (d, 1, J = 6, disappears on addition of D_2O), 5.08 (t, 1, J = 6, changes to doublet on addition of D_2O), 6.68 (d, 1, J = 8.5), 7.23 (q, 1, J = 8.5, 2), 7.43 (d, 1, J = 2), the isopropyl proton appeared as an ill-defined multiplet centered about 2.2.

Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.36 H, 5.06. Found: C, 51.70; H, 5.15.

The mother liquor remaining after the removal of crystalline III was freed of volatile solvent and distilled under reduced pressure to give 2-isopropyl-5-bromobenzofuran (V) [bp 75–76° (0.075 mm); R_f 0.54 on thin layer chromatography (10 cm) on silica gel G in petroleum ether (bp 60–90°) with detection in iodine vapor]: ν_{max}^{film} 1590, 1260, 1162, 1050, 942, 795 cm^{-1}; nmr (CCl_4) δ 1.26 (d, 6, J = 6.5 Hz), 7.98 (quintuplet, 1, J = 6.5), 6.15 (d, 1, J = 1), 7.15 (d, 2, J = 1), 7.43 (t, 1, J = 1). A product of identical ir and nmr spectra and of identical R_f was obtained by refluxing III (250 mg) in benzene in the presence of a crystal of iodine for 5.5 hr followed by washing with aqueous thiosulfate and then water, drying, and evaporation of solvent. Owing to its rapid decomposition, even in a sealed tube, a satisfactory elemental analysis could not be obtained for V. However, for comparison purposes 2-isopropylbenzofuran (VI) was prepared as previously described[6] and was found to show infrared and nmr spectra very similar to that observed for V. Thus the C-3 proton in VI appeared as a sharp doublet (J = 1) centered at δ 6.0 in its nmr spectrum (neat) and the infrared spectrum of VI (film) also showed strong bands at 1590, 1260, 1162, 942 and 795 cm^{-1}; in addition both V and VI showed a characteristic pair of bands at 738 and 758 cm^{-1}.

Preparation of *trans*-2-Isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (IV).—Acetic anhydride (3 ml) was added to a solution of 0.9 g of III in 15 ml of pyridine. After standing at room temperature overnight, the usual work-up gave 0.8 g of *trans*-2-isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (IV), which after recrystallization from ethanol gave mp 90°; ν_{max}^{Nujol} 1731, 1241 cm^{-1}; nmr (CCl_4) δ 0.97 (d, 3, J = 6 Hz), 1.15 (d, 3, J = 6), 1.97 (s, 3), 4.0 (q, 1, J = 9.5, 6.0), 6.01 (d, 1, J = 6.0), 6.65 (d, 1, J = 8.5), 7.26 (q, 1, J = 8.5, 2), 7.43 (d, 1, J = 2).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.17; H, 5.02. Found: C, 52.40; H, 5.14.

Preparation of 2-Isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (VII).—To a solution of 1.03 g of III in 10 ml of ether, cooled in an ice–water bath, was added 15 ml of 0.8 *N* butyllithium in ether solution. The cooling bath was removed after 15 min and the solution was allowed to stand at room temperature for an additional 45 min, then it was poured over solid carbon dioxide. After sublimation of the excess solid carbon dioxide, the residue was taken up in excess 10% aqueous potassium hydroxide; the latter solution was filtered and the filtrate was acidified with acetic acid and then extracted with ether. The ethereal extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue crystallized from aqueous ethanol to afford 0.37 g of 2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran, mp 189–190°. Recrystallization from aqueous ethanol gave the analytical sample: mp 196–197°; ν_{max}^{Nujol} 3322, 1686 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 65.05; H, 6.29.

Preparation of *trans*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII).—To a solution of methyllithium, prepared from 0.113 g of lithium and 0.4 ml of methyl iodide in 5 ml of diethyl ether, cooled in an ice bath was added dropwise a solution of 0.2 g of VII in 15 ml of ether. The ice bath was then removed and the solution was allowed to stand at room temperature for 1.5 hr and then hydrolyzed by the cautious addition of cold water until the initially formed precipitate dissolved. After stirring for 1 additional hr the solution was extracted with ether and the ethereal extract was washed with water, 10% aqueous potassium hydroxide, water again then dried ($MgSO_4$) and evaporated. The viscous residue solidified on addition of petroleum ether (bp 30–60°) and was recrystallized from carbon tetrachloride–petroleum ether (bp 30–60°) to give 50 mg of *trans*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran, mp 104–105°. The analytical sample was prepared after two more recrystallizations from carbon tetrachloride–petroleum ether (bp 30–60°): mp 115°; ν_{max}^{Nujol} 3360, 1658 cm^{-1}; nmr (CD_3COCD_3) δ 1.13 (d, 3, J = 6.5 Hz), 1.18 (d, 3, J = 6.5), 2.52 (s, 3), 4.11 (q, 1, J = 6, 10), 5.38 (d, 1, J = 6), 6.68–8.03 (m, 3).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.79; H, 7.60.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X).—Sodium borohydride (0.44 g) was added in small portions, over a period of 20 min, to a stirred solution containing 10.2 g of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II) in 300 ml of ethanol cooled in an ice bath. The resulting colorless solution was diluted with water, acidified with a minimum amount of acetic acid and concentrated on the steam bath under reduced pressure. The cooled turbid solution was extracted with ether, the ether extract washed with dilute sodium carbonate solution and water, then dried (Na_2SO_4) and evaporated to give 9 g of an oily residue to which was added a solution prepared by adding 2.1 g of potassium hydroxide to 70 ml of ethanol. The latter solution was allowed to stand at room temperature for 2 hr, then after filtration to remove potassium bromide the filtrate was diluted with water and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate and evaporated to give 7.1 g of crude *cis*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X) as a viscous liquid. The crude X was dissolved in petroleum ether (bp 60–90°) and chromatographed on Merck acid-washed alumina, activity II. The benzene eluent gave pure X: mp 44.5–45°; ν_{max}^{Nujol} 3289, 1595, 1460, 1235, 1170, 1119, 1055–877 (nine bands; this part of the spectrum differs significantly from that of III), 816 cm^{-1}; nmr (CCl_4) δ 0.88 (d, 6, J = 6 Hz), 3.96 (q, 1, J = 4, 6), 4.20 (d, 1, J = 6.5, disappears on addition of D_2O), 4.71 (d, 1, J = 4, after addition of D_2O), 6.55 (d, 1, J = 8.5), 7.18 (q, 1, J = 8.5, 2), 7.25 (s, 1, $W_{1/2h}$ = 2 cps), the isopropyl proton appeared as a broad pentuplet centered at 1.68.

Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.36; H, 5.06. Found: C, 51.42; H, 5.30.

Preparation of *cis*-2-Isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (XI).—Crude X (7.1 g), as a viscous liquid, was dissolved in dry pyridine (150 ml) to which was added 20 ml of acetic anhydride. After standing at room temperature overnight the solution was worked up in the usual manner to give the crude acetate as a viscous liquid (8 g). Two fractionations gave the analytical sample: single spot by the tlc, R_f 0.6, ethyl acetate eluent; bp 95° (0.3 mm), 86° (0.01 mm); ν_{max}^{film} 1739, 1233 cm^{-1}; nmr (CCl_4) δ 0.92 (d, 3, J = 6.5 Hz), 0.97 (d, 3, J = 6.5), 2.0 (s, 3), 4.31 (q, 1, J = 6, 3.5), 6.01 (d, 1, J = 3.5), 6.63 (d, 1, J = 8.5), 7.26 (q, 1, J = 8.5, 2) 7.39 (d, 1, J = 2).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.17; H, 5.02. Found: C, 52.45; H, 5.02.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (XII).—To a solution containing lithium metal (2.15 g) in dry ether (50 ml) in a nitrogen atmosphere, cooled in an ice bath, was added a solution containing *n*-butyl bromide (17.2 g) in dry ether (25 ml) with vigorous stirring. When the reaction subsided (~3 hr), the ethereal solution was rapidly filtered through glass wool and to this cooled solution in a nitrogen atmosphere, a solution of XI (4.1 g) in dry ether (25 ml) was added slowly. The reaction mixture was allowed to stand at room temperature for 1.5 hr, then poured on solid carbon dioxide. After the excess carbon dioxide sublimed, the solution was extracted with 5% potassium hydroxide solution; the alkaline solution washed with ether then acidified with acetic acid. The acidic solution was extracted with ether and the ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give a viscous liquid which was taken up in benzene. Trituration with petroleum ether (bp 60–09°) gave 734 mg of crystalline *cis*-2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran which gave mp 157.5–159° after recrystallization from ethyl acetate–petroleum ether (bp 60–90°); ν_{max}^{Nujol} 3236, 1672 cm^{-1}; nmr (CD_3COCD_3) δ 1.02 (d, 6, J = 6.5 Hz), 4.33 (q, 1, J = 6, 4.5), 5.22 (d, 1, J = 4.5), 6.86 (d, 1, J = 8.5), 7.90 (d, 0.5, J = 2, this represents one-half of the C-6 quartet, the other half lies under the C-4 broad singlet), 8.05 (broad singlet, 1.5).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.54; H, 6.56.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (Racemic Dihydrotoxol, IX).—To a solution of methyllithium, prepared from lithium metal (0.25 g) and methyl iodide (1.3 ml), in ether (15 ml) cooled in an ice bath was added a solution containing 250 mg of XII in 15 ml of dry ether in the course of 15 min. After stirring for 1.5 hr water and ether were added to the solution. The ether layer was separated, washed with water, dried and evaporated to give a viscous liquid. Distillation through a long, narrow, horizontal glass tube gave mainly a dehydrated material, presumably 5-acetylbenzofuran, and then racemic *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX): bp 86–91° (0.01 mm); λ_{max}^{film} 3390, 1664 cm^{-1}; nmr (CCl_4) δ 0.98 (d, 6, J = 6 Hz), 2.35 (s, 3), 4.21 (q, 1, J = 4, 6), 4.97 (d, 1, J = 4), 6.60 (d, 1, J = 8.5), 7.62 (q, 1, J = 2, 8.5), 7.78 (d, 1, J = 2). Racemic IX was identical in infrared and nmr spectra with active IX prepared from natural toxol.

Preparation of *cis*-2-Isopropyl-3-acetoxy-5-acetyl-2,3-dihydrobenzofuran (Racemic Dihydrotoxol Acetate, XIII).—A sample of crude *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX) was converted into the acetate XIII by treatment with acetic anhydride in pyridine. The analytical sample was obtained by distillation at reduced pressure and gave bp 110° (0.05 mm); λ_{max}^{film} 1734, 1675, 1233 cm^{-1}; nmr (CCl_4) δ 0.93 (d, 3, J = 6.5 Hz), 1.0 (d, 3, J = 6.5), 2.02 (s, 3), 2.43 (s, 3), 4.43 (q, 1, J = 3.0, 6), 6.16 (d, 1, J = 3), 6.8–8.05 (three aromatic protons).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.66; H, 7.24.

Synthetic XIII was identical by ir and nmr spectra with a sample prepared from natural toxol by hydrogenation and acetylation as described above. On standing at room temperature, XIII spontaneously lost acetic acid.

Preparation of 2-Isopropyl-5-bromocoumaran-3-one (XIV) and Its Conversion into III.—2′-Hydroxy-2,5′-dibromo-3-methylbutyrophenone (II, 0.5 g) was shaken with 3 ml of diethylamine at room temperature. After 5 min the amine hydrochloride precipitated and after 15 min the reaction mixture was diluted with ether and filtered. The filtrate was washed several times with water, dried and evaporated to give a viscous yellow oil, which on distillation gave 2-isopropyl-5-bromocoumaran-3-one: bp 85° (0.01 mm); single spot by tlc, R_f 0.81, benzene eluent; ν_{max}^{film} 1720 cm^{-1}; nmr (CCl_4) δ 0.88 (d, 1, J = 6.5 Hz), 1.13 (d, 1, J = 6.5) 4.40 (d, 1, J = 4 cps), 7.03 (d, 1, J = 9.5), 7.65 (q, 1, J = 9.5, 2), 7.72 (d, 1, J = 2); mol wt (mass spectrum), 253.992 (Calcd for $C_{11}H_{11}O_2Br$, 253.994).

The 2-isopropyl-5-bromocoumaran-3-one obtained above (0.35 g) was dissolved in ethanol (4 ml) and water (1 ml) and 0.1 g of potassium hydroxide was added to this solution. The solution was cooled to ice bath temperature and sodium borohydride (0.07 g) was added. The solution was allowed to warm to room temperature overnight. On dilution with water and acidification with acetic acid 0.11 g of III identical in all respects with III obtained as previously described was obtained. The filtrate gave only unreacted XIV on extraction with ether.

Registry No.—I, 19019-21-7; II, 19019-22-8; III, 19018-84-9; IV, 19018-85-0; V, 19019-23-9; VII, 19018-86-1; VIII, 19018-87-2; IX, 19018-88-3; X, 19018-89-4; XI, 19018-90-7; XII, 19018-91-8; XIII, 19018-92-9; XIV, 19019-24-0.

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Sulfur Dioxide Extrusion from 1,3-Diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-Dioxides. A New Synthesis of 6-Phenylbenzo[*b*]phenazines[1,2]

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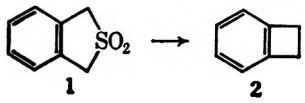
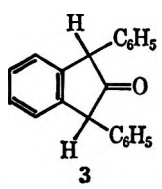
Pyrolysis of a *cis–trans* mixture of 1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**5**) produced 2,3-dibenzylquinoxaline (**12**), 6-phenylbenzo[*b*]phenazine (**13**), 3,4,7,8-tetraphenylbisquinoxalino[2,3-*a*:2′,3′-*e*]-cyclooctadiene (**14**), and 6-phenyl-5,12-dihydrobenzo[*b*]phenazine (**15**). Pyrolysis of *cis–trans* mixtures of 1-methyl- (**6**) and 1,3-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**7**) led, respectively, to 2-(α-methylbenzyl)- (**22**) and 2,3-bis(α-methylbenzyl)quinoxaline (**24**), in addition to 11-methyl-6-phenylbenzo[*b*]phenazine (**23**), obtained in both cases. Photolysis of a benzophenone-sensitized solution of **5** in dioxane produced only **12** as did sodium borohydride reduction of **5** in methanol. Alkaline hydrogen peroxide oxidation of **5** gave 2-benzyl-3-benzoylquinoxaline (**11**) while similar oxidation of **6** produced 2-(α-methylbenzyl)-3-benzoylquinoxaline (**31**). Chromic acid oxidation of **11** and **12** gave, ultimately, 2,3-dibenzoylquinoxaline (**27**); reduction of **27** under Wolff–Kishner conditions produced 1,4-diphenyl-2,3-diazaphenazine (**28**) as the major product. Sulfuric acid cyclodehydration of **11** and **31** led to **13** and **23**, respectively; similar treatment of 2-(α-bromomethyl)- (**32**) and 2-(α-hydroxybenzyl)-3-benzoylquinoxaline (**34**) gave, respectively, 11-bromo-6-phenylbenzo[*b*]phenazine (**33**) and **13**. Peracetic acid oxidation of **5** produced 2-benzyl-3-benzoylquinoxaline 1-oxide (**29**). Sodium hydrosulfite reduction of **29** led to **11**, while peracetic acid oxidation of **11** led to **29**. Similar peroxy acid oxidation of **6** gave only **31**. Sulfone **7** was unreactive to both alkaline and acid peroxide oxidation. Aromatic cyclodehydration of **29** with sulfuric acid led to 6-phenylbenzo[*b*]phenazine 12-oxide (**30**). Reduction of **30** with sodium hydrosulfite converted it into **15** which could then be oxidized to **13**; conversely, peroxy acid oxidation of **13** led only to **30**. Mechanisms for the pyrolytic, photolytic, and chemical extrusions of SO_2 from **5–7** are proposed. The condensation product between 1,3-diphenyl-2,4,5-trioxocyclopentane (**8**) and *o*-phenylenediamine was shown by nmr to exist entirely in the enol form, 1,3-diphenyl-2-hydroxy-Δ²-cyclopenta-[*b*]quinoxaline (**4b**). Methylation of **4b** gave only 1,4-dimethyl-1,3-diphenyl-4H-Δ³-cyclopenta[*b*]quinoxalin-2-one (**9**), while similar treatment of **5** led to **7** and 1,4-dimethyl-1,3-diphenyl-1,4-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**10**).

In 1959, Cava and Deana[4a] first reported that pyrolysis of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**1**) led to the extrusion of sulfur dioxide with subsequent ring closure to benzocyclobutene (**2**). Since



1 **2**



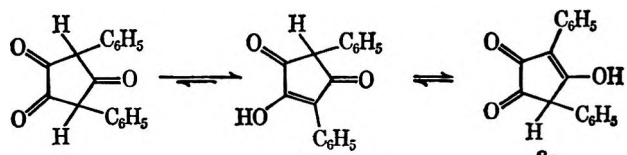
3

then, pyrolytic,[4b,c] photolytic,[4d,e] and chemical[5] eliminations of sulfur dioxide from certain benzylic sulfones have been utilized to prepare aromatic fused and/or substituted cyclobutenes.[6] The photochemical extrusion of carbon monoxide from α,α′-diphenyl cyclic ketones of type **3** provides an alternate facile entree into the cyclobutene system.[4e,7]

The reported preparation of 1,3-diphenylcyclopenta-[*b*]quinoxalin-2-one (**4a**)[8] and 1,3-diphenyl- (**5**)[9] and 1-methyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**6**)[10] provided obvious substrates for similar attempts to prepare cyclobuta[*b*]quinoxalines, three examples of which have been reported recently.[11]

This paper reports on the preparation and characterization of **4**, and the pyrolysis, photolysis, and chemical reactivity of **5**, **6**, and 1,3-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**7**).

1,3-Diphenyl-2-hydroxy-Δ²-cyclopenta[*b*]quinoxaline (4b).—The preparation reported for **4a** consisted of the condensation of the α diketone **8a**[12] with *o*-phenylenediamine.[8] The Claisen product **8a**, which was spectrally shown to exist entirely in the enol forms



8a **8b** **8c**

8b ⇌ **8c**, condensed with *o*-phenylenediamine to give a product (87%) whose melting point corresponded to

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(2) Presented before the Organic Division at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967; Abstracts of Papers, O-100.

(3) Taken entirely from the Ph.D. Theses of R. E. Misner and T. E. Brady, Fordham University, New York, N. Y., 1968.

(4) (a) M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.*, **81**, 4266 (1959); (b) M. P. Cava and R. L. Shirley, *ibid.*, **82**, 654 (1960); (c) M. P. Cava, M. J. Mitchell, and A. A. Deana, *J. Org. Chem.*, **25**, 1481 (1960); (d) M. P. Cava R. H. Schlessinger, and J. P. van Meter, *J. Amer. Chem. Soc.*, **86**, 3173 (1964); (e) M. P. Cava and D. Mangold, *Tetrahedron Lett.*, 1751 (1964).

(5) R. M. Dodson and A. G. Zielski, *Chem. Commun.*, 353 (1965).

(6) In the case of 2,4-diphenylthietane dioxides, pyrolysis has led to 1,2-diphenylcyclopropanes [R. M. Dodson and A. Klose, *Chem. Ind.* (London), 450, 1203 (1963)].

(7) G. Quinkert, K. Opitz, W. W. Wiersdorff, and J. Weinlick, *Tetrahedron Lett.*, 1863 (1963).

(8) G. C. Chakravarti, *Quart. J. Indian Chem. Soc.*, **2**, 71 (1925).

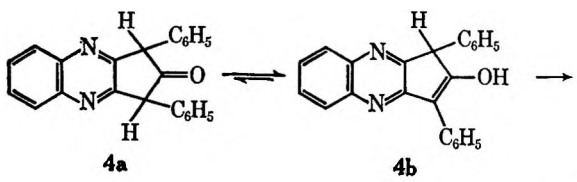
(9) C. G. Overberger, S. P. Lightheln, and E. A. Swire, *J. Amer. Chem. Soc.*, **72**, 2857 (1950).

(10) C. G. Overberger and J. M. Hoyt, *ibid.*, **73**, 3957 (1951).

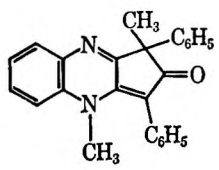
(11) (a) A. Fujuno, J. Kusuda, and T. Sakan, *Bull. Chem. Soc. Jap.*, **39** (1), 160 (1966); *Chem. Abstr.*, **64**, 12559*f* (1966); (b) W. Ried and W. Kunstmann, *Angew. Chem.*, **80**, 121 (1968); (c) S. Skujins and G. A. Webb, *Chem. Commun.*, 598 (1968). See also T. H. Markgraf and W. L. Scott, *ibid.*, 297 (1967), for a cyclobuta[*b*]quinoline.

(12) L. Claisen and T. Ewan, *Ann.*, **284**, 250 (1895).

that reported by Chakravarti.[8] This condensation product showed no carbonyl absorption in the ir, and its nmr spectrum displayed three peaks at δ 12.21 (broad singlet, 1, OH), 8.00–7.25 (m, 14, aromatic), and 4.40 (s, 1, CH). Clearly, this quinoxaline derivative existed entirely as the enol **4b**. Pyrolysis and photolysis of **4b** led only to recovery of starting material. Treatment of **4b** with potassium *t*-butoxide and methyl iodide led only to the isolation of 1,4-dimethyl-



4a **4b**



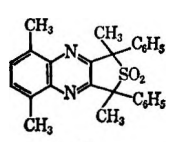
9

1,3-diphenyl-4H-Δ^3-cyclopenta[*b*]quinoxalin-2-one (**9**), in 30% yield.

Preparation and Pyrolysis of 5, 6, and 7 (Scheme I).— Sulfones **5** (as a *cis–trans* mixture,[13] 93%) and **6** (87%) were prepared by the procedures of Overberger and coworkers,[9,10] *via* the condensation of *o*-phenylenediamine and the appropriate α diketone, 2,5-diphenyl- and 2-methyl-2,5-diphenyl-3-keto-4-hydroxy-2,3-dihydrothiophene 1,1-dioxide, respectively. Treatment of **5** with potassium *t*-butoxide and excess methyl iodide led to **7** (as an inseparable 35:65 *cis–trans* mixture,[14] 16%), in addition to 1,4-dimethyl-1,3-diphenyl-1,4-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**10**, 40%)[15,16] and 2-benzyl-3-benzoylquinoxaline (**11**, 3%).[16]

(13) Based on analogy to **7** whose nmr[14] clearly establishes its *cis–trans* nature. Sulfone **5** was too insoluble for such analysis.

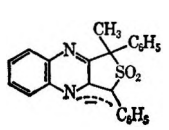
(14) Nmr ($CDCl_3$): δ 8.05 (m, 4, aromatic), 7.20 (*trans*) and 7.07 (*cis*) (each s, total 10, C_6H_5, area ratio 35:65 *cis–trans*), and 2.24 (*cis*) and 2.12 (*trans*) (each s, total 6, CH_3, area ratio 35:65 *cis–trans*). In the *trans* isomer, the protons of each methyl group are in the shielding region of a phenyl substituent, while, in the *cis* isomer, each phenyl group shields the other. In only one case, 1,3,5,8-tetramethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (i) have we been able to partially separate the *trans* isomer from the mixture.



i

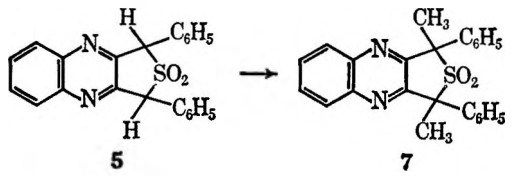
(15) In both **9** and **10**, the NCH_3 protons appeared as a singlet downfield relative to the CCH_3 by 1.42 and 0.84 ppm, respectively.

(16) The formation of both **7** and **10** can be accounted for by the further methylation of the delocalized anion ii formed initially from **6**.

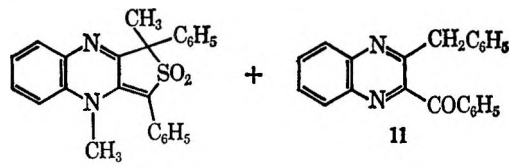


ii

In the presence of 1 equiv of KO-*t*-Bu and CH_3I and using a short reaction time, **6** was isolated. Further methylation of **6** converted it into the mixture of **7** and 10. Quinoxaline **11** was not obtained when the reaction was run under nitrogen. It must therefore be a product of the air oxidation of **5**.



5 **7**



10 **11**

Pyrolysis of **5** under a variety of conditions (Table I) produced the known 2,3-dibenzylquinoxaline (**12**),[17] 6-phenylbenzo[*b*]phenazine (**13**), 3,4,7,8-tetraphenylbisquinoxalino[2,3-*a*:2′,3′-*e*]cyclooctadiene (**14**), and, in one instance, 6-phenyl-5,12-dihydrobenzo[*b*]phenazine (**15**).[18]

TABLE I

PYROLYSIS OF 5

Matrix	Reaction temp, °C	Products, % yield 12	13	14	15
Ethylene glycol	180	14	32		
Diethylene glycol	240	8	32		
Dimethyl phthalate	260		30	6	
Triethylene glycol	280	5	6		27
$NaHCO_3$[a]	550		22	27	

[a] Solid–solid reaction.

The 6-phenylbenzo[*b*]phenazine (**13**) [$\lambda_{max}^{95\%EtOH}$ 210 mμ (ϵ 20,000), 252 (27,000), and 285 (83,000)] was obtained as a brilliant red crystalline material whose most striking spectral feature was the display of a deshielded proton on C-11 appearing as a singlet at δ 8.95.[19] Further, the small but perceptible conjugative effect in the uv relative to **16**[19] suggests a considerably nonplanar conformation of the C-6 phenyl substituent. Ultimately, **13** was independently prepared by the sulfuric acid catalyzed aromatic cyclodehydration of 2-benzyl-3-benzoylquinoxaline (**11**) (*vide infra*).

The formation of dimers under pyrolytic conditions is precedented,[4a,20a] and the structure of **14** was based, *inter alia*, on a molecular weight, and an nmr spectrum which showed a 4 H singlet at δ 5.56 and a complex aromatic multiplet (8.20–7.20) in the ratio of 1:7, respectively.[20b] In the uv, the bathochromic shift (50 mμ) of dimer **14** compared with that of **12** suggests a tub form (**14a**) which would allow considerable overlap of the π electrons of the aromatic nuclei.[20a] All

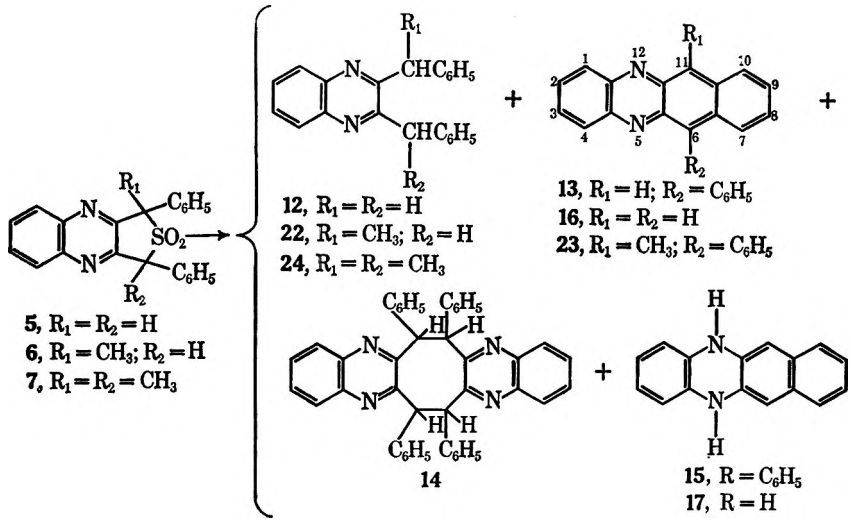
(17) P. Ruggli and P. Zeller, *Helv. Chim. Acta*, **28**, 741 (1945).

(18) Under all conditions reported in Table I, polymeric and tarry products (40–50%) were obtained. In the solid reaction with sodium bicarbonate, thin layer chromatography (tlc) indicated the presence of at least 17 different products, only two of which (**13** and **14**) could be identified.

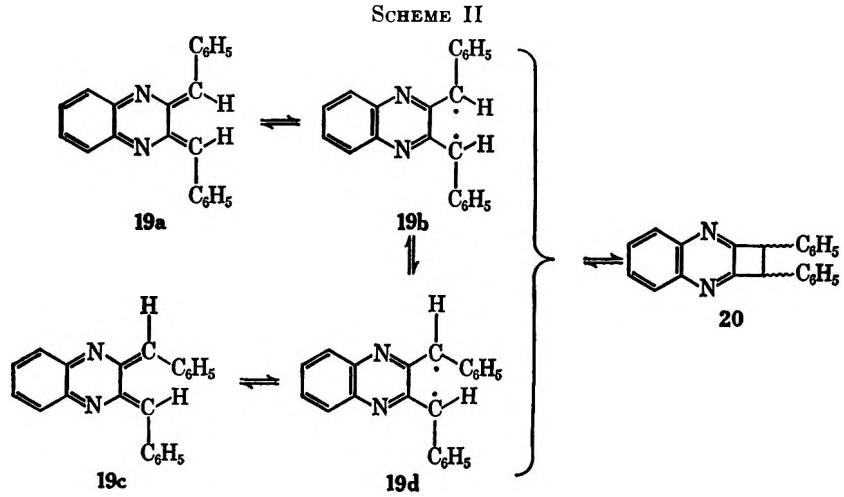
(19) Benzo[*b*]phenazine (**16**) prepared by the procedure of G. Hinsberg [*Ann.*, **319**, 257 (1901)] showed a $\lambda_{max}^{95\%EtOH}$ 210 mμ (ϵ 13,000), 250 (25,000), and 281 (80,000); $\delta_{TMS}^{DMSO\text{-}d_6}$ 8.89 (s, 2, C-6, 11 hydrogens) as well as 8.40–7.72 (m, 8, aromatic).

(20) (a) J. K. Stille and R. T. Foster, *J. Org. Chem.*, **28**, 2708 (1963). (b) Dimer **14** contains four asymmetric C atoms. The product obtained must be a mixture of isomers.

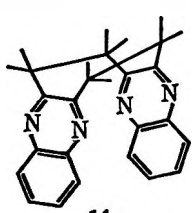
SCHEME I



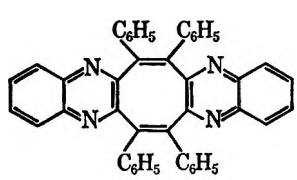
SCHEME II



attempts to oxidize **14** to the extremely crowded cyclooctatetraene derivative **18** were unsuccessful.



14a



18

The light green pyrolysis product **15** was identical with that obtained *via* the catalytic reduction of **13** over Pd–C.[21] Dihydro derivative **15** is unstable in both solid state and solution and is rapidly air oxidized to **13**.

The Woodward–Hoffmann rules predict that pyrolysis of a *cis–trans* **5** mixture would lead to a concerted disrotatory process[22a,b] to the isomeric *o*-quinodimethanes **19a** and **19c**,[4a–c,22c] or to the diradicals **19b** and **19d** (depending on the multiplicity of the excited state), either or both of which are in equilibrium with the thermally labile quinoxaline[2,3-*c*]cyclobutene (**20**) (Scheme II). Although these primary pyrolysis intermediates could not be trapped,[23] **12**, **13**, and **14** can be explained as rational transformation products of the very reactive **19**. Thus hydrogen abstraction from solvent (or **5**) would yield **12**, dimerization would lead to **14**, and a precedented[4c,24,25–27] intramolecular cyclization[28] of **19c** would produce **13** *via* the allyl isomers **21a** ⇌ **21b**.[29] The suggestion that **12** and **14** arise from the common intermediate **19** is consistent with the formation of **12** only in protic media and **14** only in

(21) Its nmr spectrum also displayed the C-11 proton singlet at δ 8.68. The uv spectrum of freshly prepared, blue-fluorescent **15** [$\lambda_{max}^{95\%EtOH}$ 247 mμ (ε 14,000), 280 sh (18,000), and 288 (28,000)] compared favorably with that of the blue-fluorescent 5,12-dihydrobenzo[*b*] phenazine (**17**) [$\lambda_{max}^{95\%EtOH}$ 248 mμ (ε 17,000), 283 (33,000), and 286 sh (31,000)] prepared *via* Hinsberg's procedure.[19] Unlike **15**, however, the dihydro derivative **17** is very stable and its reoxidation to **16** can only be effected with sodium dichromate in acetic acid.[16]

(22) (a) W. L. Mock, *J. Amer. Chem. Soc.*, **88**, 2857 (1966); (b) S. G. McGregor and D. A. Lemal, *ibid.*, **88**, 2858 (1966); (c) M. P. Cava, R. L. Shirley, and B. W. Erickson, *J. Org. Chem.*, **27**, 755 (1962).

(23) By thermolysis of **5** in the presence of dienophilic scavengers, 1,4-naphthoquinone and 1,3-diphenylisobenzofuran.

(24) F. R. Jensen and W. E. Coleman, *J. Amer. Chem. Soc.*, **80**, 6149 (1958).

(25) H. Kloosterziel and H. J. Backer, *Rec. Trav. Chim.*, **71**, 1235 (1951).

(26) G. Wittig and M. Leo, *Chem. Ber.*, **648**, 2395 (1931).

(27) H. Staudinger and F. Pfenninger, *ibid.*, **49**, 1941 (1916).

(28) This concerted process would relieve the severe steric interaction between the phenyl and vinyl hydrogens as suggested by models.

(29) A possible alternate route to **13** is the formation of carbanion iii (thermally or in the presence of even a weak base) from **5** followed by intramolecular nucleophilic displacement of the SO_2 [*cf.* H. Drews and E. K. Fields, *Chem. Ind.* (London), 143 (1961)].

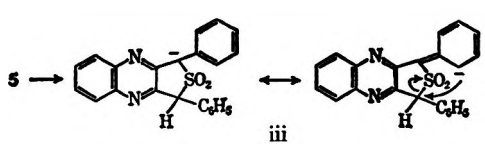
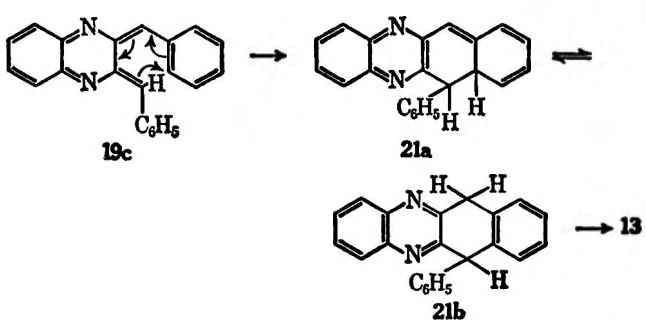


TABLE II

MASS SPECTRUM OF 5[a]

m/e	Peak height, arbitrary scale divisions	Relative intensity	Our spectrum of SO_2
47	0		
48	131	70.0	69.0
49	3		
50	18		
51	37		
63	15		
64	187	100.0	100.0
65	6		
66	10		
101	9		
101 − ⅓	5		
101 − ⅔	7		
102	15	3.1	Triply charged ions
102 − ⅓	3		
102 − ⅔	3		
103	5		
152 − ½	138		
153	141	29.2	Doubly charged ions
153 − ½	56		
154	60		
154 − ½	14		
305	427	88.4	
306	483	100.0	
307	190	39.3	
308	442	91.5	
309	124	25.7	
310	29	6.0	
311	6	1.2	
338	7	1.4	
Low-voltage measurements[b]			
305	37	2.2	
306	1648	100.0	
307	443	26.9	
308	1484	90.0	
309	378	22.9	
310	97	5.9	
311	17	1.0	
338	26	1.6	

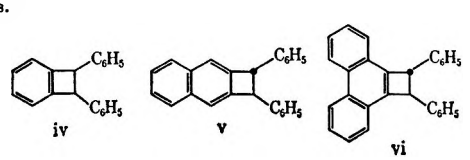
[a] See ref 32. [b] Ionizing voltage = 7.5 V, uncorrected.



dimethyl phthalate and the solid-state fusion with sodium bicarbonate (Table I). Like its benzene[4c] and naphthalene[4d] analogs, the effective pyrolysis temperature of sulfone **5** must be higher than the temperature at which the thermally labile **20** must rearrange to secondary pyrolysis products.[30] Finally, since **15** was not obtained at the lower pyrolysis temperature, its formation seems to be an oxidation–reduction[31] reaction involving **15**, unreacted **5** and/or SO_2, and/or the glycol matrix.

The mass spectrum of **5**[32] (Table II), showed no trace at *m/e* 372 corresponding to its molecular weight. By far the strongest peaks in the spectrum occur in the mass region 305 to 310. At low voltage, intensities at *m/e* 305 and 307 drop, but intensity distribution over *m/e* 306, 308, 310, and 338 remain essentially constant, and the peaks at *m/e* 306 and 308 stand out prominently over all others. Moreover, the second most intense group of peaks in the 70-V spectrum corresponds to doubly charged ions of masses 305 to 309, and the spectrum shows a group of peaks, though considerably less intense, corresponding to triply charged ions of masses 304 to 308. Evidently, the major components contributing to the spectrum are highly stable, radiation-resistant species of masses 306 and 308. The *m/e* 308 peak can be ascribed to **20**, or **21a** ⇌ **21b**, while the peak at *m/e* 306 must be due to **13**. The small peak at *m/e* 310 can be assigned to **12**. Thus **5**

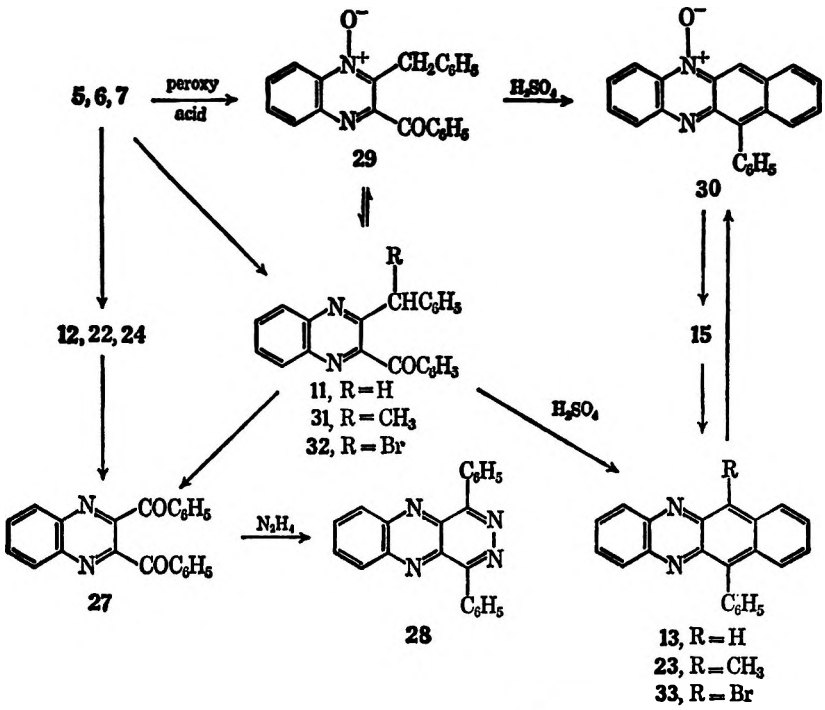
(30) Thus, iv,[4c,24] v,[4d] and vi,[4e] independently prepared, thermally rearrange to their respective dihydroanthracene, -naphthacene, and -dibenz[*a*,*c*]anthracene derivatives.



(31) Only in this pyrolysis was hydrogen sulfide evolved.

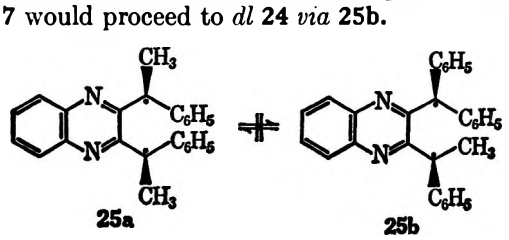
(32) We are grateful to Mr. Seymour Meyerson and Dr. Ellis K. Fields for determining the mass spectrum of **5** and its interpretation.

SCHEME III



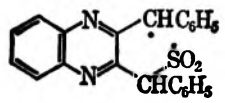
must have decomposed thermally in the inlet system (temperature 325°, pressure 20–50 μ Hg). The view that the mass spectrum is due to thermolysis products gains additional support from prominent peaks at masses **48** and **64**, standing out prominently above neighboring peaks and almost certainly due to SO_2.[32,33]

Pyrolysis of **6** and **7** at 180° for 3–4 hr led only to recovery of starting material. At 240°, however, **6** gave 2-(α-methylbenzyl)-3-benzylquinoxaline (**22**, 12%) and 11-methyl-6-phenylbenzo[*b*]phenazine (**23**, 22%) with a 38% recovery of unreacted **6**. At 280°, **7** (35:65 *cis–trans* mixture) led to **23** (4%) and an inseparable 38:62 *meso–dl* mixture of 2,3-bis(α-methylbenzyl)quinoxaline (**24**, 14%), with a 32% recovery of unreacted **7**. The conversion **7** → **24** seems to be very nearly stereospecific; *i.e.*, the ratio of diastereoisomers in the product mixture **24** is very nearly equal to the ratio of geometric isomers in reactant mixture **7**. This suggests that intermediates **25a** and **25b** once formed do not interconvert, and that hydrogen addition to these diradicals must occur in the same manner. Thus, *cis* **7** would lead to *meso* **24** *via* planar **25a** while *trans* **7** would proceed to *dl* **24** *via* **25b**.



25a **25b**

Photolysis of 5.—A benzophenone-sensitized solution of **5** in dioxane was irradiated, under nitrogen, with a 125-W Hanovia medium pressure Hg arc for 48 hr. Evaporation of the solvent followed by chromatography of the residue over alumina led only to **12** (23%) and considerable amounts of tars. Assuming the photolytic process to occur *via* homolytic cleavage of the C–S bond,[4d,34] the initially formed **26** would then lose SO_2 to form a **19b–19d** mixture. Hydrogen abstractions from solvent by these biradicals to form **12** must proceed at a



26

rate greater than all other processes of dimerization and intramolecular cyclization. The insolubility of **5** in most organic solvents precluded any significant solvent study.[13]

Chemical Reactivity of 5, 6, and 7 (Scheme III).—Treatment of a suspension of **5** in ethanol with equimolar amounts of hydrogen peroxide and sodium hydroxide resulted in a vigorous reaction from which **11** was isolated in 85% yield. The monomethyl derivative **6** underwent a similar reaction to give 2-(α-methylbenzyl)-3-benzoylquinoxaline (**31**, 69%) while **7** did not react. The unprecedented reduction of **5** with sodium borohydride in methanol gave **12** (74%)[35] while **6** led to **22** (29%). Oxidation of **12** and **11** with excess chromic acid converted each into 2,3-dibenzoylquinoxaline (**27**) (80 and 93%, respectively), while a limited amount of oxidant converted **12** into **11** and **27**. Selenium dioxide in dioxane also oxidized **11** to **27** (52%). Reduction of **27** in ethylene glycol with 85% hydrazine hydrate and sodium hydroxide led to both the Wolff–Kishner product **12** (2%) and 1,4-diphenyl-2,3-diazaphenazine (**28**, 43%).[36] The latter condensation

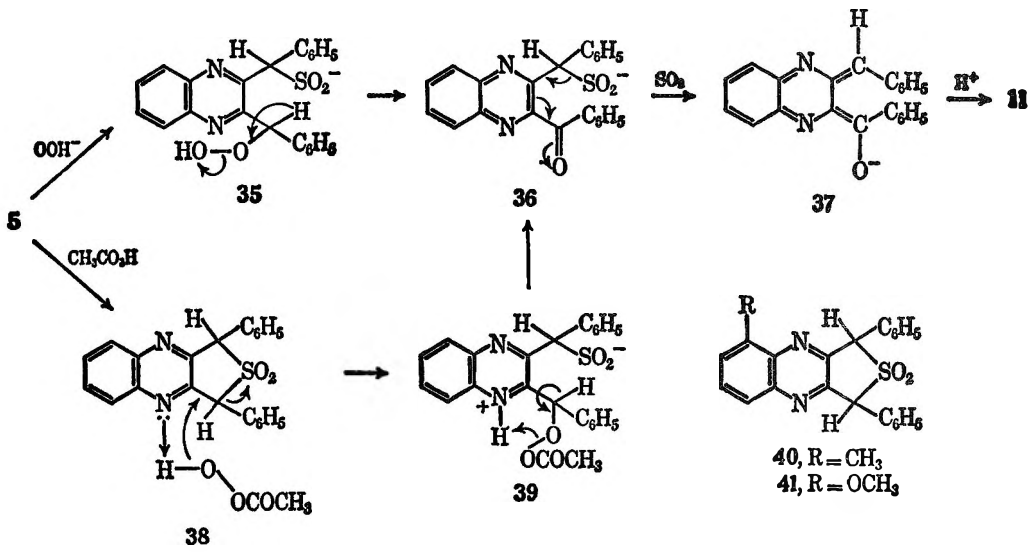
(33) Generally, if SO_2 is lost in an ionic process under electron impact, it does not take the charge and therefore it is not observed directly in the spectrum.

(34) P. B. Asycough, K. J. Ivin, and J. H. O'Donnell, *Trans. Faraday Soc.*, **61**, 1110 (1965).

(35) Equilibration studies using CH_3OD and $NaOCH_3$ (followed by D_2O hydrolysis) and reductions with $NaBH_4$ in CH_3OD and $NaBD_4$ in CH_3OH suggest initial hydride attack on **5**, followed by SO_2 extrusion, and proton abstraction to give **12**. Reduction of **5** with ω-Raney nickel led to **12** in 48% yield.

(36) This seems to be the first authentic example of the 2,3-diazaphenazine system: *cf.* J. Wegler, *J. Prakt. Chem.*, **148**, 135 (1935). In the absence of sodium hydroxide, the yield of **28** rose to 73%, while none of **12** was isolated. After this work was completed, M. J. Haddadin and C. H. Issidorides [*Tetrahedron Lett.*, 4609 (1968)] communicated the isolation of 1-phenyl-2,3-diazaphenazine.

SCHEME IV



product is thermally stable and resistant to further oxidation and reduction.

Aromatic cyclodehydration[37,38] of **11** with concentrated sulfuric acid led to **13** (85%) after heating for 5 min on a steam bath. This synthetic route to 6-phenylbenzo[*b*]phenazines using concentrated sulfuric acid or polyphosphoric acid seems to be a general one.[39] Thus, **31**, 2-(α-bromomethyl)-3-benzoylquinoxaline (**32**),[40] and 2-(α-hydroxybenzyl)-2-benzylquinoxaline (**34**)[41] led, respectively, to **23** (78%), 11-bromo-6-phenylbenzo[*b*]phenazine (**33**, 84%), and **13** (62%).

Treatment of **5** in chloroform with 2 equiv of peroxy acid (*m*-chloroperbenzoic acid, peracetic acid, or hydrogen peroxide in acetic acid) also resulted in the extrusion of SO_2 to give ultimately 2-benzyl-3-benzoylquinoxaline 1-oxide (**29**, 32–47%). With 1 equiv of peroxy acid, **29** (30%) was also obtained, together with 45% unreacted **5**. When the oxidation was quenched before reaction was complete, both **11** and **29** were isolated, suggesting that **11** was the precursor of **29** after the oxidative extrusion of SO_2. Both were interrelated by oxidation of **11** with peracetic acid to **29** (76%), while the reduction of **29** with sodium hydrosulfite[42] led to **11**. Although peracetic acid oxidation converted **6** into **31** (60%), the reaction must be sensitive to steric influences, since **7** was recovered unchanged under identical oxidative conditions.

The site of the N-oxide function in **29** was based on its cyclodehydration with concentrated sulfuric acid to 6-phenylbenzo[*b*]phenazine 12-oxide (**30**) in 66% yield. The C-1 and C-11 hydrogens, *peri* to the N-oxide function, now show the expected deshielding[43] (δ 8.66 m and 9.35 s, respectively), the latter appearing even further downfield than the C-11 hydrogen in **13**. Reduction of **30** with sodium hydrosulfite converted it into **15** (75%) which could then be oxidized to **13**; conversely, peroxy acid oxidation of **13** led only to **30** (67%).

Reaction Mechanism (Scheme IV).—Alkaline hydrogen peroxide extrusion of SO_2 from **5** and **6** can be depicted simply as occurring with initial nucleophilic attack on the α carbon by the perhydroxyl anion to give the hydroperoxide **35**.[44] Attack of base on the α hydrogen of this allyl hydroperoxide **35** results in the formation of ketone **36**,[45] enolization of which facilitates the loss of SO_2 to form **37**.[46] Regeneration of the ketonic moiety accompanied by proton addition would lead finally to **11**. The intermediacy of the perhydroxyl anion dictates an indiscriminate attack on both α carbons in sulfone **5**, and this has been observed with both 5-methyl- (**40**) and 5-methoxy-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (**41**) to give two ketones in each case.[47]

In the presence of peracetic acid, oxidative extrusion from **5** to **6** is believed to commence with coordination of the peroxy acid molecule with the nitrogen (as in **38**). Transfer of the NH proton to the acetate anion leaving group (**39**) would then proceed *via* **36** → **37**, to **11**, further peroxidation of which would lead to the observed product **29**. Since attack on **6** by OOH^- and peroxy acid occurs only at the less hindered side to give **31**, the sterically hindered α carbons in **7** consequently are unresponsive to both the nucleophilic and electrophilic oxidants. In the case of oxidation product **31** (from **6**), the combined steric effect on one side and electron-withdrawing influence of the $-COC_6H_5$ substituent on the other prevent further peroxidation at either nitrogen.[48]

Finally, bromination of **12** in carbon tetrachloride with 2 equiv of NBS gave a 63% mixture of *meso*- and *dl*-2,3-bis(α-bromobenzyl)quinoxaline (**42**). A Finkelstein reaction (sodium iodide in acetone) on **42** was un-

(37) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

(38) F. A. Vingiello and J. R. Thornton, *J. Org. Chem.*, **31**, 659 (1966).

(39) The remarkably few benzo[*b*]phenazines available (G. A. Swan and D. G. I. Felton in "The Chemistry of Heterocyclic Compounds," Vol. II, A. Weissberger Ed., Interscience, New York, N. Y. 1957, pp 213–216) have all been prepared by condensation of the appropriate naphthalene derivative with *o*-phenylenediamine.

(40) Prepared in 48% yield by bromination of **11** in CCl_4 with NBS under irradiation with a high intensity lamp.

(41) Prepared in 75% yield by sodium borohydride reduction of **11** in the presence of sodium hydroxide.

(42) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Amer. Chem. Soc.*, **80**, 3009 (1958).

(43) Y. Morita, *Chem. Pharm. Bull. Tokyo*, **14**, 419 (1966).

(44) J. O. Edwards, "Peroxide Reaction Mechanisms," Interscience, New York, N. Y., 1962, pp 11–28.

(45) H. G. Davies, "Organic Peroxides," Butterworth, London, 1961, Chapter 13.

(46) This is somewhat analogous to the decarboxylation of β-keto acids.

(47) E. J. Moriconi, T. E. Brady, and R. E. Misner, unpublished work.

successful in converting it into a cyclobutene derivative, as was treatment of **34** with dicyclohexylcarbodiimide.

Experimental Section[49]

1,3-Diphenyl-2-hydroxy-Δ^2-cyclopenta[*b*]quinoxaline (4b) was prepared in 89% yield by Chakravarti's procedure:[8] mp 253–254° (lit.[8] mp 253°); ir (KBr) 6.10 μ (enol C=C); uv max (95% EtOH) 224 mμ (ϵ 22,000), 266 (13,400), 310 (11,600), and 325 (10,000); nmr (DMSO-d_6) δ 12.21 (broad singlet, 1, OH), *ca.* 8.00–7.25 (m, 14, aromatic), and 4.40 (s, 1, CH).

Preparation of 1,4-Dimethyl-1,3-diphenyl-4H-Δ^3-cyclopenta[*b*]quinoxaline-2-one (9).—Potassium *t*-butoxide (0.80 g, 7.1 mmol) was added to a suspension of **4b** (1 g, 2.98 mmol) in 50 ml of dry *t*-BuOH and the whole was refluxed for 1 hr and then cooled to ambient temperature. A solution of 3 ml (5.1 g, 0.036 mol) of CH_3I in 10 ml of *t*-BuOH was added and the solution was refluxed for an additional 2 hr. The green solution was cooled, added to 200 ml of ice, and then extracted with two 100-ml portions of ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to a yellow-green oil. The oil was dissolved in 5 ml of CH_2Cl_2 and deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I). The column was eluted with 1 l. of ether. The ether was evaporated *in vacuo* to yield 0.32 g (30%) of **9** as yellow-green needles: mp 177–178° (from CH_3OH); ir (KBr) 6.00 μ (C=O); uv max (95% EtOH) 222 mμ (ϵ 21,500), 226 (22,000), 263 (10,200), 306 (10,000), and 323 (8700); nmr ($CDCl_3$) δ 7.85–7.20 (m, 14, aromatic), 3.25 (s, 3, NCH_3), and 1.83 (s, 3, CCH_3).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69; mol wt, 364. Found: C, 82.26; H, 5.37; N, 7.92; mol wt. 355 (isothermal distillation).

1,3-Diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (5) was prepared in 93% yield by the procedure of Overberger, Lightheln, and Swire:[9] darkened at 220° with decomposition between 243 and 254°; ir (KBr) 7.50, 8.56, and 8.95 μ (SO_2); uv (95% EtOH) 222 mμ (ϵ 37,000), 240 (36,000), 297 (10,800), and 327 (8300).

Anal. Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.94; H, 4.33. Found: C, 70.97; H, 4.35.

1,3-Diphenyl-1-methyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (6) was prepared in 87% yield by the procedure of Overberger and Hoyt:[10] mp 206–207° (lit.[10] mp 206–207°); ir (KBr) 7.52, 8.80, and 8.85 μ (SO_2); uv max (95% EtOH) 241 mμ (ϵ 34,000) and 324 (7200); nmr ($CDCl_3$) δ 8.17 (A_2B_2 multiplet, 4, quinoxaline), 7.52 (s, 10, C_6H_5), 5.72 (s, 1, CH), and 2.38 (s, 3, CH_3).

Reaction of 5 with KO-*t*-Bu and CH_3I.—KO-*t*-Bu (1.5 g, 13.4 mmol) was added in one portion to 2.0 g (5.4 mmol) of **5** suspended in 50 ml of dry *t*-BuOH (distilled over potassium). The suspension was refluxed until a dark red homogeneous solution was obtained. The solution was cooled to room temperature and an excess of CH_3I (5 ml, 8.5 g, 0.06 mol) in 10 ml of dry *t*-BuOH was added dropwise (10 min) to the stirred solution. The solution was then refluxed for an additional 2 hr. On heating, the dark red colored solution initially darkened and then lightened to a yellow solution, at which time a highly fluorescent yellow solid became visible. The mixture was cooled and added to 200 ml of an ice–water mixture and the whole treated with two 100-ml portions of ether. Each time, the bright yellow insoluble solid which formed between the two layers was filtered to yield a total of 0.92 g (40%) of crude **1,4-dimethyl-1,3-diphenyl-1,4-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxide (10)** as brilliant yellow plates: mp 236–236.5° (from CH_3OH; Norit); ir (KBr) 7.82, 7.90, and 8.82 μ (SO_2); uv max (95% EtOH) 219 mμ (ϵ 37,000), 245 (53,000), and 327 (13,000); nmr ($CDCl_3$) δ 7.70–6.90 (m, 14, aromatic), 3.06 (s, 3, NCH_3), and 2.22 (s, 3, CCH_3).

Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.97; H, 5.03; N, 6.99; mol wt, 400. Found: C, 72.19; H, 5.00; N, 7.20; mol wt, 410 (Rast).

The two layer filtrates were separated and the combined ether layers were washed successively with 100 ml of H_2O, 100 ml of 10% HCl, and 100 ml of H_2O. The ether solution was dried (Na_2SO_4), and evaporated to a dark orange oil which was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I). Elution with hexane produced a small amount of a tan solid, identified as **2-benzyl-3-benzoylquinoxaline (11,** 0.05 g, 3%), mp 96–97° (*vide infra*). Continued elution with 1:1 hexane–ether resulted in the isolation of 0.35 g (16%) of an inseparable mixture of *cis*- and *trans*-**1,3-dimethyl-1,3-diphenyl-1,3-dihydrothieno[3,4-*b*]quinoxaline 2,2-dioxides (7):** mp 200–204°; ir (KBr) 7.63, 8.70 and 8.75 μ (SO_2); uv (95% EtOH) 241 mμ (ϵ 30,500) and 325 (7600).

Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99; mol wt, 400. Found: C, 72.06; H, 5.11; N, 7.14; mol wt, 384 (isothermal distillation).

Pyrolysis of 5–$NaHCO_3$ Mixture.—A mixture (mortar and pestle) of **5** (1 g. 2.7 mmol) and 5.0 g of anhydrous $NaHCO_3$ was heated in an open evaporating dish over a Bunsen flame until it turned deep red (*ca.* 5 min, slight charring). The solid pyrolysate was then extracted with 200 ml of CH_2Cl_2 (Soxhlet) until further washings were colorless. The extract was evaporated *in vacuo* and the residue was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I). The column was eluted successively with 1:1 CCl_4–CH_2Cl_2, and CH_2Cl_2, each elution being continued until the eluent became colorless.

1:1 CCl_4–CH_2Cl_2 Fraction.—Evaporation of the eluate *in vacuo* led to a dark red tarry residue, shown by tlc to contain one major and five minor components. Chromatography of the residue on a 2.5 × 25 cm column of Florisil (60–200 mesh) with 1:4 CH_2Cl_2–CCl_4 led to ten 100-ml fractions. Fractions 4–8 were combined, reduced in volume to 10 ml (steam bath), and rechromatographed on Florisil (eluent, CCl_4) to give ultimately 0.206 g (27%) of **1,2,5,6-bis(2,3-quinoxalino)-3,4,7,8-tetraphenylcyclooctadiene (14):** softened at 190°, mp 203–205°; uv max (95% EtOH) 254 mμ (ϵ 14,000) and 288 (48,500); nmr ($CDCl_3$) δ 8.40–7.00 (m, 28, aromatic) and 5.56 (s, 4, CH).

Anal. Calcd for $C_{44}H_{32}N_4$: C, 85.68; H, 5.23; N, 9.08; mol wt, 612. Found: C, 85.42; H, 5.45; N, 9.13; mol wt, 582 (isothermal distillation).

CH_2Cl_2 Fraction.—Evaporation of the eluate *in vacuo* led to 0.19 g (22%) of crude **6-phenylbenzo[*b*]phenazine (13).** One recrystallization from 1,2-dichloroethane gave pure **13** as tiny red needles: mp 254–255°; nmr[50] ($CDCl_3$) δ 8.95 (s, 1, C-11 hydrogen), 8.30–7.40 (m, 8, aromatic), and 7.60 (s, 5, C_6H_5).

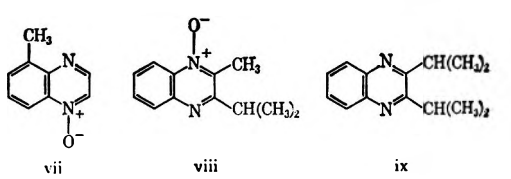
Anal. Calcd for $C_{22}H_{14}N_2$: C, 86.25; H, 4.61; N, 9.15; mol wt, 306. Found: C, 86.29; H, 4.56; N, 9.15; mol wt, 306 (*m/e*), 300 (Rast).

Pyrolysis of 5 in Solution.—One gram (2.7 mmol) of **5** suspended in 30 ml of ethylene glycol was refluxed for 2 hr at 200° (Wood's metal bath). On heating, the solid dissolved slowly and the entire solution turned a deep red. The glycol solution was cooled and added to 50 ml of water. The resultant brown solid was filtered, dried, and deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I) with 5 ml of CH_2Cl_2. Elution of the column with 1:1 pentane–ether produced two colored fractions, one pink (250 ml) and the second orange (200 ml). On evaporation of the eluate (Rinco), the pink fraction yielded 0.11 g (14%) of **2,3-dibenzylquinoxaline (12)** as long white needles: mp 118–118.5° (from hexane, Norit) (lit.[17] mp 117–118°); uv max (95% EtOH) 239 mμ (ϵ 37,000), 294 sh (9500), and 320 (17,000); nmr (CCl_4) δ 8.20–7.50 (m, 4, quinoxaline), 7.20 (s, 10, C_6H_5), and 4.29 (s, 4, CH_2).

Evaporation of the orange fraction (Rinco) gave 0.27 g (32%) of **13.**

The pyrolysis of **5** (2 g, 5.4 mmol) suspended in 25 ml of tri-

(48) Thus, *e.g.*, 5-methyl- and 2-methyl-3-isopropylquinoxaline form only the N-oxides vii and viii, respectively, while 2,3-diisopropylquinoxaline (ix)



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is recovered unchanged from peroxy acid [J. K. Landquist, *J. Chem. Soc.*, 2816 (1953); J. K. Landquist and G. J. Stacey, *ibid.*, 2822 (1953)]. In addition, **27** did not form an N-oxide with peroxy acids.

(49) (a) Melting points were determined on a Koffler hot-stage melting point apparatus and are corrected; (b) the ir spectra were recorded on a Model 337 Perkin-Elmer grating spectrophotometer; (c) the uv spectra were recorded on a Cary 15 dual-beam recording spectrophotometer; (d) unless otherwise stated, the nmr spectra were obtained on a Varian Associates Model A-60 spectrometer using dilute (*ca.* 100 mg/ml) solutions, and chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane.

(50) We are grateful to Leroy F. Johnson, Varian Associates, for obtaining the 100-Mc nmr spectrum of this compound.

ethylene glycol led to a dark green mixture which was added to 100 ml of an ice–water mixture. The resulting emulsion was extracted with 500 ml of pentane. Evaporation of the pentane extracts (Rinco) left **6-phenyl-5,12-dihydrobenzo[*b*]phenazine (15)** (0.38 g, 27%) as a yellow solid: darkened at 160°, mp 205–207° dec; ir (KBr) 2.99 and 3.04 μ (NH); nmr (DMSO-d_6) δ 8.28 (s, 1, C-11 hydrogen), 7.80–7.00 (m, 8, aromatic), 6.94 (s, 5, C_6H_5), and 6.25 (broad mound, 2, NH). This material was unstable in the solid state and in solution and was rapidly oxidized to **13**.

The aqueous glycol solution was then extracted with 200 ml of CH_2Cl_2. The methylene chloride extracts were evaporated to dryness (Rinco); the residue was deposited on an 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I) and eluted with 500 ml of 1:1 ether–pentane solution. The first 150 ml led, after evaporation, to 0.1 g (5%) of **12**, while evaporation of the remaining eluate ultimately gave 0.12 g (6%) of **13**. A final elution of the column with ether led only to tars.

Compound **15** was also prepared by the catalytic reduction of **13** and by the sodium hydrosulfite reduction of 6-phenylbenzo[*b*]-phenazine 12-oxide (**30**):

Catalytic Reduction of 13.—A suspension of 1 g (3.2 mmol) of **13** and 5% Pd–C in 125 ml of ethyl acetate was hydrogenated at 50 psi (Paar shaker) for 3 hr. The catalyst was removed, and the solvent was evaporated (Rinco) to yield **15** (0.56 g, 57%), identical with that obtained in the pyrolysis of **5** in triethylene glycol.

$Na_2S_2O_4$ Reduction of 30.—A suspension of 1 g (3.1 mmol) of **30** in 50 ml of 80% ethanol, to which 1 g (6.3 mmol) of $Na_2S_2O_4$ had been added, was refluxed for 30 min; upon cooling, the yellow solid was filtered to yield 0.73 g (75%) of **15**.

5,12-Dihydrobenzo[*b*]phenazine (17) was prepared from *o*-phenylenediamine and 2,3-dihydroxynaphthalene in 68% yield:[19] darkened at 201–215° but did not melt below 400°; ir (KBr) 2.92 μ (NH); nmr (DMSO-d_6) δ 7.78–7.42 (m, 2, C-6 and C-11 hydrogens) 7.38-6.96 (m, 2, C-6 and C-11 hydrogens), 7.38–6.96 (m, 4, C-7, C-8, C-10 hydrogens), 6.74–6.26 (m, 4, C-1, C-2, C-3, and C-4 hydrogens), and 5.70 (broad mound, 2, NH, exchangeable with D_2O).

Benzo[*b*]phenazine (16), mp 231–232° (lit.[19] mp 233°), was obtained in 21% yield *via* the chromic acid oxidation of **17**.[19]

Pyrolysis of 6.—A suspension of **6** (1.0 g, 2.6 mmol) in 30 ml of diethylene glycol was refluxed (240°) for 3 hr. On cooling, the glycol solution was added to 100 ml of water and the resultant mixture was filtered. The solid material was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I) and eluted successively with hexane (100 ml), 1:1 hexane–ether (100 ml), and ether (200 ml). Evaporation of the hexane fraction gave a light yellow oil (0.1 g, 12%) which was spectrally identified as **2-(α-methylbenzyl)-3-benzylquinoxaline (22)**: uv max (95% EtOH) 240 mμ (ϵ 30,000), 311 sh (9500), and 321 (11,000); nmr (CCl_4) δ 7.85 (center of A_2B_2 multiplet, 4, quinoxaline), 7.18 (s, 10, C_6H_5), 4.49 (q, 1, J = 7 Hz, CH), 4.28 (s, 2, CH_2), and 1.65 (d, 3, J = 7 Hz, CH_3).

Evaporation of the hexane–ether fraction led to 0.19 g (22%) of **6-phenyl-11-methylbenzo[*b*]phenazine (23)** as red needles: mp 253–254° (from 1,2-dichloroethane); uv max (95% EtOH) 250 mμ (ϵ 51,000), 288 (94,500), and 322 (8500); nmr ($CDCl_3$) δ 8.50–7.20 (m, 8, C-1, C-2, C-3, C-4, C-6, C-7, C-8, and C-9 hydrogens), 7.50 (s, 5, C_6H_5), and 3.28 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.74; mol wt, 320. Found: C, 86.45; H, 4.74; N, 8.81; mol wt, 350 (isothermal distillation).

Evaporation of the ether fraction produced 0.38 g (38%) of unreacted **6**.

Pyrolysis of 7.—A suspension of **7** (1.0 g, 2.5 mmol) in 30 ml of triethylene glycol was refluxed (280°) for 4 hr. On cooling, the glycol solution was added to 100 ml of water and the whole was extracted with two 100-ml portions of ether. The ether extracts were combined, dried (Na_2SO_4), and evaporated to a reddish oil which was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I). Elution of the column with 200 ml of pentane led, after evaporation of the solvent, to a clear oil which was dissolved in 50 ml of petroleum ether (bp 60–70°), charcoaled (Norit), and filtered, and the filtrate was reduced in volume to 20 ml. On standing, 0.11 g (14%) of an inseparable *meso–dl* mixture of **2,3-bis(α-methylbenzyl)quinoxaline (24)** deposited as white crystals: mp 89–90.5°; uv max (95% EtOH) 238 mμ (ϵ 38,000), 310 (10,000), and 321 (12,000); nmr ($CDCl_3$) δ 7.82 (center of A_2B_2 multiplet, 4, quinoxaline), 7.20 and 7.01 (each singlet, 10, *dl* and *meso* C_6H_5, respectively), 4.52 (m, 2. overlapping pair of quartets from *meso* and *dl* isomers), 1.76 and 1.54 (each doublet, 6, J = 7 Hz, *meso* and *dl* CH_3, respectively).

Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28; mol wt, 338. Found: C, 84.88; H, 6.85; N, 8.36; mol wt, 326 (isothermal distillation).

Continued elution of the column with 100 ml of ether led ultimately to 0.05 g (4%) of **23** and recovery of 0.32 g (32%) of **7**.

Photolysis of 5.—A solution of **5** (1.0 g, 2.7 mmol) in 125 ml of dioxane (distilled from CaH_2), sensitized with 0.1 g of benzophenone, was irradiated (Vycor filter, >2200 Å; 125-W Hanovia medium pressure Hg arc) under N_2 for 48 hr during which the color changed from bright yellow to deep red. Evaporation of the solvent (Rinco) gave a dark red oil which was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I). Elution of the column with 250 ml of CCl_4, followed by evaporation of the eluate (Rinco), left a light pink oil which slowly solidified on standing to give 0.19 g (22%) of **2,3-dibenzylquinoxaline (12)**, mp 118–118.5°.

Continued elution of the column with CH_2Cl_2, $CHCl_3$, and ether resulted only in the isolation of tars which could not be further characterized.

Alkaline Hydrogen Peroxide Oxidation of 5.—A suspension of **5** (1.0 g, 2.7 mmol) in 30 ml of 95% ethanol, 5 ml of 30–35% hydrogen peroxide, and 5 ml of 2 *N* sodium hydroxide was heated on a steam bath with stirring for 20 min. The dark red solution slowly faded during the vigorous reaction and a tan crystalline solid appeared. The mixture was cooled, diluted with 50 ml of water, and filtered to yield 0.75 g (85%) of crude **2-benzyl-3-benzoylquinoxaline (11)**. Recrystallization from hexane (Norit) gave pure **11** as white chunky crystals: mp 96–96.5°; ir (KBr) 5.99 and 6.02 μ (C=O); uv max (95% EtOH) 230 mμ (ϵ 17,000), 259 (21,700), and 326 (11,300); nmr ($CDCl_3$) δ 8.30–7.10 (m, 14, aromatic) and 4.60 (s, 2, CH_2).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.46; mol wt, 324. Found: C, 81.48; H, 4.93; N, 8.52; mol wt, 326 (Rast).

Alkaline Hydrogen Peroxide Oxidation of 6.—To a solution of 1 g (2.6 mmol) of **6** in 30 ml of 95% ethanol was added 5 ml of 30–35% hydrogen peroxide and 5 ml of 2 *N* NaOH. The mixture was heated on a steam bath for 20 min, until the vigorous reaction had subsided and the solution turned a light yellow. The solution was cooled and added to 100 ml of ice water. The aqueous solution was extracted with two 100-ml portions of pentane. The combined pentane extracts were dried (Na_2SO_4), treated with Norit, and filtered, and the filtrate was reduced in volume to 20 ml. On standing, a white crystalline solid appeared which was filtered to give 0.64 g (69%) of **2-(α-methylbenzyl)-3-benzoylquinoxaline (31)**, as tiny white needles: mp 77.5–78.5° (from pentane); ir (KBr) 6.01 μ (C=O); uv max (95% EtOH) 246 mμ (ϵ 38,000) and 323 (9000); nmr ($CDCl_3$) δ 8.35–7.20 (m, 14, aromatic), 4.94 (q, 1, J = 7 Hz, CH), and 1.86 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.46; H, 5.36; N, 8.28; mol wt, 338. Found: C, 81.64; H, 5.50; N, 8.37; mol wt, 330 (Rast).

Alternatively, **31** was prepared in 10% yield by methylation (CH_3I) of **11** in dry *t*-BuOH in the presence of KO-*t*-Bu.

Sodium Borohydride–Methanol Reduction of 5 and 6.—Sodium borohydride (1.0 g, 0.026 mol) was added in small portions of 1 g of **5** suspended in 50 ml of warm (steam bath) absolute methanol. The first addition of $NaBH_4$ led to a vigorous reaction and a transient orange color which darkened on further addition. After addition was complete, the solution was filtered to remove unreacted starting material. On cooling, the color of the dark red filtrate faded to yellow and a white crystalline solid [$NaB(OCH_3)_4$] appeared. Distilled water (100 ml) was added and the solution was extracted with two 100-ml portions of pentane. The combined pentane extracts were dried (Na_2SO_4) and evaporated to a light pink oil. The oil was redissolved in 50 ml of pentane, treated with Norit, filtered, and cooled to yield 0.62 g (74%) of **2,3-dibenzylquinoxaline (12)**.

Similar addition of 1.0 g of $NaBH_4$ in portions to 1.0 g of **6** in 50 ml of absolute CH_3OH also led to a vigorous reaction. After addition was complete, the solution was heated for an additional 10 min and filtered. Distilled water was added and the aqueous solution was extracted with two 100-ml portions of pentane.

The combined pentane extracts were dried (Na_2SO_4), filtered and evaporated to dryness (Rinco) to give 0.33 g (29%) of **22**.

Preparation of 2,3-Dibenzoylquinoxaline (27).—A solution of 2-benzyl-3-benzoylquinoxaline **11** (1.0 g, 3.1 mmol) in 30 ml of glacial HOAc and 0.5 g (5 mmol) of CrO_3 in 10 ml of 50% acetic acid was heated on a steam bath for 10 min, and then added to 150 ml of an ice–water mixture. The resultant light green solid was filtered and dried to yield 0.97 g (93%) of **27**, as a white powder: mp 169–170° (from methanol, Norit); ir (KBr) 6.03 μ (C=O); uv max (95% EtOH) 257 mμ (ϵ 48,000) and 324 (8000); nmr (DMSO-d_6) δ 8.35–7.30 (m, aromatic).

Anal. Calcd for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28; mol wt, 338. Found: C, 78.01; H, 4.31; N, 8.12; mol wt, 350 (Rast).

Preparation of 1,4-Diphenyl-2,3-diazaphenazine (28).—A solution of 1.0 g (2.96 mmol) of **27** in 30 ml of ethylene glycol was refluxed for 4 hr at 180–200° in the presence of 0.33 g (5.9 mmol) of solid KOH and 3 ml of 85% hydrazine hydrate. After cooling, the reaction mixture was diluted with 150 ml of distilled water and then filtered. The filtrate was extracted with two 100-ml portions of pentane; evaporation to dryness of the combined pentane extracts gave 2,3-dibenzylquinoxaline (**12**) in 2% yield.

The insoluble material, originally filtered, was dissolved in 200 ml of methanol, heated with charcoal (Norit), filtered, and evaporated to 50 ml. On cooling, 0.44 g (43%) of **28** crystallized as pale yellow needles: mp 239–240.5° (from CH_3OH, Norit); uv max (95% EtOH) 245 mμ (ϵ 62,000), 274 sh (20,000) and 345 (7000); nmr ($CDCl_3$)[50] δ 8.43 (m, 4, *ortho* hydrogens of C_6H_5), 8.15 (center of A_2B_2 pattern, 4, C-6, C-7, C-8, and C-9 hydrogens), and 7.60 (m, 6, *meta* and *para* hydrogens of C_6H_5).

Anal. Calcd for $C_{22}H_{14}N_4$: C, 79.02; H, 4.22; N, 16.75; mol wt, 336. Found: C, 79.18; H, 4.37; N, 16.48.

Preparation of 2-(α-Bromobenzyl)-3-benzoylquinoxaline (32).—A suspension of 2.0 g (6.2 mmol) of **11** and 1.1 g (6.2 mmol) of NBS in 100 ml of CCl_4 was irradiated with a 225 W high intensity white light for 1 hr. The mixture was cooled, filtered to remove the precipitated succinimide (0.62 g), and then evaporated *in vacuo* to a light green oil which was deposited on a 2.5 × 25 cm column of Woelm alumina (neutral, activity grade I) and eluted with 250 ml of 1:1 hexane–ether. The eluate was treated with charcoal (Norit), filtered, and evaporated to 50 ml. On cooling, 1.20 g (48%) of **32** was obtained as light green needles: mp 91–92.5° (from hexane); ir (KBr) 6.01 μ (C=O); uv max (95% EtOH) 254 mμ (ϵ 32,000) and 327 (6400); nmr ($CDCl_3$) δ 8.30–7.20 (m, 14, aromatic) and 6.96 (s, 1, CH).

Anal. Calcd for $C_{22}H_{15}N_2OBr$: C, 65.52; H, 3.75; N, 6.94; mol wt, 403. Found: C, 65.32; H, 3.67; N, 7.15; mol wt, 387 (isothermal distillation).

Compound **32** was unstable to light and heat and slowly decomposed to a gray powder.

Preparation of 2-(α-Hydroxybenzyl)-3-benzylquinoxaline (34).—To a solution of 1.0 g (3.1 mmol) of **11** in 30 ml of 95% ethanol was added a solution of 0.16 g (4.2 mmol) of $NaBH_4$ and 2 ml of 2 *N* NaOH in 10 ml of 95% EtOH, and the whole was refluxed 1 hr. On cooling, the mixture was added to 50 ml of ice–water and neutralized (litmus) with 10% HCl. The aqueous solution was extracted with two 100-ml portions of pentane. The combined pentane extracts were dried (Na_2SO_4), treated with charcoal (Norit), filtered, and evaporated to 50 ml. On standing, the white flocculent solid was filtered to yield 0.76 g (75%) of **34**: mp 83–84.5°; ir (KBr) 3.25 and 3.30 μ (OH); uv max (95% EtOH) 240 mμ (ϵ 29,500), 311 sh (7800), and 321 (10,000); nmr ($CDCl_3$) δ 8.22–7.50 (m, 4, quinoxaline), 7.47–7.03 (m, 10, C_6H_5), 5.88 (s, 1, CH), 5.20 (broad singlet, 1, OH exchangeable with D_2O), and 4.16 (s, 2, CH_2).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.58; N, 8.58; mol wt, 326. Found: C, 81.84; H, 5.73; N, 8.76; mol wt, 330 (isothermal distillation).

All attempts to prepare the tosylate of **34** were unsuccessful.

Cyclodehydration Reactions.—The general procedure for this reaction was as follows. The appropriate quinoxaline (1.0 g) was treated with 5 ml of concentrated H_2SO_4 and warmed briefly on a steam bath (5 min for **11** and **34**; 30 min for **31** and **32**). The cooled solution was added to 100 g of ice, and the aqueous solution was extracted with two 100-ml portions of CH_2Cl_2. The methylene chloride extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to yield the crude benzo[*b*]phenazine product. Thus **11** and **34** gave, respectively, 0.81 g (85%) and 0.54 g (62%) of **6-phenylbenzo[*b*]phenazine (13)**, mp 254–255° (from 1,2-dichloroethane).

2-(α-Methylbenzyl)-3-benzoylquinoxaline (31) gave 0.75 g (78%) of **6-phenyl-11-methylbenzo[*b*]phenazine (23)**, as red needles: mp 253–254° (from 1,2-dichloroethane, Norit); uv max (95% EtOH) 250 mμ (ϵ 51,000), 288 (94,500), and 322 (8500); nmr ($CDCl_3$) δ 8.50–7.20 (m, 8, C-1, C-2, C-3, C-4, C-7, C-8, C-9, and C-10 hydrogens), 7.50 (s, 5, C_6H_5), and 3.28 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.74; mol wt, 320. Found: C, 86.45; H, 4.74; N, 8.81; mol wt, 350 (isothermal distillation).

2-(α-Bromobenzyl)-3-benzoylquinoxaline (32) gave 0.81 g (84%) of **6-phenyl-11-bromobenzo[*b*]phenazine (33)**, as red needles: mp 263–264° (from CH_2Cl_2, Norit); uv max (95% EtOH) 254 mμ (ϵ 40,000) and 288 (87,500); nmr[51] ($CDCl_3$) δ 8.72 (m, 1, C-10 hydrogen), 8.35 (m, 1, C-7 hydrogen), 8.20–7.10 (m, 6, C-1, C-2, C-3, C-4, C-8, and C-9 hydrogens), and 7.57 (s, 5, C_6H_5).

Anal. Calcd for $C_{22}H_{13}N_2Br$: C, 68.57; H, 3.40; N, 7.27; mol wt, 385. Found: C, 68.74; H, 3.25; N, 7.05; mol wt, 400 (isothermal distillation).

Peroxy Acid Oxidation of 5.—A mixture of 2.0 g (5.4 mmol) of **5** and 2.5 g (14 mmol) of *m*-chloroperbenzoic acid in 125 ml of $CHCl_3$ was refluxed for 2 hr. The clear amber solution was reduced in volume to 50 ml (Rinco) and cooled. The precipitated *m*-chlorobenzoic acid was filtered, and the filtrate was evaporated to a dark yellow-brown oil, which solidified on standing to yield 0.86 g (47%) of crude **2-benzyl-3-benzoylquinoxaline 1-oxide (29)**. Recrystallization from 95% ethanol (Norit) gave pure **29** as yellow needles: mp 139–140°; ir (KBr) 6.01 μ (C=O); uv max (95% EtOH) 243 mμ (ϵ 32,500), 248 (26,000), 276 (14,500), and 326 (7300); nmr ($CDCl_3$) δ 8.68 (m, 1, C-8 hydrogen), 8.4–7.0 (m, 13, aromatic), and 4.52 (s, 2, CH_2).

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.64; H, 4.70; N, 8.23; mol wt, 340. Found: C, 77.78; H, 4.83; N, 8.30; mol wt, 350 (Rast).

Sodium Hydrosulfite Reduction of 29.—A mixture of **29** (0.45 g, 1.3 mmol) and sodium hydrosulfite (0.25 g, 1.6 mmol) in 25 ml of 80% EtOH was refluxed for 1 hr. The resultant deep purple solution was added to 20 ml of ice and the aqueous solution was extracted twice with 50-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered, treated with charcoal (Norit), and again filtered. Evaporation of the filtrate to dryness gave 0.38 g (90%) of **11**, mp 96–97°, identical by all the usual criteria with **11** prepared by the oxidation of **5** with alkaline hydrogen peroxide.

Oxidation of **11** with peracetic acid (40%) in chloroform (reflux, 2 hr) gave a 76% yield of **29**.

6-Phenylbenzo[*b*]phenazine 12-Oxide (30). *Via* **Cyclodehydration of 29.**—2-Benzyl-3-benzoylquinoxaline 1-oxide (**29**, 1.0 g, 2.9 mmol) in 5 ml of concentrated H_2SO_4 was warmed on a steam bath for 10 min. Work-up was identical with that employed in the cyclization of **11**, **31**, **32**, and **34**. Crude **6-phenylbenzo[*b*]phenazine 12-oxide (30)** was obtained as a red powder from CH_2Cl_2 and deposited on a 2.5 × 25 cm column of Florisil (60–200 mesh). Elution with CH_2Cl_2 resulted in the development of two red bands. Evaporation of the first 150 ml of eluent gave **30** (0.62 g, 66%) as dark red plates: mp 248–249.5° (from 1,2-dichloroethane); uv max (95% EtOH) 244 mμ (ϵ 16,000), 242 (36,000), and 286 (77,500); nmr[51] ($CDCl_3$) δ 9.35 (s, 1, C-11 hydrogen), 8.66 (m, 1, C-1 hydrogen), 8.25–7.30 (m, 7, quinoxaline), and 7.60 (s, 5, C_6H_5).

Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69; mol wt, 322. Found: C, 81.72; H, 4.36; N, 8.45; mol wt, 320 (Rast).

Via Peracetic Acid Oxidation of 13.—The two-layer suspension of **13** in 30 ml of 1,2-dichloroethane and 5 ml of 40% peracetic acid was refluxed for 4 hr. The cooled mixture was added to 100 ml of ice–water and the whole was extracted with 100 ml of CH_2Cl_2. The organic extracts were washed successively with two 50-ml portions of water, 50 ml of 10% $NaHCO_3$ solution, and 50 ml of distilled water and then dried (Na_2SO_4). Filtration, followed by evaporation *in vacuo* to dryness, gave 0.65 g (67%) of **30**.

Bromination of 5.—One gram (2.7 mmol) of **5** and 0.5 g (2.8

(51) We are grateful to William Jankowski, Varian Associates, for determining the 100-Mc nmr spectrum of this compound, using a CAT.

mmol) of NBS were suspended in 125 ml of carbon tetrachloride and irradiated with a 225-W high intensity white light for 30 min. The suspension was cooled and filtered. The volume of the filtrate was reduced to 50 ml (steam bath) and the solution was again cooled and filtered. Final evaporation of the filtrate *in vacuo* left a light tan oil which solidified, with darkening, to give 0.67 g (58%) of crude **1,3-diphenyl-1-bromo-1,3-dihydrothieno-[3,4-*b*]quinoxaline 2,2-dioxide.** Recrystallization from chloroform gave the monobromo product as a light yellow, heat-sensitive, crystalline solid: darkened at 130°, mp 230–232° dec; uv max (95% EtOH) 248 mμ (ε 28,000), 279 sh (10,000) and 326 (7200); nmr ($CDCl_3$) δ 8.25–7.20 (m, 14, aromatic) and 6.15 (s, 1, CH).

Bromination of 11.—A solution of 0.25 g (0.81 mmol) of **11** and 0.30 g (1.7 mmol) of NBS in 25 ml of CCl_4 was refluxed for 2 hr. On cooling, the succinimide was filtered, and the filtrate was evaporated to leave a pink oil which solidified to give 0.21 g (63%) of a mixture of *meso*- and *dl*-**2,3-*bis*(α-bromobenzyl)-quinoxaline (42)** as pale pink needles: mp 163–165° (from hexane); uv max (95% EtOH) 247 mμ (ε 29,000) and 329 (6500); nmr (CCl_4) δ 8.17–7.08 (m, 14, aromatic) and 6.64 (*meso*) and 6.48 (*dl*) (each singlet, 2, CH).

Anal. Calcd for $C_{22}H_{16}N_2Br_2$: C, 56.54; H, 3.45; N, 7.21. Found: C, 56.54; H, 3.65; N, 7.05.

Registry No.—Sulfur dioxide, 7446-09-5; **5,** 19029-25-5; *cis* **7,** 19029-79-9; *trans* **7,** 19029-80-2; **9,** 19029-26-6; **10,** 19029-27-7; **11,** 19029-28-8; **13,** 19029-29-9; **14,** 19029-30-2; **15,** 19029-31-3; **17,** 19029-32-4; **22,** 19029-33-5; **23,** 19029-34-6; *meso* **24,** 19029-81-3; *dl* **24,** 19029-82-4; **27,** 19029-35-7; **28,** 19029-36-8; **29,** 19029-37-9; **30,** 19029-38-0; **31,** 19029-39-1; **32,** 19029-40-4; **33,** 19029-41-5; **34,** 19029-42-6; *meso* **42,** 19029-83-5; *dl* **42,** 19029-84-6; 1,3-diphenyl-1-bromo-1,3-dihydrothieno[3,4-*b*]-quinoxaline 2,2-dioxide, 19029-43-7.

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Preparation and Reactions of *o*-(Cyanomethyl)benzeneboronic Acid[1]

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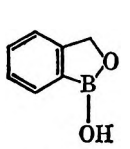
The synthesis of *o*-(cyanomethyl)benzeneboronic acid **3** is described. Conversion of the nitrile to the amide, acid, alcohol, and amine and cyclodehydration of these substances yield, respectively, the cyclic imide of *o*-boronophenylacetic acid **4**, the cyclic anhydride of *o*-boronophenylacetic acid **5**, the lactone of 2-(*o*-boronophenyl)-ethanol **15** and the lactam of 2-(*o*-boronophenyl)ethylamine **18**. The reaction of cyclic imide **4** and cyclic anhydride **5** with catechol is reported, as is the reaction of **5** with *o*-aminophenol and *o*-phenylenediamine. The ease with which *ortho*-substituted arylboronic acids undergo cyclodehydration and further dehydration to dimeric anhydrides is discussed.

Alkaline hydrolysis of *o*-(bromomethyl)benzeneboronic acid yields boronophthalide **1**,[2,3] the lactone of *o*-(hydroxymethyl)benzeneboronic acid. This lactone is more stable than would be predicted on the basis of the chemistry of simple boronic esters.[3–5] Similarly, reaction of *o*-formylbenzeneboronic acid with hydroxylamine gives a cyclic product **2**.[3,6,7] It seems likely that additional compounds analogous to **1** and **2** will result from the interaction of an aromatic boronic acid group and a second function suitably located on a side chain in the *ortho* position. *o*-(Cyanomethyl)benzeneboronic acid (**3**) should be a useful precursor for such substances because of the ease with which a nitrile group can be converted into other reactive functions.



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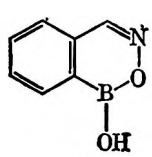


2

Lennarz,[8] in attempts to displace the bromide atom of *o*-(bromomethyl)benzeneboronic anhydride with cyanide, employing strongly basic cyanides and various solvent systems, observed only the formation of boronophthalide **1**. In the present work replacement of the bromine atom is effected when *o*-(bromomethyl)-benzeneboronic anhydride reacts with cyanide ion introduced as the ion associated with a strongly basic ion-exchange resin. The general method is one introduced by Griffin, *et al.*,[9] as a means of avoiding undesirable base-promoted processes brought about by alkali cyanides.

Hydrolysis of *o*-(cyanomethyl)benzeneboronic acid (**3**) with dilute base gives cyclic imide **4** which is further hydrolyzed in acid to cyclic anhydride **5**; neither *o*-(boronophenyl)acetamide nor *o*-(boronophenyl)acetic

(1) This work was supported by Grant AT(11-1)-314 from the Atomic Energy Commission, Report No. C00-314-13.

(2) K. Torssell, *Arkiv Kemi*, **10**, 509 (1957).

(3) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Amer. Chem. Soc.*, **80**, 835 (1958).

(4) W. J. Lennarz and H. R. Snyder, *ibid.*, **82**, 2172 (1960).

(5) M. F. Lappert, *Chem. Rev.*, **56**, 959 (1956).

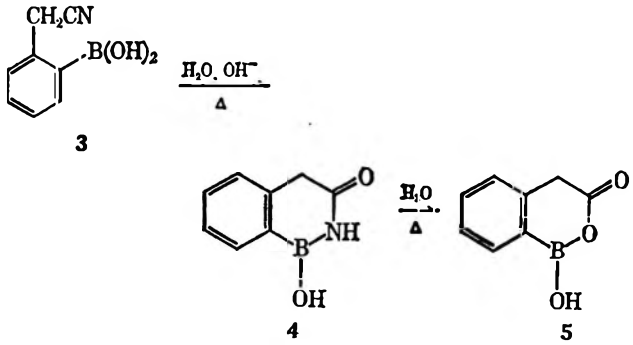
(6) M. J. S. Dewar and R. C. Dougherty, *J. Amer. Chem. Soc.*, **86**, 433 (1964).

(7) For additional examples of cyclic boronic acid derivatives, see P. M. Maitlis, *Chem. Rev.*, **62**, 223 (1962); M. J. S. Dewar, Advances in Chemistry Series, No. 42, American Chemical Society, Washington, D. C., 1964, p 227; M. J. S. Dewar, "Progress in Boron Chemistry," Vol. 1, H. Steinberg and A. L. McCloskey, Ed., The Macmillan Co., New York, N. Y., 1964, p 235.

(8) W. J. Lennarz, Thesis, Doctor of Philosophy, University of Illinois, 1959.

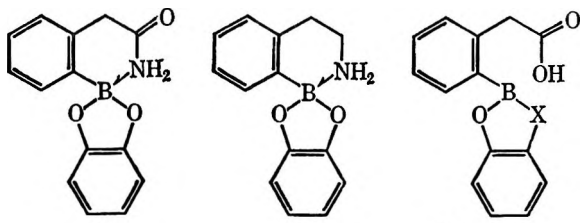
(9) M. Gordon, M. L. DePamphilis, and C. E. Griffin, *J. Org. Chem.*, **28**, 698 (1963).

acid could be isolated as an intermediate. Cyclic imide **4** and cyclic anhydride **5** react with catechol; in both



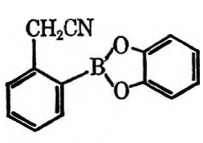
3 **4** **5**

cases ring opening occurs yielding, respectively, the catechol derivative of *o*-(boronophenyl)acetamide **6** and the catechol derivative of *o*-(boronophenyl)acetic acid **8a**. Opening of the imide ring of **4** with subsequent



6 **7** **8a**, X = O; **b**, X = NH

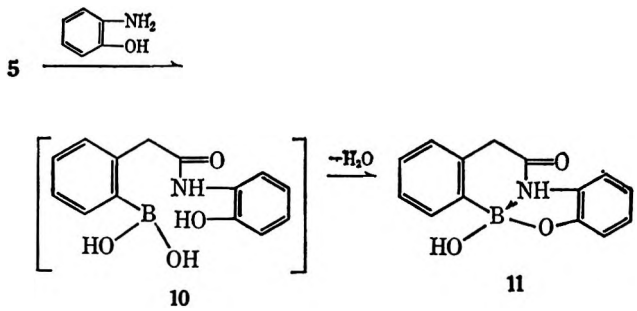
formation of a cyclic catechol derivative is evident from a comparison of the infrared spectra of the catechol derivative of *o*-boronophenylacetamide **6**, the cyclic imide (**4**), and the catechol derivative of *o*-(2-aminoethyl)benzeneboronic acid **7**.[10] The bands from 1350 to 1400 cm^{-1} in the infrared spectrum of **4** are indicative of a tricovalent boronic acid derivative.[11] In the infrared spectrum of **6** these bands are absent and there is a strong infrared absorption at 1240 cm^{-1} which can be attributed to the boron-nitrogen dative bond stretch (>NB<).[11] That **6** and **7** have analogous structures is best indicated by the fact that their infrared spectra are nearly identical; in both cases the boron–nitrogen stretch is observed at 1240 cm^{-1}. The similarity of the infrared spectrum of the catechol derivative of *o*-(cyanomethyl)benzeneboronic acid **9**



9

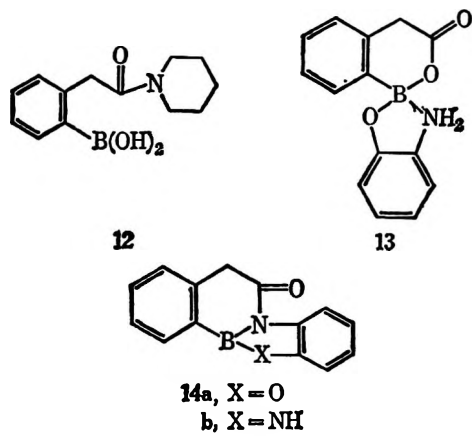
to the infrared spectrum of the catechol derivative of the cyclic anhydride, *i.e.*, **8a**, suggests that **9** and **8a** have similar structures; they are both cyclic catechol derivatives of arylboronic acids. The infrared spectra indicate that the boron atom is tricovalent; the boron–oxygen absorption in **8a** is found at 1330 cm^{-1} and that in **9** at 1325 cm^{-1}.[11] This indicates the lack of coordination between the hydroxyl oxygen of the carboxyl and the boron atom in **8a**.

Cyclic anhydride **5** also reacts with *o*-aminophenol, ring cleavage occurring as in the case of its reaction with catechol; however, in this case the boronic acid function is incorporated into a nine-membered ring (**11**) rather than a five-membered ring. In the macrocyclic ring there is a cross-annular interaction between the boron and the nitrogen, *i.e.*, a boron–nitrogen dative bond. The boron–nitrogen dative bond is indicated by the major infrared absorption band at 1250 cm^{-1}.[11] Formation of **11** is believed to proceed *via* amide **10**, which undergoes spontaneous dehydration to yield **11**. The facile dehydration is due to the phenolic hydroxyl being held in proximity to the boronic acid function.



10 **11**

Amide **12**, analogous to **10**, has been prepared by reaction of cyclic anhydride **5** with piperidine. In this case there was no opportunity for cyclodehydration to



12 **13** **14a**, X = O; **b**, X = NH

occur. If the first step in the formation of **11** had been reaction of the phenolic function with the boronic acid, an ester would have been formed in which the amine would be coordinated to the boron[12] (**13**) and would presumably have reacted with the boron to form a catechol-like derivative (**8b**). Vacuum sublimation at 200° of the nine-membered ring component, **11**, causes it to be dehydrated with concurrent formation of a boron–nitrogen bond. This cross-annular reaction yields tetracyclic product **14a**.

A tetracyclic product, analogous to **14a**, **14b** is formed by the reaction of *o*-phenylenediamine with cyclic anhydride **5**; in this case, no intermediate similar to **11** was observed. Boronophthalide (**1**) does not react with *o*-phenylenediamine under similar conditions;[8] the failure of **1** to react indicates that the five-membered

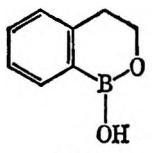
(10) J. C. Catlin, Thesis, Doctor of Philosophy, University of Illinois, 1966.

(11) R. L. Letsinger, Advances in Chemistry Series, No. 42, American Chemical Society, Washington, D. C., 1964, p 3.

(12) R. L. Letsinger and J. R. Nazy, *J. Org. Chem.*, **23**, 914 (1958).

lactone, *i.e.*, boronophthalide (**1**), is more stable than the six-membered anhydride, **5**.

Reduction of cyclic anhydride **5** with lithium aluminum hydride yields, after an aqueous work-up, the lactone of 2-(*o*-boronophenyl)ethanol (**15**), a homolog of boronophthalide (**1**). In contrast, under similar conditions cyclic amide **4** gives 1,2-boraztetralin (**16**);



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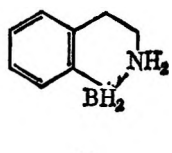
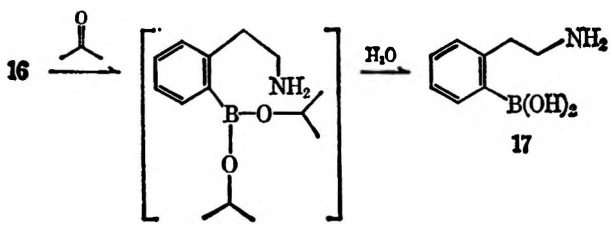


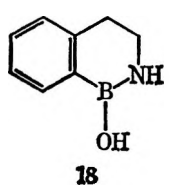
16

16 was hydrolyzed in refluxing aqueous acetone to 2-(*o*-boronophenyl)ethylamine (**17**). 1,2-Boraztetralin (**16**) reacts with acetone, presumably to form a boronic ester[13] which in the aqueous acetone medium is hydrolyzed to acid **17**, as predicted[14] (see Scheme I).

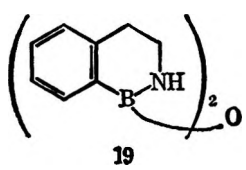
SCHEME I



In the mass spectrometer 2-(*o*-boronophenyl)ethylamine (**17**) is thermally dehydrated to a mixture of lactam **18** and anhydride **19** (molecular ion peaks at *m/e* 147 and *m/e* 276).

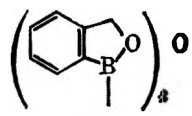


18



19

The ease with which *ortho*-substituted boronic acid derivatives undergo cyclic dehydration appears to depend upon the basicity of the *ortho* substituent. Compounds with weakly basic *ortho* substituents, with the exception of N-substituted *o*-boronophenylacetamides (for example **11**), have not been isolated because of their facile cyclic dehydration. The boronic acid derivatives which undergo this facile dehydration resist further dehydration except under the most stringent conditions. There is no indication that cyclic imide **4**, cyclic anhydride **5** and the lactone of 2-(*o*-boronophenyl)ethanol (**15**) undergo dehydration to their dimeric anhydrides in the mass spectrometer. The dimeric anhydride of boronophthalide **20** is prepared by vacuum distillation of boronophthalide **1** [bp 136° (0.4 mm)].[15] In contrast 2-(*o*-boronophenyl)ethylamine (**17**), a compound with a relatively basic *ortho* substituent, has been isolated, but in the mass spectrometer **17** is dehydrated to its lactam (**18**) and the lactam anhydride (**19**).



20

Experimental Section[16]

Preparation of *o*-(Cyanomethyl)benzeneboronic Acid (3).—Following the procedure of Griffin, *et al.*,[9] 100 ml of Amberlite IRA 400 was washed three times with three times its volume of 20% aqueous sodium cyanide solution. Each time after stirring for 5 min the slurry was diluted with 150 ml of distilled water, and after the resin had settled the cyanide solution was decanted. The resin was washed with distilled water until the wash water gave a negative silver nitrate test for cyanide. The resin was then washed three times with 100-ml portions of tetrahydrofuran (THF). At this point the resin can be stored in THF until needed.

The ion-exchange resin in the cyanide form, 200 ml of THF, and 20 g of *o*-(bromomethyl)benzeneboronic anhydride were stirred under reflux for 4 hr. The resin then was placed in a Soxhlet extractor and extracted overnight with the THF from the reaction mixture. The THF solution was filtered and evaporated *in vacuo*. The oil obtained was placed in 25 ml of water and chilled until it crystallized, yielding 13.0 g (81%) of crude product. An analytically pure sample (6.9 g, 43%) was prepared by recrystallizing the crude material twice from water with Darco treatment (mp 150–152°, dehydration 85°).

Anal. Calcd for $C_8H_8BO_2N$: C, 59.68; H, 5.01; N, 8.70. Found: C, 59.79; H, 4.91; N, 8.93.

Preparation of the Cyclic Imide of *o*-Boronophenylacetic Acid (4).—A mixture of 6.4 g of *o*-(cyanomethyl)benzeneboronic acid and 80 ml of 5% aqueous potassium hydroxide was heated on the steam bath for 2 hr and then chilled. The cold solution was treated with Darco; following acidification with concentrated hydrochloric acid, the cyclic imide (4.1 g, 63%) was collected by filtration. An analytical sample, melting at 202–204°, was prepared by washing with hot acetone.

Anal. Calcd for $C_8H_8BO_2N$: C, 59.68; H, 5.01; N, 8.70; mol wt, 161. Found: C, 59.35; H, 4.97; N, 8.31; mol wt (by mass spectrum), 161.

Preparation of the Cyclic Anhydride of *o*-Boronophenylacetic Acid (5).—A mixture of 6.4 g of *o*-(cyanomethyl)benzeneboronic acid and 80 ml of 5% aqueous potassium hydroxide was heated on the steam bath for 2 hr, acidified by addition of concentrated hydrochloric acid and heated again until a solution was obtained. This solution was heated for 1 hr and chilled overnight. The cyclic anhydride was collected by filtration (5.9 g, 90%). An analytical sample, melting at 136–136.5°, was prepared by recrystallization from water.

Anal. Calcd for $C_8H_7BO_3$: C, 59.31; H, 4.36; mol wt, 162. Found: C, 59.59; H, 4.27; mol wt (by mass spectrum), 162.

Reaction of the Cyclic Imide of *o*-Boronophenylacetic Acid with Catechol.—A stirred slurry of 1.61 g of the cyclic imide of *o*-boronophenylacetic acid, 1.10 g of catechol and 100 ml of xylene was heated at reflux until it appeared that water was no longer being removed. The solution was chilled and the product was washed with ether. The catechol derivative of *o*-boronophenylacetamide (**6**) was obtained in 30% (0.75 g) yield. Recrystallization from benzene–hexane gave an analytical sample melting at 135–137°.

Anal. Calcd for $C_{14}H_{12}BO_3N$: C, 66.46; H, 4.78; N, 5.54; mol wt, 253. Found: C, 66.86, 66.33; H, 4.80, 5.08; N, 5.14,

(13) F. G. A. Stone, *Quart. Rev.*, (London) **9**, 174 (1955).
(14) K. Torssell, *Acta Chem. Scand.*, **8**, 1779 (1954).
(15) R. R. Haynes and H. R. Snyder, *J. Org. Chem.*, **29**, 3229 (1964).

(16) Microanalyses were performed by Josef Nemeth and his associates. Infrared spectra were determined by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering of the University of Illinois, using a Perkin-Elmer Model 21 infrared spectrophotometer (equipped with sodium chloride optics). All melting points are uncorrected and were obtained on a Kofler microstage apparatus. Evaporations done *in vacuo* were carried out on a rotary evaporator unless specified otherwise. The mass spectra were obtained by Mr. Joseph Wrona on an Atlas CH4 spectrometer.

5.24. In the mass spectrum the $(m + 1)/e$ peak at 254 is more intense than the m/e peak at 253.

Reaction of the Cyclic Anhydride of o-Boronophenylacetic Acid with Catechol.—A solution of 0.81 g of the cyclic anhydride of o-boronophenylacetic acid and 0.55 g of catechol in 25 ml of benzene was heated at reflux for 1 hr. The solution was chilled and 0.78 g (39%) of the catechol derivative of o-boronophenylacetic acid **8a** was collected by filtration. Recrystallization from benzene yielded an analytical sample which changed form at about 119° and melted at 131–132°.

Anal. Calcd for $C_{14}H_{11}BO_4$: C, 66.14; H, 4.33; mol wt, 254. Found: C, 66.20; H, 4.37; mol wt (by mass spectrum), 254.

Preparation of the Catechol Derivative of o-(Cyanomethyl)benzeneboronic Acid (9).—Water was azeotropically removed from a benzene solution of 1.6 g of o-(cyanomethyl)benzeneboronic acid and 1.1 g of catechol. The hot solution was filtered and concentrated under a stream of air to yield 1.4 g (59%) of the catechol derivative of o-(cyanomethyl)benzeneboronic acid. An analytical sample melting at 123–125° was prepared by recrystallization from hexane.

Anal. Calcd for $C_{14}H_{10}BO_2N$: C, 71.55; H, 4.29; N, 5.96. Found: C, 71.79; H, 4.37; N, 5.95.

Reaction of the Cyclic Anhydride of o-Boronophenylacetic Acid with o-Aminophenol.—A solution of 1.62 g of the cyclic anhydride of o-boronophenylacetic acid and 1.09 g of o-aminophenol in 100 ml of xylene was heated at reflux until water was no longer removed. The reaction mixture was poured into hexane and chilled, and the product (1.4 g, 55%) was collected by filtration. Recrystallization from chloroform followed by sublimation at a pot temperature of 150–180° at reduced pressure gave an analytical sample of **11** melting at 179–180°.

Anal. Calcd for $C_{14}H_{12}BO_3N$: C, 66.46; H, 4.78; N, 5.54; mol wt, 253. Found: C, 66.53; H, 4.74; N, 5.57; mol wt (by mass spectrum), 253.

Dehydration of the Product from the Reaction of the Cyclic Anhydride of o-Boronophenylacetic Acid with o-Aminophenol.—A sample of crude material from the above reaction was washed with ether and sublimed *in vacuo* at a pot temperature of 200–210°. The dehydration product which was obtained in 64% yield after 3 hr was recrystallized from acetone. The analytical sample of **14a** melted at 204–206°.

Anal. Calcd for $C_{14}H_{10}BO_2N$; C, 71.55; H, 4.29; N, 5.96; mol wt, 235. Found: C, 71.46; H, 4.34; N, 5.73; mol wt (by mass spectrum), 235.

Reaction of the Cyclic Anhydride of o-Boronophenylacetic Acid with Piperidine.—A benzene solution (100 ml) of 0.81 g of the cyclic anhydride of o-boronophenylacetic acid and 1 ml of piperidine was heated at reflux for 1 hr. The solution was poured into twice its volume of hexane and the product was collected by filtration (yield 0.77 g, 63%). An analytical sample of **12** melting at 125–126° was prepared by crystallization from benzene to which had been added a few drops of piperidine.

Anal. Calcd for $C_{13}H_{18}BO_3N$: C, 63.21; H, 7.35; N, 5.67. Found: C, 63.51; H, 7.62; N, 5.23.

Reaction of the Cyclic Anhydride of o-Boronophenylacetic Acid with o-Phenylenediamine.—A stirred solution of 0.81 g of the cyclic anhydride of o-boronophenylacetic acid and 0.54 g of o-phenylenediamine in xylene was heated under reflux until water was no longer removed. The remaining solvent was evaporated *in vacuo* yielding 0.87 g, 74%. An analytical sample of **14b** was prepared by washing with acetone and recrystallizing from benzene, mp ~200° dec.

Anal. Calcd for $C_{14}H_{11}BON_2$: C, 71.85; H, 4.74; N, 11.97; mol wt, 234. Found: C, 71.60; H, 4.93; N, 11.89; mol wt (by mass spectrum), 234.

Preparation of the Lactone of 2-(o-Boronophenyl)ethanol (15).—A solution of 0.81 g of the cyclic anhydride in 25 ml of THF was added slowly to a stirred slurry of 0.23 g of lithium aluminum hydride in 30 ml of THF. Upon the completion of the addition the reaction mixture was heated at reflux for 1 hr. The excess hydride was decomposed (1% HCl), and the solution was extracted with THF. Upon evaporation of the THF solution a 30% yield of lactone was obtained. After recrystallization from water, the melting point was found to be 60–61°.

Anal. Calcd for $C_8H_9BO_2$: C, 64.92; H, 6.13; mol wt, 148. Found: C, 64.86; H, 5.86; mol wt (by mass spectrum), 148.

Reduction of the Cyclic Imide of o-Boronophenylacetic Acid.—A stirred mixture of 1.61 g of the cyclic imide and 0.76 g of $LiAlH_4$ in THF was heated under reflux 2.5 hr and then stirred overnight. The excess hydride was decomposed (water) and the mixture was filtered. The filtrate was concentrated and extracted with ether. Evaporation of the ethereal solution gave 0.83 g (62%) of 1,2-boraztetralin **16** (mp 135–138° dec) which was identified by comparison of its infrared spectrum with the spectrum of an authentic sample.[10]

Preparation of 2-(o-Boronophenyl)ethylamine (17).—A solution of 0.5 g of 1,2-boraztetralin in 30 ml of 5:1 acetone–water was heated at reflux for 1 hr. The solution was concentrated under a stream of air, and the product was collected in 60% yield by filtration. A sample melting at 116–118° was prepared by recrystallization from benzene.

Anal. Calcd for $C_8H_{12}BO_2N$: C, 58.23; H, 7.33; N, 8.49. Calcd for $C_8H_{11}BON$: mol wt, 147. Calcd for $C_{16}H_{18}B_2ON_2$: mol wt, 276. Found: C, 58.74; H, 7.42; N, 7.70; mol wt (by mass spectrum), 147 and 276.

Registry No.—**3**, 16538-46-8; **4**, 19206-44-1; **5**, 19206-45-2; **6**, 19214-80-3; **8a**, 19206-46-3; **9**, 19206-47-4; **11**, 19227-69-1; **12**, 19206-48-5; **14a**, 19206-49-6; **14b**, 19206-50-9; **15**, 19206-51-0.

Synthesis, Reactions, and Mass Spectral Studies of Some Cyclic Amine–Boranes and Their Catechol Derivatives[1,2]

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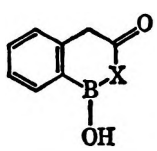
Received July 24, 1968

Several cyclic amine–boranes are prepared by lithium aluminum hydride reduction of appropriate aminoboronic acids or boronic acids containing potential amine functions. The cyclic amine–boranes are found to be more stable than an acyclic model compound. The mass spectral fragmentations of the cyclic amine–boranes and of their spirocatechol derivatives are discussed.

Hawthorne[3] has prepared a number of acyclic amine–boranes by lithium aluminum hydride reduction of boronic anhydrides in the presence of appropriate amines. The preparation of a number of cyclic amine–boranes, in which ring closure is effected through the formation of a boron–nitrogen dative bond,[4] has been accomplished by the hydroboration of aminoolefins.[5–7] Reaction of appropriate aminoboronic acids with catechol yields a second class of boronic acid derivatives in which a ring is formed as a result of coordination between the boron and nitrogen.[8] As a continuation of our interest in the preparation of aromatic boronic acid derivatives which are stabilized by incorporation of the boron within a cyclic system,[2] the synthesis of a number of cyclic amine–boranes was undertaken. A qualitative measure of the stability of the cyclic amine–boranes prepared was obtained by a comparison of the conditions for certain of their reactions with those conditions that afforded analogous products from an acylic model. The data obtained (see below) show that amine–boranes are stabilized by incorporation of the boron–nitrogen bond in a cyclic system. The closely related amine–boranes and their catechol derivatives which were prepared gave us a unique opportunity to study the mass spectral fragmentation of these two classes of compounds.

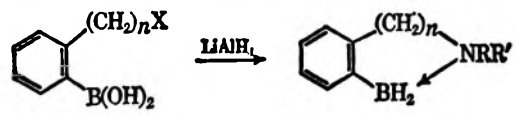
Lithium aluminum hydride reduction of an *o*-(aminoalkyl)arylboronic acid derivative (**1e**) and of boronic acids which potentially contain the *o*-(aminoalkyl) group (**1a–d, f**) gave a series of cyclic amine–boranes (**2a–f**) (Scheme I). 1,2-Boraztetralin (**2a**) can be prepared by lithium aluminum hydride reduction of either the cyclic imide of *o*-boronophenylacetamide (**3a**)[2a] or *o*-(cyanomethyl)benzeneboronic acid (**1a**),



3a, X = NH
b, X = O

4

SCHEME I



1a, $n = 1$; X = —CN
b, $n = 1$; X = —CNHCH$_2$CH$_2$C$_6$H$_5$ (O)
c, $n = 0$; X = —CH=NOCH$_3$
d, $n = 0$; X = —CH=NCH$_2$CH$_2$C$_6$H$_5$
e, $n = 1$; X = —NC$_5$H$_{10}$ (catechol derivative)
f, $n = 0$; X = —CH=NC$_6$H$_5$

2a, $n = 2$; R = R′ = H
b, $n = 2$; R = H; R′ = CH$_2$CH$_2$C$_6$H$_5$
c, $n = 1$; R = R′ = H
d, $n = 1$; R = H; R′ = CH$_2$CH$_2$C$_6$H$_5$
e, $n = 1$; R—R′ = C$_5$H$_{10}$
f, $n = 1$; R = H; R′ = C$_6$H$_5$

the latter compound affording the higher yield of product. Reaction of the cyclic anhydride of *o*-boronophenylacetic acid (**3b**)[2a] with 2-phenylethylamine presumably gave **1b**, which was reduced with lithium aluminum hydride to yield 2-(2′-phenylethyl)-1,2-boraztetralin (**2b**).

Three 3,2-borazindans were also prepared *via* lithium aluminum hydride reductions. Reduction of N-(*o*-boronobenzal)methoxyamine (**1c**)[2b] and N-(*o*-boronobenzal)phenylethylamine (**1d**) yields 3,2-borazindan (**2c**) and 2-(2′-phenylethyl)-3,2-borazindan (**2d**), respectively. The third borazindane, 3,2-borazindan-2-spiro-1′-piperidine (**2e**) was prepared by reduction of the crude adduct obtained by reaction of the catechol derivative of *o*-(bromomethyl)benzeneboronic acid with piperidine, **1e**. An attempt to prepare 2-phenyl-3,2-borazindan (**2f**) by the lithium aluminum hydride reduction of N-(*o*-boronobenzal)aniline (**1f**) did not lead to the desired product. It is probable that **2f** formed but was lost during attempted isolation, as a result of hydrolysis to the corresponding aminoboronic acid.[2b]

The acyclic model, ethylamine–(N–B)-*o*-tolylborane (**4**), was prepared by lithium aluminum hydride reduction of a solution of *o*-toluneboronic anhydride and ethylamine in tetrahydrofuran.

Hawthorne reported that, upon dissolution of an alkylamine–(N–B)-alkylborane in a benzene solution of *o*-phenylenediamine at room temperature, hydrogen was evolved and the derived 1,3,2-benzodiazaborolidine was formed.[9] No reaction occurred when a benzene solution of ethylamine–(N–B)-*o*-tolylborane (**4**) and *o*-phenylenediamine was brought to reflux (~80°); however, 2-(*o*-tolyl)-1,3,2-benzodiazaborolidine (**5**)

(1) This work was supported in part by Grant AT(11-1)-314 from the Atomic Energy Commission, Report No. C00-314-14.

(2) For the previous papers, see (a) J. C. Catlin and H. R. Snyder, *J. Org. Chem.*, **34**, 1660 (1969); (b) H. E. Dunn, J. C. Catlin, and H. R. Snyder, *ibid.*, **33**, 4483 (1968).

(3) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **80**, 4291 (1958).

(4) K. Niedenzu and J. W. Dawson, "Boron–Nitrogen Compounds," Academic Press, New York, N. Y., 1965, p 8.

(5) See ref 4, p 46.

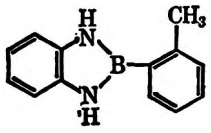
(6) G. B. Butler, G. L. Statton, and W. S. Brey, Jr., *J. Org. Chem.*, **30**, 4194 (1965).

(7) G. B. Butler and G. L. Statton, *J. Amer. Chem. Soc.*, **86**, 518 (1964).

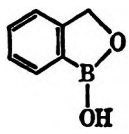
(8) H. E. Dunn, Thesis, Doctor of Philosophy, University of Illinois, 1965; See also ref 2a.

(9) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **83**, 831 (1961).

formed when a mixture of **4** and *o*-phenylenediamine was heated on the steam bath (~100°). The more strenuous conditions required for reaction of **4** with the



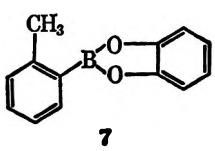
5



6

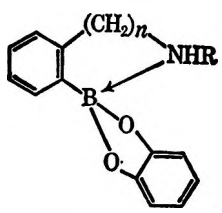
diamine suggest that amine–arylboranes are more stable than amine–alkylboranes. 1,2-Boraztetralin (**2a**) was found to be much less reactive toward *o*-phenylenediamine than the model compound, **4**. No reaction was observed even when a solution of 1,2-boraztetralin (**2a**) and the diamine was heated under reflux in xylene. The enhanced stability of **2a** is comparable with the increased stability of the cyclic boronic ester, boronophthalide, **6**.[10]

The increased stability of cyclic amine–boranes, relative to the acyclic model, **4**, is further indicated by a comparison of the conditions which lead to reaction of 1,2-boraztetralin (**2a**), 2-(2′-phenylethyl)-3,2-borazindan (**2d**), and ethylamine–(N–B)-*o*-tolylborane (**4**) with catechol. The acylic amine–borane **4** reacts with catechol in refluxing benzene to give the catechol derivative of *o*-toluneboronic acid (**7**). Neither



7

1,2-boraztetralin (**2a**) nor 2-(2′-phenylethyl)-3,2-borazindan (**2b**) reacts with catechol under these conditions; however, both **2a** and **2d** react with catechol in refluxing xylene to yield spirocatechol derivatives[11] **8a**



8a, $n = 2$; R = H
b, $n = 1$; R = $C_2H_4C_6H_5$.
c, $n = 1$; R = H

and **8b**. Contrary to expectation, 3,2-borazindan (**2c**) reacted with catechol in benzene solution at room temperature to form **8c**. Of the amine–boranes prepared in this work, **2a–e** and **4**, only 3,2-borazindan (**2c**) decomposed upon melting. It has been reported that both the thermal decomposition and the hydrolysis of simple amine–boranes are strongly influenced by traces of impurities;[12] it is possible that some impurity, perhaps inorganic, catalyzed the reaction of **2c** with catechol and also caused its decomposition near the melting point. That the catechol derivatives of the cyclic amine–boranes have spiro structures **8a–c** is indicated by their infrared spectra. The absence of the characteristic boron–oxygen stretch in the region 1350–1400 cm^{-1} indicates the boron to be tetrahedrally substituted.[13]

Ethylamine–(N–B)-*o*-tolylborane (**4**) is hydrolyzed in refluxing aqueous acetonitrile as is pyridine–(N–B)-phenylborane.[14] 1,2-Boraztetralin (**2a**), 3,2-borazindan-2-spiro-1′-piperidine (**2e**), and surprisingly, in view of its ready reaction with catechol and its low thermal stability, 3,2-borazindan (**2c**) are not hydrolyzed under these conditions. Refluxing aqueous acetone hydrolyzes 1,2-boraztetralin (**2a**).[2a] Presumably these conditions would also hydrolyze the other cyclic amine–boranes.

The ease with which amine–boranes react with olefins depends upon the strength of the boron–nitrogen coordination. The first step is dissociation of the amine–borane; the free borane then reacts with the olefin.[15] Ethylamine–(N–B)-*o*-tolylborane (**4**) does not react with cyclohexene at room temperature over a 24-hr period, but reaction occurs when a solution of **4** in cyclohexene is heated at reflux for 3 hr. 1,2-Boraztetralin (**2a**) does not react with cyclohexene even when the solution is heated at reflux for 12 hr, thus indicating again that the cyclic structure increases the stability of the amine–borane.

The difference between the ease of reaction of ethylamine–(N–B)-*o*-tolylborane (**4**) and the cyclic amine–boranes with *o*-phenylenediamine, catechol, and cyclohexene, and the difference in hydrolytic stability clearly indicate that cyclic amine–boranes are stabilized by incorporation of the boron and nitrogen atoms within a five- or six-membered nonaromatic ring.

Mass Spectral Studies.—With the preparation of a series of closely related amine–boranes and their catechol derivatives, we were in a unique position to study the mass spectral fragmentations of these heterocyclic compounds. The mass spectra of three cyclic amine–boranes (**2a, b,** and **d**) and two of their catechol derivatives (**8a** and **b**) were obtained. The results are of interest in part because these molecules contain functional groups which have not previously been studied under electron impact, and in part because they offer an opportunity to observe new modes of interaction between suitably located functional groups under electron impact.[16]

The major mass spectral fragmentations of 1,2-boraztetralin (**2a**) (Table I) involve loss of one, two, and three hydrogens (M − 1, 2, and 3). The base peak occurs at *m/e* 131 (M − 2). The next most intense peaks occur at *m/e* 104, 103, and 91.[17–19] (Support for the proposed structures comes from the presence of analogous fragments in the spectrum of **8a**.)

(10) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *ibid.*, **80**, 835 (1958).

(11) Similar spiro compounds have been previously reported; see ref 8 and R. L. Letsinger and D. B. MacLean, *ibid.*, **85**, 2230 (1963).

(12) Reference 4, p 19, and H. Nöth and H. Beyer, *Chem. Ber.*, **93**, 928 (1960).

(13) R. L. Letsinger, Advances in Chemistry Series, No. 42, American Chemical Society, Washington, D. C., 1964, p 3.

(14) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **80**, 4291 (1958).

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(16) (a) For a comprehensive review of mass spectrometry, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967. (b) M. I. Bruce, *Advan. Organometal. Chem.*, 273 (1968). We wish to thank a referee for bringing this review to our attention.

(17) The tropylium ion structures for the *m/e* 91 and 103 peaks are suggested by analogy to the structure assigned in other work to the hydrocarbon fragment occurring at *m/e* 91: see ref 16a, p 76.

(18) The structural formulas, *i.e.*, the bicyclic structure of the *m/e* 104 fragment, are formal representations; see ref 16a, p 6.

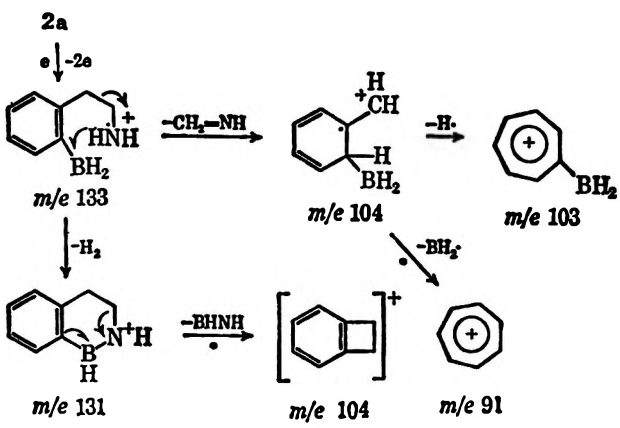
(19) Fragmentation pathways supported by metastable peaks are indicated by asterisks.

TABLE I

THE MASS SPECTRA OF 1,2-BORAZTETRALIN (2a), 2-(2′-PHENYLETHYL)1,2-BORAZTETRALIN (2b), AND 2-(2′-PHENYLETHYL)-3,2-BORAZINDAN (2d)

2a		2b				2d			
m/e	%[a,b]	m/e	%[a,b]	m/e	%[a,b]	m/e	%[a,c]	m/e	%[a,c]
134	4	238	8	119	2	225	2	115	2
133	44	237	39	118	17	224	17	114	1
132	78	236	26	117	7	223	100	106	5
131	100	235	10	116	5	222	72	105	52
130	87	234	7	115	6	221	31	104	3
129	32	233	2	114	3	220	19	103	10
128	60	194	2	113	4	219	6	102	3
127	16	160	2	106	10	218	3	101	3
126	3	159	3	105	100	217	4	100	2
117	2	158	2	104	10	180	1	93	2
116	12	157	2	103	10	145	1	92	24
115	16	146	2	102	3	144	2	91	14
114	5	145	8	101	3	143	1		
113	3	144	63	100	2	133	1		
105	16	143	18	92	4	132	10		
104	65	142	4	91	22	131	6		
103	29	134	3			130	29		
102	10	132	8			129	8		
101	18	131	47			128	4		
100	9	130	22			127	1		
92	3	129	6			118	2		
91	24	128	8			117	16		
90	2	127	2			116	8		

[a] The peaks are reported as per cent height relative to the largest peak in the spectrum. No peak below *m/e* 90 is reported. [b] No peak is reported which has a relative height of less than 2%. [c] No peak is reported which has a relative height of less than 1%.



In the mass spectrum of 2-(2′-phenylethyl)-1,2-boraztetralin (**2b**) and 2-(2′-phenylethyl)-3,2-borazindan (**2d**) the major fragmentations involve the 2′-phenylethyl moiety (see Table I). The peaks in the spectrum of borazindan **2d** occur 14 *m/e* units lower than the corresponding peaks in the spectrum of **2b** (see Table II). The only difference in structures **2b** and **2d** is that the former contains two methylene carbons in the heterocyclic ring while the latter contains only one methylene group. As in the case of 1,2-boraztetralin (**2a**), **2b** and **2d** easily lose one, two, and three protons. The largest fragmentation peak in the spectra of both 2-(2′-phenylethyl)-1,2-boraztetralin (**2b**) and 2-(2′-phenylethyl)-3,2-borazindan (**2d**) is due to the 2′-phenylethyl group (*m/e* 105). The 2′-phenylethyl group is lost from the appropriate M − 1 fragment (metastable peaks); in each case the other "half" of the molecule is also observed (*m/e* 131 and 117). N-Substituted amine–boranes **2b** and **2d** have fragments *m/e* 144 and 130, respectively, which are presumed to be due to loss of a tropylium ion from the M − 2 fragments; a peak corresponding to the tropylium ion is also observed in both spectra.[17] In the spectrum of **2b** there is a fragment at *m/e* 159 which corresponds to the formal loss of C_6H_6 from the molecular ion; the corresponding fragment in the spectrum of **2d** occurs at *m/e* 144, not *m/e* 145 as would be predicted. 2-(2′-Phenylethyl)-1,2-boraztetralin (**2b**) and 2-(2′-phenlyethyl)-3,2-borazindan (**2d**) can undergo the formal loss of ethylenimine (43 mass units) with phenyl migration. In the spectrum of **2d** there is a metastable peak corresponding to the loss of ethylenimine. 2-(2′-Phenylethyl)-3,2-borazindan (**2d**) also yields a major fragment at *m/e* 92; none of the other

TABLE II

MAJOR FRAGMENTS IN THE MASS SPECTRA OF 2b AND 2d

m/e		
2b	2d	Δ
237	223	14
236	222	14
194	180 (*)	14
159	144	15
144	130	14
131	117	14
105 (*)	105 (*)	0
91	91	0

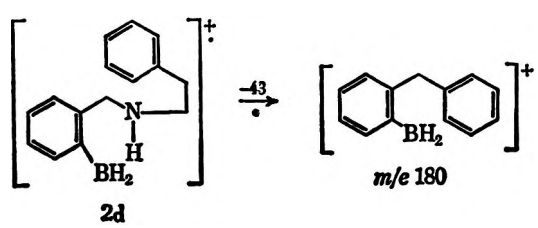


TABLE III

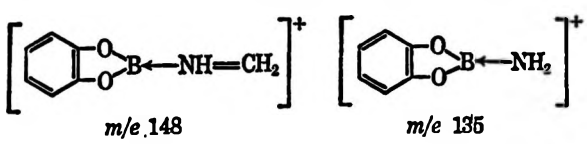
THE MASS SPECTRA OF THE CATECHOL DERIVATIVE OF 1,2-BORAZTETRALIN (8a) AND 2-(2′-PHENYLETHYL)3,2-BORAZINDAN (8b)

8a		8b	
m/e	%[a]	m/e	%[a]
240	18	330	7
239	100	329	27
238	30	328	7
237	3	239	12
211	4	238	76
210	24	237	20
209	24	236	4
208	5	210	15
165	8	209	100
149	5	208	25
148	20	165	5
147	8	119	4
146	5	117	3
145	3	105	7
144	4	104.5	20
136	3	104	6
135	4	91	7
128	3		
119.5	4		
117	6		
104	8		
103	7		
92	4		
91	9		
90	3		

[a] The peaks are reported as per cent height relative to the largest peak in the spectrum. No peak which has a relative height of less than 3% and no peak below m/e 90 is reported.

compounds studied had an important fragment with this mass-to-charge ratio.

The mass spectrum of the catechol derivative of 1,2-boraztetralin (**8a**) (see Table III) contains the m/e 104 and 91 fragments which were observed in the spectrum of 1,2-boraztetralin (**2a**). In each case the other "half" of **8a** is also seen (m/e 148 + 91 = 135 + 104 = 239 = mol wt). The fragments m/e 209 and 210 in the spectrum of **8a** are analogous to the m/e 103 and 104 fragments in the spectrum of **2a**. A peak is observed at 119.5 due to the doubly charged molecular ion.



The mass spectrum of the catechol derivative of 2-(2′-phenylethyl)-3,2-borazindan (**8b**) (Table III) is similar to that of 2-(2′-phenylethyl)-3,2-borazindan (**2d**), except that the fragmentations of **2d** are complicated by cleavage of the boron–hydrogen bonds.

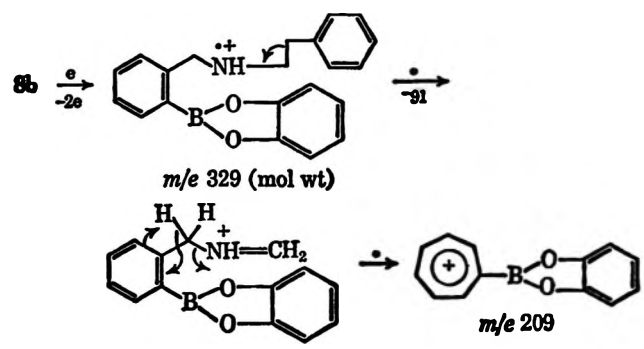


TABLE IV

PREPARATION OF AMINE–BORANES

Precursor	Amine-borane	Crystallization solvent	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mol wt[a] Calcd	Mol wt[a] Found
1a[b]	2a	H_2O, EtOH	83	150–151	72.24	9.09	10.53	72.11	9.32	10.54	133	133
1b[c]	2b	Benzene	29	120–122	80.68	8.41	5.91	80.51	8.51	5.95	237	237
1c[d]	2c	Benzene	17	88–90[e]	70.65	8.47	11.77	70.42	8.49	10.62	119	117
1d[f]	2d	EtOH–H_2O	43	122.5–123	80.72	8.07	6.23	80.68	8.01	5.87	233	233
1e	2e	Benzene–hexane	48	81–83	77.07	9.70	7.49	77.03	9.85	7.02		
Ethylamine + o-tolylboronic anhydride	4	H_2O	50	69–70	72.54	10.80	9.40	72.20	11.01	8.90; 9.34		

[a] Molecular weights were obtained by mass spectrum. [b] See ref 2a for the preparation of 1a. [c] See ref 2a for the preparation of an analogous compound. [d] See ref 2b. [e] Melted with decomposition. [f] See ref 2b for the preparation of analogous compounds.

TABLE V

PREPARATION OF CATECHOL DERIVATIVES OF AMINE–BORANES

Amine-borane	Catechol derivative	Reaction solvent	Crystallization solvent	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mol wt[a] Calcd	Mol wt[a] Found
4	7	Benzene	Benzene–hexane	33	90–92	74.35	5.28		74.06	5.26			
2a	8a	Xylene	Chloroform	50	257–259	70.35	5.90		70.43	5.84		239	239
2d	8b	Xylene	Benzene	63	198–200	76.59	6.08	4.25	77.41	6.15	4.06	329	329
2c	8c	Benzene[b]	Benzene	62	272–274	69.33	6.22		69.07	5.91		225	225

[a] Molecular weights were obtained by mass spectrum. [b] Room temperature for 0.5 hr.

The major electron-induced fragmentations of the catechol derivative of 2-(2′-phenylethyl)-3,2-borazindan (**8b**) involve the stepwise cleavage of the 2′-phenylethyl moiety. The *m/e* 209 fragment is identical with that in the spectrum of **8a**, and in both cases arises from the loss of CH_2NH. A doubly charged species was observed at *m/e* 104.5 (*m/2e* 209); no doubly charged peak was observed corresponding to the molecular ion.

In the mass spectra of the amine–boranes (**2a, b,** and **d**) and their catechol derivatives (**8a** and **b**), there are many fragments which are either analogous or identical in these closely related compounds (see Table II). Support for assignments made is obtained by comparing related spectra.

Experimental Section[20]

Preparation of Amine–Boranes.—A solution of the appropriate aminoboronic acid, or potential aminoboronic acid, in tetrahydrofuran (THF) was slowly added to an excess of lithium aluminum hydride in THF. The resulting mixture was refluxed for 1 hr, and the excess $LiAlH_4$ was decomposed by the careful addition of water. The mixture was filtered and the residue was washed with THF. Evaporation of the combined THF solutions gave the desired amine–boranes which were purified by crystallization (see Table IV).

Preparation of Catechol Derivatives of Amine–Boranes.—Equivalent molar amounts of catechol and the appropriate amine–borane were heated under reflux for 1 hr in either benzene or xylene. When benzene was used as solvent, the reaction mixture was evaporated *in vacuo*. The reactions in xylene were chilled and the catechol derivatives were collected by filtration. The catechol derivatives were purified by crystallization (see Table V).

Preparation of the Catechol Derivative of *o*-(Bromomethyl)-benzeneboronic Acid.—The water was azeotropically removed from a carbon tetrachloride solution of 5.9 g of *o*-tolueneboronic anhydride and 5.5 g of catechol. Carbon tetrachloride was added as required to keep the total volume at about 300 ml. The flask was then equipped with a reflux condenser and addition funnel. A solution of 2.56 ml of bromine in 100 ml of carbon tetrachloride was added slowly to the solution of the catechol derivative of tolueneboronic acid which was heated under reflux and irradiated overnight with a Hanovia 215-W ultraviolet light (No. 30400). The dark solution was concentrated *in vacuo* and poured into an equal volume of hexane. The solution was treated with Darco and filtered. Upon concentration nearly to dryness at room temperature, 8.2 g (56%) of crude product was obtained. After having been recrystallized several times from hexane, the sample melted from 104 to 105°.

Anal. Calcd for $C_{13}H_{13}BO_2Br$: C, 54.02; H, 3.47. Found: C, 53.91; H, 3.48.

o-(Bromomethyl)benzeneboronic anhydride can also be converted into the catechol derivative by azeotropic removal of water from a solution of *o*-(bromomethyl)benzeneboronic anhydride and catechol.

Preparation of 3,2-Borazindan-2-spiro-1′-piperidine (2e).—To a solution of 2.89 g of the catechol derivative of *o*-(bromomethyl)benzeneboronic acid in 25 ml of THF was added 2 ml of piperidine. The slurry which formed was allowed to stand for 0.5 hr. Then the THF solution was added to a stirred slurry of 0.78 g of $LiAlH_4$ in 100 ml of THF. The piperidine hydrogen bromide was then washed with two 25-ml portions of THF which were also added to the $LiAlH_4$ slurry and the reaction mixture was heated at reflux for 1 hr. The excess $LiAlH_4$ was decomposed with water, the mixture was filtered, and the filtrate was evaporated. The residue obtained upon evaporation of the filtrate was extracted with two 50-ml portions of ether. Evaporation of the combined ether extracts yielded 0.9 g (48%) of 3,2-borazindan-2-spiro-1′-piperidine which, after recrystallization from benzene–hexane and washing with ethanol, melted at 81–83° (see Table IV).

Reaction of Ethylamine–(N–B)-o-Tolylborane with *o*-Phenylenediamine.—A mixture of 0.15 g of ethylamine–(N–B)-*o*-tolylborane and 0.11 g of *o*-phenylenediamine was heated on the steam bath for 0.5 hr. 2-(*o*-Tolyl)-1,3,2-benzodiazaborolidine (**5**, 0.17 g), after having been recrystallized from benzene–hexane, melted at 81–82°.

Anal. Calcd for $C_{13}H_{13}BN_2$: C, 75.06; H, 6.30. Found: C, 75.18; H, 6.22.

Registry No.—**2a,** 19214-72-3; **2b,** 19214-73-4; **2c,** 19214-74-5; **2d,** 19214-75-6; **2e,** 19214-76-7; **5,** 19206-12-3; **7,** 19206-13-4; **8a,** 19214-77-8; **8b,** 19214-78-9; **8c,** 19214-79-0; catechol derivative of *o*-(bromomethyl)benzeneboronic acid, 19206-14-5.

(20) Microanalyses were performed by Josef Nemeth and his associates. Infrared spectra were determined by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering of the University of Illinois, using a Perkin-Elmer Model 21 infrared spectrophotometer (equipped with sodium chloride optics). All melting-point determinations were uncorrected and were obtained on a Kofler microstage melting-point apparatus. Evaporations done *in vacuo* were carried out on a rotary evaporator unless specified otherwise. The mass spectra were obtained by Mr. Joseph Wrona on an Atlas CH4 spectrometer.

Arylboronic Acids. A Medium-Size Ring Containing Boronic Ester Groups[1]

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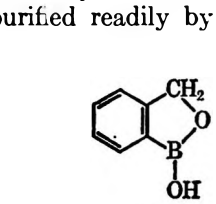
Dehydration of hydroxyethylboronophthalide (**2**) is shown to occur by a bimolecular route giving a dimeric boronic ester (**4**). This ester is not easily hydrolyzed, and under mild conditions it does not react with such reagents as 2-aminoethanol and *o*-phenylenediamine. Such remarkable stability is attributed to an intramolecular coordination of oxygen atoms to electron-deficient boron atoms. Conditions of aromatic nitration cause aromatic substitution along with solvolysis of the borate bond to form 5-nitroboronophthalidylethyl nitrate. The nitration and esterification of boronophthalidylacetic acid and the esterification of 5-nitroboronophthalidylacetic acid are also studied. Ir and nmr spectra of α-substituted boronophthalides are discussed.

The unusual stability of the boronolactone ring in boronophthalide (**1**) and in many of its functional derivatives[2-6] suggests an examination of the hydroxyethylboronophthalide (**2**), particularly with reference to its behavior under conditions of dehydration. The simplest possible paths of dehydration of **2** are intermolecular esterification of the remaining B–OH function by the primary alcohol group, a process that would lead to a linear polymer, and the corresponding intramolecular esterification, which would lead to the tricyclic monomeric ester (**3**); but there are many possible dehydration paths, including the bimolecular equivalent of the intermolecular esterification, a process which would produce the "dimeric" ester (**4**), opening of the boronophthalide ring to the boronocinnamyl alcohol, which might react further both by esterification and boronic anhydride formation, and others.

To obtain 2-boronophthalidylethanol (**2**) for study, boronophthalidylacetic acid (**5**) was prepared from *o*-formylbenzeneboronic acid by condensation with either malonic acid or isopropylidene malonate,[6] and the acetic acid derivative was reduced with lithium aluminum hydride. The crude oily product from the reduction reacted with phenyl isocyanate to give a crystalline derivative having the composition of the phenylurethan of **2**. But the alcohol proved to be remarkably sensitive to dehydration, and it was not possible to obtain it in the pure state. On storage over a desiccant or even on trituration with cyclohexane, it changed to a colorless high-melting solid. The solid was of low solubility in the common solvents, but it could be purified readily by sublimation at low pressure (2–4 mm). Volatility sufficient to permit sublimation suggests that the substance is one of the cyclic esters (**3** or **4**); microanalysis and molecular weight determinations (by the Rast method and by mass spectrometry) show that it is the "dimeric" ester **4**.



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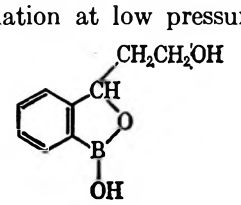

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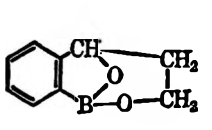

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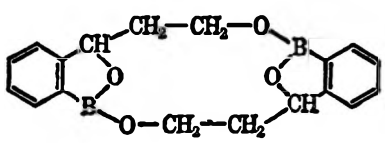

4

Although simple boronic esters are very easily solvolyzed, derivatives obtained from 2-aminoethanol[7,8] are remarkably stable as the result of coordination between the nitrogen and boron atoms. Similarly, stablilized derivatives have been obtained from *o*-phenylenediamine.[8] Dimeric ester **4**, however, was recovered from treatment with these reagents. It is apparently slowly hydrolyzed by water alone, for it does dissolve in water on prolonged heating and the solutions so formed do not deposit solid material on cooling. However, extraction of such solutions with benzene and evaporation of the solvent permit the recovery of the dimeric ester **4**, evidently as the result of hydrolysis, extraction of the monomer into the benzene, and re-formation of the dimer during the concentration of the solution. Finally, the dimeric ester gave no indication of the formation of an adduct with pyridine, a reagent which yields isolable solid derivatives with many boronic anhydrides.[9]

The stability of the cyclic dimer suggests that the boron atoms are coordinated with oxygen atoms and that the actual structure may be somewhat similar to that of tribenzotaralene (**6**).[10] The novel feature of the latter structure is the superposition of the trimethylenetriamine ring and the boroxine ring so that each boron atom is near enough a nitrogen atom that coordination occurs and the groups are locked in the multicyclic arrangement (**6**). In the models of the cyclic dimer (**4**), the boron atoms and oxygen atoms of the boronolactone rings are found to be quite near each other. If coordination occurs across the ring system (**7**), the structure can be regarded as equivalent to that having the two six-membered boronic ester rings disposed one above the other and linked by oxygen–boron coordination (**7**). The four-membered ring central to structure **7** is similar to the type proposed to explain the dimerization of methyl difluoroboronite and *n*-butyl difluoroboronite in the liquid state.[11,12]

In a test of the behavior of dimeric ester **4** under

(1) This work was supported by Grant AT(11-1)-314 from the Atomic Energy Commission, Report No. C00-314-15.

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(7) R. K. Kurz, Ph.D. Thesis, University of Illinois, 1961.

(8) R. L. Letsinger and S. B. Hamilton, *J. Amer. Chem. Soc.*, **80**, 5411 (1958).

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(10) The authors are indebted to Professor Dewar for permission to reproduce the tribenzotaralene structure shown by M. J. S. Dewar, R. C. Dougherty, and E. B. Fleischer, *ibid.*, **84**, 4882 (1962).

(11) J. Goubeau and K. E. Lüeke, *Ann.*, **575**, 37 (1952).

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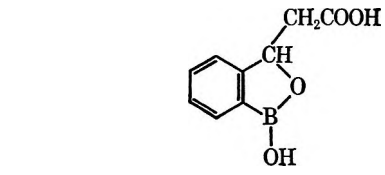

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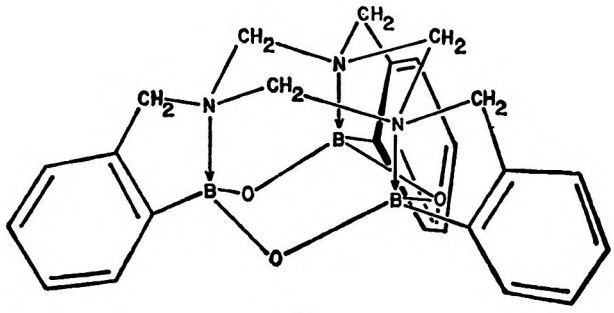

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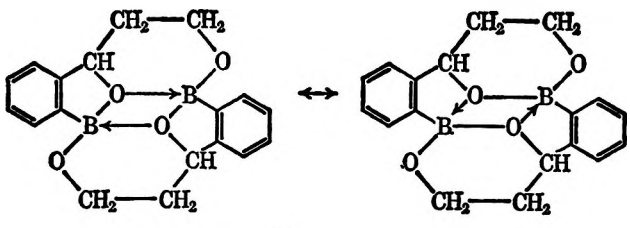

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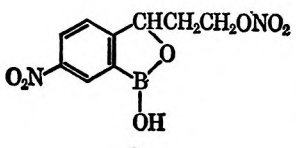

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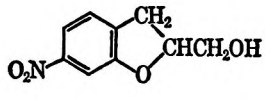

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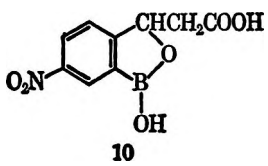

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conditions of aromatic substitution, the substance was treated with fuming nitric acid at −40°. Both nitration and cleavage occurred, the product being nitro nitrate **8**. The nitrate ester function in **8** was unaffected by aqueous or methanolic sodium hydroxide under conditions that cause the solvolysis of ethyl nitrate. Alkaline hydrogen peroxide effected both oxidative removal of the boron and solvolysis of the nitrate function, the product obtained after acidification being 2-(hydroxymethyl)-6-nitro-2,3-dihydrobenzofuran (**9**). This structure, rather than that of the isomeric hydroxycinnamyl alcohol, for the deboronation product was suggested by the failure of the substance to give a color with ferric chloride and is in agreement with the nmr spectral measurements (see Experimental Section).

Because of the unexpected course of the dehydration of alcohol **2**, it would be of interest to examine the behavior of the next lower homolog, α-hydroxymethylboronophthalide. α-Carboxyboronophthalide is readily available,[6] and it was assumed that its reduction with lithium aluminum hydride would parallel that of the higher homolog. Surprisingly, the reduction took an entirely different course; the only product obtained upon working up the reaction mixture in the usual way, without exclusion of air, was *o*-tolueneboronic acid, isolated as its anhydride. It is tempting to consider that at some stage in the process the boronophthalide ring was opened reductively and the B–H link so formed underwent oxidation during handling in the air; the question has not been studied, nor is the fate of the carbon atom lost in the reduction known.

Structure **5** of boronophthalidylacetic acid was originally assigned on the basis of its infrared spectrum.[6] Study of the nmr spectrum (see below) confirms the structure and, together with molecular weight measurements in solution, indicates coordination between the boron atom and a carboxylate oxygen atom. Although mixed anhydrides do not readily form from boronic and carboxylic acids, the proximity of the two functions in **5** might promote such anhydride formation. The other possible consequence of the proximity of the two functions, however, is facilitation of acid-catalyzed deboronation. The latter influence is the dominating one. When the acid was heated under diminished pressure near its melting point, cinnamic acid was the only organic product isolated. The action of thionyl chloride under mild conditions also caused extensive deboronation of **5**. The acid could be converted into its methyl ester by the action of methanol. In the mass spectrometer the methyl ester gave peaks corresponding to the expected molecular weight (mass 206) and to that of the anhydride (mass 394) formed by combination of two molecules by elimination of water between >B-OH functions.

Boronophthalidylacetic acid also could be nitrated by fuming nitric acid at −40°, the nitro group entering the 5 position (**10**). The infrared spectrum of the nitration product does not alone suffice for the assignment of the boronophthalide structure (rather than the isomeric cinnamic acid), but the nmr evidence favors this formulation and confirms the position of the nitro group. The nitro acid also gives a methyl ester which in the mass spectrometer gave only the peak corresponding to its anhydride (mass 484).

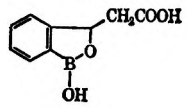
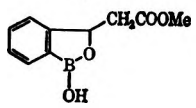
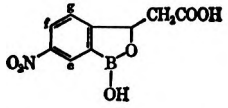
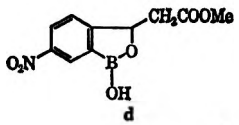
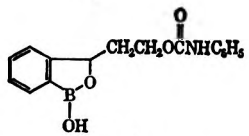
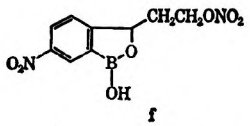
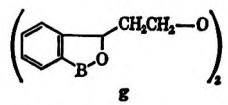
Spectral Data.—The structures suggested for the various compounds above rest in part on ir and nmr spectral data. The infrared spectra (Table I) contain three features which have been reported earlier in the spectra of various boronophthalides.[6,13] (1) Except in c, the oxygen–hydrogen stretching frequency of these systems is in the range 3350–3450 cm^{-1}. (2) Two bands appear in the 1340–1380-cm^{-1} region. These have been attributed to the symmetric and asymmetric B–O stretching frequencies, respectively. However, for d and f, the band near 1350 cm^{-1} is assigned to the asymmetric NO_2 stretching frequency because of the known intensity of this band which would obscure the band due to the asymmetric B–O stretching frequency. (3) All spectra contain a band in the 1070–1100-cm^{-1} region. This band has been assigned previously to the C–O stretch in five-membered cyclic ethers.[14] All boronophthalide spectra studied previously[5,6,13] had a band in the region 970–1005 cm^{-1}, which had been attributed to a C–O stretching frequency. All but c and e show this band. Why c and e do not show this absorption is not clear, but other properties of the compounds support their formulation as boronophthalides. The carbonyl frequencies of a and c, taken

(13) W. J. Dale and J. E. Rush, *J. Org. Chem.*, **27**, 2598 (1962).

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1956, p 119.

TABLE I

SPECTRAL DATA OF α-SUBSTITUTED BORONOPHTHALIDES

Compound	Infrared[a] OH	B–O	Cyclic ether	C–O			Nmr Solvent	H_X	$H_{B(endo)}$	$H_{A(exo)}$	H^b	Aromatic	Coupling constants, cps
 a					C=O	1740	TFA[c]	4.13 (dd)	6.72 (dd)	7.25 (dd)			J_{AB} = 16.0 J_{AX} = 9.0
	3350	1340, 1365	1090	1002 (s)		1740 (Nujol)	DMSO-d_6	4.48 (dd)	6.95 (dd)	7.50 (dd)			J_{BX} = 4.0
 b	3400	1340, 1370	1100	990 (m)	C=O	1725	Acetone-d_6	4.42 (dd)	7.05 (dd)	7.51 (dd)	6.30 (s)		J_{AB} = 15.0 J_{AX} = 8.5 J_{BX} = 4.5
					C=O	1690						H_e 1.85 (s)	J_{AB} = 15.5, J_{ortho} = 9.0
 c	3100	1365	1090			1690 (Nujol)	DMSO-d_6	4.36 (dd)	6.88 (dd)	7.50 (dd)		H_f 2.05 (d)	J_{AX} = 9.5, J_{meta} = 2.0
					NO_2							H_g 2.65 (d)	J_{BX} = 5.0
					(asym)	1510							
					(sym)	1340							
 d					C=O	1720							
	3400	1370	1070	980 (m)	NO_2		Acetone-d_6	4.30 (dd)	6.95 (dd)	7.34 (dd)	6.30 (s)		J_{AB} = 16.0
					(asym)	1520							J_{AX} = 8.0
					(sym)	1350							J_{BX} = 5.0
 e					C=O	1660							
	3400	1340, 1365	1070			(amide I) 1620 (amide II)	$CDCl_3$	4.65 (dd)	8.0 (m)	8.0 (m)	5.65 (t)		J_{AX} = 8.0 J_{BX} = 5.0
 f					ONO_2 (asym)	1635							J_{AX} = 9.0
					NO_2 (asym)	1510							J_{BX} = 5.0
	3450	1355	1080	965 (m)	NO_2 (sym)	1340	$CDCl_3$	4.55 (dd)	8.0 (m)	8.0 (m)	5.30 (t)		
					ONO_2 (sym)	1285							
 g		1345, 1365	1100	975 (s)									

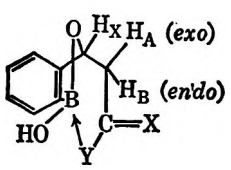
[a] All spectra were taken in potassium bromide disks unless otherwise noted. [b] Other aliphatic hydrogens. [c] TFA (trifluoroacetic acid). H_X = the hydrogen on the borono hetero ring. H_A and H_B = the methylene hydrogens in the position α to the hetero ring.

from spectra in potassium bromide disks and Nujol mulls, are separated by 50 cm^{-1}. A frequency of 1740 cm^{-1} might be expected for the carbonyl of a if there is internal coordination by the hydroxyl group of the carboxyl group with the boron atom forming a pseudo[3.2.1] system similar to a cyclic acyl derivative of a boronic acid. The low value for the carbonyl absorption of c (1690 cm^{-1}) cannot be explained in this fashion. This low carbonyl frequency could result from the coordination of the carbonyl oxygen with the boron atom, creating an effect similar to that of hydrogen bonding.[15] The carbonyl frequencies of the methyl esters of a and c are almost the same but still 15–20 cm^{-1} lower than the carbonyl absorptions for normal methyl esters.[16] Again, this can be explained by a perturbation of the carbonyl oxygen by the boron atom.

The nuclear magnetic resonance spectra of these α-substituted boronophthalides (Table I) are more complex than would be expected *a priori*. All (a–f) contain a one-proton double doublet between τ 3.95 and 4.75. This absorption has been previously assigned to the proton of the boronophthalide ring system (in boronophthalide[17] itself, τ 4.98). The two-proton absorptions in the τ 6.72–8.00 region are assigned to the methylene protons adjacent to the boronophthalide ring. These methylene proton absorptions in a–d are characterized by two well-defined double doublets while in e and f only a complex multiplet is observed. In addition to these absorptions, e and f each have a well-defined, two-proton triplet in the τ 5.30–5.65 region.

This pattern of double doublets in a–d is characteristic of an ABX system in which two nonequivalent protons attached to the same carbon are splitting each other in the presence of a third proton on an adjacent carbon. In e and f, the AB part of the spectrum is further split by two additional adjacent protons, producing a very complex multiplet.

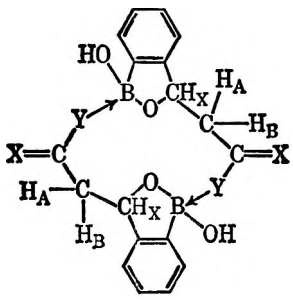
There are three ways to explain this ABX splitting pattern: (1) there is internal coordination by the electrons of a heteroatom to an empty orbital of boron, forming a pseudobicyclic[3.2.1] system; (2) there



A, X = methylene or heteroatom
Y = grouping containing heteroatom

is a head–tail association of two molecules, again with available electrons filling the vacant orbital of boron, thereby restricting the rotation of the methylene group by locking it into a cyclic conformation;[18] (3) the AB nonequivalence results from the asymmetry of the methylene hydrogens caused by the adjacent asymmetric center.[19]

(15) L. A. Duncanson, W. Gerrard, M. F. Lappert, H. Pyszora, and R. Shafferman, *J. Chem. Soc.*, 3652 (1958).
(16) R. G. Sinclair, A. F. McKay, and R. N. Jones, *J. Amer. Chem. Soc.*, **74**, 2570 (1952).
(17) R. T. Hawkins, W. J. Lennarz, and H. R. Snyder, *ibid.*, **82**, 3053 (1960).
(18) R. F. Watson and J. F. Eastman, *ibid.*, **87**, 665 (1965).
(19) G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1113 (1962).



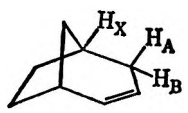
B

Molecular weight studies in acetone or chloroform indicate that these compounds are monomeric in these solvents. Spectra obtained in these solvents and in more polar solvents [DMSO and TFA (trifluoroacetic acid)] should be of a monomeric species.

Infrared studies indicate that there is some type of internal coordination to the boron atom. This is particularly evident in a whose acid carbonyl is at 1740 cm^{-1} [14] and in the methyl esters of b and d whose carbonyl frequencies are 15–20 cm^{-1} lower than would normally be expected in methyl esters.[16] These data suggest some type of perturbation by the boron atom. Molecular models of these compounds show that there is very little bond distortion in forming a pseudo[3.2.1] bicyclic ring system from the most stable conformer.

Generally, then, the spectra of a–f can best be explained on the basis of a structure such as A with the appropriate heteroatom forming the weak bond to the boron atom.

The geminal coupling constants for a–d are 15.0–16.0 cps. These are quite similar to the geminal coupling constants found for bicyclo[3.2.1]oct-2-ene.[20]



J_{AB} = 17.0 cps
J_{AX} = 4.7 cps
J_{BX} = 2.0 cps

The vicinal coupling constants, however, are quite different. Both in the bicyclo[3.2.1]oct-2-ene series[20] and in the dibenzobicyclo[3.2.1]octadiene,[21] J_{BX}(*endo*) was found to be *ca.* 1.5–2.5 cps and J_{AX}(*exo*) = 4.7–5.5 cps. Since the *exo* proton is shown to couple more strongly than the *endo* in these bicyclic systems, the larger coupling (8.0–9.0 cps) can be assigned to the pseudo-*exo* proton in the pseudobicyclo[3.2.1] system. The highest chemical shift can then be assigned to the pseudo-*exo* proton.

Compounds with more than one heteroatom in proximity (e and f) to the boron atom could coordinate to give systems other than pseudobicyclo[3.2.1] systems. However, the invariance of the vicinal coupling constants J_{AX} and J_{BX} of the ABX system suggests that the steric relationship between these protons remains the same throughout the series. A preference for bicyclo[3.2.1] coordination is thus seen.

Nuclear magnetic resonance studies of the dimeric ester were accomplished with more difficulty. In most common nmr solvents, the solubility of this dimer was so low that good spectra could not be obtained. Even

(20) C. W. Jefford, B. Waegel, and K. Ramey, *J. Amer. Chem. Soc.*, **87**, 2191 (1965).
(21) S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).

in DMSO-d_6 only a 4% solution could be obtained. However, this ester did dissolve in TFA and gave a spectrum similar to those of e and f.

A low-field triplet at τ 5.45 indicates that the dimeric ester has been solvolyzed and most likely a trifluoroacetate of the monomer has formed. If solvolysis had not occurred, a chemical-shift value for this triplet would be expected to occur near τ 6.3 (*n*-butyl borate, 6.25). This shift of almost 1 ppm can most easily be explained by this solvolysis of the dimeric ester. A similar shift for alcohols in TFA has been noticed before. Peterson[22] reports a value of τ 6.02 for the α-methylene hydrogens of ethyl trifluoroacetate, a shift of 0.63 ppm from value of τ 6.65 for ethanol itself.

The nuclear magnetic resonance spectrum of urethan e has two one-proton, singlet absorptions at very low field (τ 0.4 and 0.8). The position of the former (the other being the amido proton absorption) is consistent with the BO–H proton absorptions found for boronophthalidylacetic acid (τ 0.5) and 2-(5-nitroboronophthalidyl)ethyl nitrate and with that found for α-(nitromethyl)boronophthalide (τ 0.3).[6] This low-field, singlet BO–H proton absorption thus appears to be a characteristic feature in the nuclear magnetic resonance spectra of α-substituted boronophthalides containing a heteroatom in the side chain capable of coordination with the electron-deficient boron atom of the boronophthalide ring system. Its appearance in the spectrum of urethan e is evidence that the phenyl isocyanate has indeed added to the alcoholic hydroxyl group, and not to the boronic hydroxyl group.

Mass Spectrometric Measurements.—The course of decomposition of thermally unstable compounds can sometimes be determined by mass spectrometry. Compounds a, c, and e decompose in the mass spectrometer when the samples are heated. The mass spectrograms of cinnamic and *p*-nitrocinnamic acids were obtained when a and c were so heated. When urethan e was heated *in vacuo* decomposition to its precursors (*o*-boronophthalidylethanol and phenyl isocyanate) occurred. This mode of breakdown in the mass spectrometer is characteristic of urethans containing a phenyl group as a N substituent.[23] Water was also immediately lost, forming dimeric ester g. The newly formed water reacted with phenyl isocyanate to give the expected products (aniline and symmetrical diphenylurea). All these molecular ions are observed in the low-voltage mass spectrogram.

This thermal behavior is also noted outside the mass spectrometer. Subjecting a, c, and e to heat and reduced pressure in a sublimation apparatus gives cinnamic acid, *p*-nitrocinnamic acid, and dimeric ester g, respectively.

Experimental Section[24]

Boronophthalidylacetic Acid (a).—The following modification of Tschampel's preparation from *o*-formylbenzeneboronic acid and malonic acid[6] is about three times more productive and hence also superior to the preparation from isopropylidene malonate.[6] Into 30 ml of reagent grade dioxane was put 3.0 g (20 mmol) of *o*-formylbenzeneboronic acid along with 3.0 g (34 mmol) of malonic acid. After the addition of 5 drops of pyridine, the reaction solution was heated on a steam bath for 24 hr during which time the evolution of carbon dioxide was noticed. The reaction mixture was cooled to ambient temperature and saturated with ammonia. A light yellow solid precipitated which was collected and dried *in vacuo* to give 4.5 g of product. It was dissolved in 20 ml of water and extracted three times with 20-ml portions of ether. These extracts were discarded. The aqueous portion was acidified to pH 3 with concentrated hydrochloric acid and extracted three times with 20-ml portions of ether. These ethereal portions were combined and the ether then allowed to evaporate into the air, leaving a colorless oil which crystallized within 24 hr. After the wet, light yellow crystals had dried on a porous clay plate, 2.0 g of *o*-boronophthalidylacetic acid (53%), mp 120–130°, was collected.

Again these crystals were dissolved in 10 ml of water; this solution was saturated with ammonia and then extracted three times with 20-ml portions of ether which were discarded. After acidification, the aqueous solution was extracted three times with 20-ml portions of ether. The ethereal portions were combined and the ether was allowed to evaporate into the air. Again, crystallization occurred within 24 hr, giving an off-white product, mp 128–130° (lit.[6] mp 129–130°). Lack of any absorption in the 1670-cm^{-1} region of the infrared spectrum of this product showed that there was no starting aldehyde present. The molecular weight, determined in acetone, was 177 (calcd 192). In subsequent preparations, rapid crystallization (within 8 hr) could be induced by seeding the colorless oil with a crystal of *o*-boronophthalidylacetic acid.

This acid (50 mg) was heated at 120° at 2.0-mm pressure in a microsublimation apparatus. From the cold finger, 35 mg (95%) of cinnamic acid, mp 132–133° (lit.[25] mp 132.5–133°), was recovered.

5-Nitroboronophthalidylacetic Acid (c).—To 2 ml of fuming nitric acid held at −40 to −50° was added 0.32 g (1.7 mmol) of boronophthalidylacetic acid. The addition was done in small portions and completed within 15 min. The mixture was then stirred and maintained at −30 to −40° until all the solid had gone into solution. This solution was poured into ice water and allowed to remain at 0° for 2 hr. White crystals (0.25 g, 62%) were collected by filtration. An analytical sample, mp 217–218°, was prepared by recrystallizing twice from water, followed by drying at 55° over phosphorus pentoxide at 0.1 mm overnight.

Anal. Calcd for $C_9H_8BNO_6$: C, 45.61; H, 3.40; N, 5.91, mol wt, 237. Found: C, 45.55; H, 3.53; N, 5.73, mol wt, 240 (in acetone).

This acid (50 mg) was heated at 240° at 2.0-mm pressure in a microsublimation unit. From the cold finger was collected 30 mg (75%) of 4-nitrocinnamic acid, mp 284–286° (lit.[26] mp 285–286°).

Methyl Boronophthalidylacetate (b).—Into 10 ml of methanol was added 400 mg (2.1 mmol) of boronophthalidylacetic acid along with 3 drops of concentrated hydrochloric acid. This mixture was heated at reflux for 20 hr. After cooling to room temperature, the solvent was removed *in vacuo* to give 360 mg (84%) of product, mp 88–90°. An analytical sample was prepared by recrystallization from a chloroform–petroleum ether (bp 30–60°) mixture.

Anal. Calcd for $C_{10}H_{11}BO_4$: C, 58.16; H, 5.51. Found: C, 58.30; H, 5.38.

Methyl 5-nitroboronophthalidylacetate (d), mp 118–120°, was prepared in a manner similar to preparation of methyl boronophthalidylacetate. An analytical sample was prepared by one recrystallization from water.

Anal. Calcd for $C_{10}H_{10}BNO_6$: C, 47.85; H, 4.02; N, 5.58. Found: C, 47.92; H, 4.17; N, 5.48.

Dimeric Ester of 2-Boronophthalidylethanol (g).—To 1.0 g (26 mmol) of lithium aluminum hydride suspended in 20 ml

(22) P. E. Peterson, *ibid.*, **31**, 439 (1966).

(23) E. Budzibiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 501.

(24) All melting points were taken on a Kofler hot-stage microscope and are uncorrected. Microanalysis and molecular weight determinations (with a Mechrolab Model 310A vapor-pressure osmometer) were performed by Mr. Josef Nemeth and his associates. Infrared spectra in potassium bromide pellets were determined with a Perkin-Elmer Model 21 infrared spectrophotometer and nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 nuclear magnetic resonance spectrophotometer. These were done by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering of the University of Illinois. Other infrared spectra were obtained in Nujol mulls on a Perkin-Elmer Model 137. Mass spectra were obtained by Mr. Joseph Wrona on an Atlas CH4 spectrometer.

(25) J. H. Mathews, *J. Amer. Chem. Soc.*, **39**, 1132 (1917).

(26) E. Knoevenagel, *Ber.*, **31**, 2612 (1898).

of ether was added 1.0 g (6 mmol) of boronophthalidylacetic acid in 40 ml of ether at such a rate that the reaction solution refluxed gently. After the addition, the mixture was allowed to reflux for 1 hr and then allowed to cool to room temperature. It was chilled by means of an ice bath, and the excess lithium aluminum hydride decomposed by the dropwise addition of 10 ml of water. Next, 40 ml of 10% hydrochloric acid was added and the layers were separated. The aqueous layer was extracted three times with 30-ml portions of ether; the combined ethereal portions were washed with 5% hydrochloric acid and then dried over magnesium sulfate. The ether was removed *in vacuo*, giving a colorless oil which, after 1 day over phosphorus pentoxide at 3-mm pressure, changed to a white solid. This was washed with acetone or cyclohexane, giving 600 mg (65%) of the dimeric ester of 2-boronophthalidylethanol, mp 226–229°. An analytical sample was prepared by subliming a sample at 225° at 3-mm pressure.

Anal. Calcd for $C_9H_9BO_2$: C, 67.56; H, 5.67; B, 6.76; mol wt, 160 (monomer), 320 (dimer). Found: C, 67.35, H, 5.68; B, 6.44; mol wt, 320 (mass spectrum).

2-Boronophthalidylethyl N-Phenyl Carbamate (e).—As described previously, 1.9 g (10 mmol) of *o*-boronophthalidylacetic acid was reduced with lithium aluminum hydride to give a clear, colorless oil. This oil was treated with 1.1 ml of phenyl isocyanate with warming on a steam bath. After drying for 2 days over phosphorus pentoxide, the oily, yellow solid obtained changed to 2.8 g of a pale yellow solid. This solid was heated in 20 ml of carbon tetrachloride. The solid residue (0.8 g) was collected by filtration and was identified as *sym*-diphenylurea, mp 236–238° (lit.[27] mp 235°). From the filtrate, upon evaporation, was obtained 2.0 g (67%) of 2-boronophthalidylethyl N-phenyl carbamate. This was recrystallized twice from petroleum ether, methylene chloride, and carbon tetrachloride (1:1:1), giving white needles, mp 103–105°.

An analytical sample was prepared by two additional recrystallizations from cyclohexane–benzene, followed by drying at 55° under reduced pressure.

Anal. Calcd for $C_{16}H_{16}BNO_4$: C, 64.67; H, 5.43; N, 4.72; mol wt, 297. Found: C, 64.68; H, 5.41; N, 4.45; mol wt (in chloroform), 266.

Attempted Hydrolysis of Dimeric Ester of Boronophthalidylethanol. In Water.—To 10 ml of water was added 160 mg (0.5 mmol) of the dimeric ester, and the reaction mixture was heated until no precipitate formed upon cooling. This aqueous solution was extracted three times with 15-ml portions of anhydrous benzene. The benzene extracts were combined and dried over molecular sieves. To this solution were added 12 drops of phenyl isocyanate. As the solution was being concentrated, a white solid began to precipitate. The solution was then concentrated to 10 ml and the white solid collected to give 100 mg of starting material (62% recovery), mp 230–232°.

In Dimethyl Sulfoxide.—Into 7 ml of dimethyl sulfoxide was placed 50 mg (0.18 mmmol) of the dimeric ester, along with three drops of water. This solution was heated gently on a steam bath for 2 days and cooled to room temperature; a 25-ml portion of a cold, saturated sodium chloride solution was added. Then this aqueous solution was extracted three times with 25-ml portions of ether. The ethereal extracts were combined and dried over anhydrous magnesium sulfate. After the ethereal solution had been concentrated to 10 ml, 3 drops of phenyl isocyanate were added to it. No visible reaction occurred. After 0.5 hr, the ether was removed *in vacuo*, giving a sticky, yellowish solid. This solid was placed in a porous clay plate to dry. Both the infrared spectrum of this compound and its melting point, 228–238°, indicated that it was a mixture of *sym*-diphenylurea and the dimeric ester.

In similar experiments, the dimer was recovered from solutions of ethanol and pyridine. When the dimeric ester was treated with 2-aminoethanol, *o*-phenylenediamine, and *n*-propylamine, no boron-containing organic compounds could be isolated.

2-(5-Nitroboronophthalidyl)ethyl nitrate (f) was prepared in 85% yield by the same procedure used to prepare 5-nitroboronophthalidylacetic acid. The cream-colored product melted at 100–102°.

(27) A. Sonn, *Ber.*, **47**, 2440 (1914).

A sample was prepared for analysis by twofold recrystallization from benzene and subsequent twofold recrystallization from benzene–cyclohexane. This analytical sample melted at 105–106°.

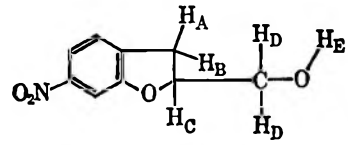
Anal. Calcd for $C_9H_9BN_2O_7$: C, 40.33; H, 3.39; N, 10.45; mol wt, 268. Found: C, 40.24; H, 3.58; N, 10.31; mol wt, 278 (in chloroform).

Treatment of 2-(5-Nitrophthalidyl)ethyl Nitrate with Basic Hydrogen Peroxide Solution.—To 4.0 ml of 3% hydrogen peroxide in 15 ml of ethanol was added 100 mg (0.4 mmol) of 2-(5-nitrophthalidyl)ethyl nitrate, along with 100 mg (2.5 mmol) of sodium hydroxide. This solution was stirred at room temperature for 24 hr. Then, it was acidified to pH 4 with concentrated hydrochloric acid. This clear, colorless solution was concentrated to 5 ml. After chilling in an ice bath, 50 mg (66%) of 2-hydroxymethyl-6-nitro-2,3-dihydrobenzofuran, mp 124–125°, was collected.

An analytical sample was prepared by recrystallization from ethanol–water followed by drying over phosphorus pentoxide at 3 mm for 24 hr.

Anal. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.65; N, 7.17; mol wt, 195. Found: C, 55.45; H, 4.86; N, 7.28; mol wt, 195 (mass spectrum).

The structure assigned to this compound depends mostly on nmr spectral data taken in DMSO-d_6.



H_A or H_B, τ 7.91 or 8.12, J_{AB} = 10.0 cps
H_C (m), τ 6.30
H_D (t), τ 5.71
H_E (t), τ 5.28, $J_{CD} \cong J_{DE} \cong 5.0$ cps

α-Cyanoboronophthalide.—α-Cyanoboronophthalide, mp 113–115° (lit.[6] mp 118–119°), was prepared according to the method of Tschampel[6] in 80–90% yields.

α-Carboxyboronophthalide.—α-Cyanoboronophthalide (1 g, 6 mmol) was dissolved in 15 ml of concentrated hydrochloric acid and stirred at room temperature for 24 hr. The clear solution was extracted three times with 20-ml portions of ether. The ethereal extracts were combined and dried over magnesium sulfate. The solvent was then allowed to evaporate into the air giving a colorless oil. This oil crystallized within 24 hr to give 600 mg (54%) of α-carboxyboronophthalide, mp 140–145° (lit.[6] mp 140–142°).

Treatment of α-Carboxyboronophthalide with Lithium Aluminum Hydride.—To a slurry of 600 mg (16 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether was added 480 mg (2.6 mmol) of α-carboxyboronophthalide in 20 ml of ether at such a rate to maintain a gentle reflux. After the addition, the reaction mixture was refluxed for 3 hr. Water was added dropwise to the reaction mixture now chilled by an ice bath to decompose the excess lithium aluminum hydride. Then concentrated hydrochloric acid was added until pH 1 was attained. The layers were separated and the aqueous layer extracted three times with 20-ml portions of ether. The ethereal portions were combined, washed once with 20 ml of water, and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give 250 mg of white product, mp 145–155°. One recrystallization from carbon tetrachloride raised the melting point to 155–158°. An infrared spectrum of this impure substance was almost identical with that of authentic *o*-toluene-boronic anhydride. A mass spectrogram gave *m/e* 354 (*o*-tolueneboronic anhydride *m/e* 354).

Registry No.—a, 19203-45-3; b, 19203-46-4; c, 19203-47-5; d, 19203-48-6; e, 19203-49-7; f, 19203-50-0; g, 19214-71-2; 2-hydroxymethyl-6-nitro-2,3-dihydrobenzofuran, 19203-51-1.

Boron Photochemistry. V. Photochemical Syntheses of the Borazarophenanthrene, Boroxarophenanthrene, and Borathiarophenanthrene Ring Systems

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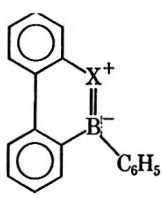
The 2-iodo-substituted anilino- and phenoxyboranes resulting from the reaction between chlorodiphenylborane and 2-iodoaniline and 2-iodophenol, respectively, have been photocyclized in cyclohexane solution to the corresponding phenylborazaro- and phenylboroxarophenanthrenes. A similar reaction with 2-iodothiophenol has yielded the 10-phenyl derivative of the recently reported 10,9-borathiarophenanthrene ring system.[1] This system is considerably less stable toward base than the corresponding borazaro- or boroxarophenanthrene systems, although ultraviolet spectral evidence indicates a delocalized π-electron system.

In previous studies we have examined the photochemistry of tetraaryl boron compounds and complexes formed between triarylboranes and electron-donating species.[2,3] In contrast to the triarylboranes, these tetrahedral molecules are photochemically reactive. For example, on photolysis, sodium tetraphenylborate yields biphenyl and phenylcyclohexadienes by an intramolecular reaction,[2a] whereas triphenylborane is inert.[2b] Of interest in connection with this study was the photochemistry of the borazarophenanthrene system (**1a**). In this system the boron atom adopts



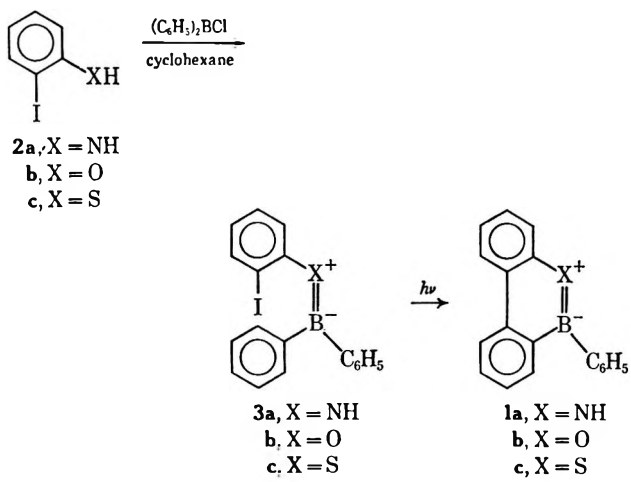
1a, X = NH
b, X = O
c, X = S

an sp^2 configuration but the molecule resembles the tetrahedral complexes mentioned earlier in that there is a high electron density around the boron atom due to donation from the adjacent nitrogen atom. However, **1a** proved to be extremely stable to photolysis under a variety of conditions, which prompted us to consider possible photochemical routes to **1a** and the related boron-containing heterocyclic systems, **1b** and **1c**. Previously the borazarophenanthrene system (**1a**) and its derivatives have been prepared from 2-aminobiphenyls.[4,5]

Recently, Kupchan and Wormser described the photochemical conversion of iodostilbenes into phenanthrenes.[6] We therefore studied the reactions shown in Scheme I.

Treatment of 2-iodoaniline (**2a**) with chlorodiphenylborane was assumed to yield **3a**. Irradiation

SCHEME I



2a, X = NH
b, X = O
c, X = S

3a, X = NH
b, X = O
c, X = S

1a, X = NH
b, X = O
c, X = S

of the solution yielded the desired compound, **1a**, identical in every respect with an authentic sample.[4] Excess iodoaniline was used to absorb the hydrogen chloride released during the formation of **3a**. Similarly, **2b** yielded boroxarophenanthrene **1b**, identical with an authentic sample.[7] Under similar conditions the conversion of **2c** into **1c** failed. Although the borathiarophenanthrene system has not been described, we were unable to detect a parent ion in the mass spectrum of the crude irradiation product corresponding to that expected for **1c**. However, the reactions between thiols and chloroboranes tend to be incomplete.[8] We therefore studied the reaction sequence in the presence of 2,6-lutidine. This modification resulted in the formation of the desired 10-phenyl-10,9-borathiarophenanthrene (**1c**). The assignment of such a structure rests on method of synthesis and analytical and spectroscopic data. Figure 1 shows the close correspondence between the ultraviolet spectra of **1a** and **1c**. Compound **1c** showed a parent ion of *m/e* 272 in its mass spectrum, as required for the proposed structure. The effect of 2,6-lutidine on the formation of **1a** and **1b** has been studied briefly. In the formation of **3**, hydrogen chloride is evolved, and, in the photocyclization, hydrogen iodide is evolved. We were interested in learning if the yield of the desired products could be improved by trapping these hydrogen halides. Table I summarizes the variations we have studied.

The increased yields of the heterocycles in the presence of a twofold excess of chlorodiphenylborane

(1) After the preparation of this manuscript the synthesis of bis(10,9-borathiarophenanthryl) ether was described [F. A. Davis and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **90**, 3511 (1968)]. The B–S bond in the 10-phenyl-10,9-borathiarophenanthrene reported here appears to be considerably more stable toward hydrolysis than that in the ether. We encountered no problems in obtaining the ultraviolet spectrum in cyclohexane (Figure 1). Even in methanol a diffuse form of the spectrum was recorded.

(2) (a) J. L. R. Williams, J. C. Doty, P. J. Grisdale, R. Searle, T. H. Regan, G. P. Happ, and D. P. Maier, *J. Amer. Chem. Soc.*, **89**, 5153 (1967); (b) J. L. R. Williams, P. J. Grisdale, and J. C. Doty, *ibid.*, **89**, 4538 (1967).

(3) J. L. R. Williams, J. C. Doty, P. J. Grisdale, T. H. Regan, G. P. Happ, and D. P. Maier, *ibid.*, **90**, 53 (1968).

(4) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

(5) M. J. S. Dewar and V. P. Kubba, *J. Org. Chem.*, **25**, 1722 (1960).

(6) S. M. Kupchan and H. C. Wormser, *ibid.*, **30**, 0792 (1965).

(7) M. J. S. Dewar and R. Dietz, *J. Chem. Soc.*, 1344 (1960).

(8) G. E. Coates and K. Wade, "Organometallic Compounds," Vol. 1, "The Main Group Elements," Methuen and Co. Ltd., London, 1967, p 284.

TABLE I

DEPENDENCE OF THE YIELD OF THE HETEROCYCLIC COMPOUNDS ON THE REACTANT COMPOSITION

Run	Iodo derivative, Compd	Iodo derivative, (mmol)	$(C_6H_5)_2BCl$, mmol	2,6-Lutidine, mmol	Time for max yield, hr	Yield,[a] Compd	Yield,[a] %
1	**2a**	(10)	5		4	**1a**	35
2	**2a**	(15)	5		4.5	**1a**	49
3	**2a**	(10)	5	5	4.5	**1a**	39
4	**2a**	(5)	5	5	5	**1a**	49
5	**2a**	(5)	10	10	10	**1a**	80[b]
6	**2b**	(5)	5		4.5	**1b**	43
7	**2b**	(5)	5	5	5	**1b**	42
8	**2b**	(5)	5	10	5	**1b**	37
9	**2b**	(5)	10	10	6	**1b**	43[b]
10	**2c**	(5)	5		5	**1c**	0
11	**2c**	(5)	5.5	10	5	**1c**	41
12	**2c**	(5)	10	10	4	**1c**	91[b]

[a] These are yields calculated from spectral data. [b] Yields of isolated materials are quoted for these runs in the Experimental Section.

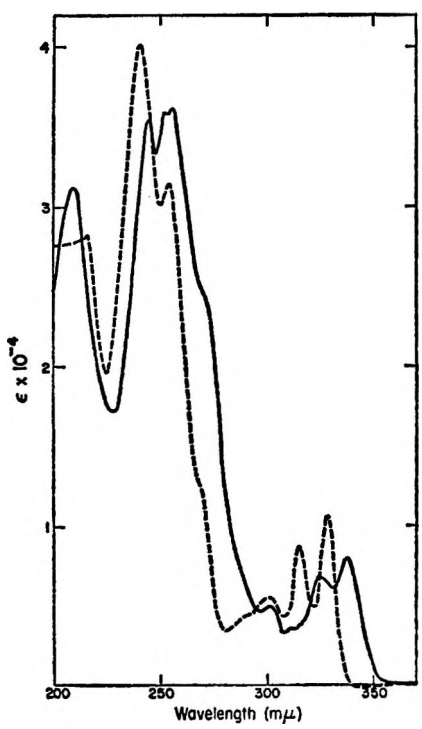
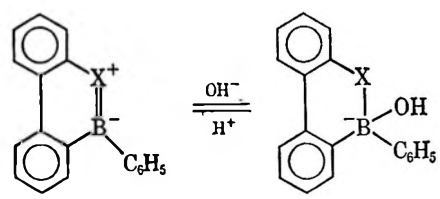


Figure 1.—Ultraviolet spectra of 10-phenyl-10,9-borazarophenanthrene (- - -) and 10-phenyl-10,9-borathiarophenanthrene (——) in cyclohexane.

was unexpected. Such an excess either increases the yield of the intermediates, **3**, or may serve as a trap for residual traces of water, even though very thorougn precautions were taken to exclude all water.

During this study we have observed that the stabilities of the heterocyclic ring systems decrease in the order **1a** > **1b** > **1c**. We were surprised when, during the work-up of the photochemical reaction mixture containing **1b**, compound **1b** was extracted from a cyclohexane solution with 1% sodium hydroxide solution. Studies with authentic **1b** revealed that it could be completely removed from a cyclohexane solution with 1% sodium hydroxide solution but 78% could be recovered by acidification of the aqueous solution (glpc analyses). These results suggest the equilibrium shown below to be similar to that reported for the B–OH derivative.[9] Spectroscopic evidence



1b, X = O
c, X = S

4a, X = O
b, X = S

supports this interpretation. When sodium hydroxide solution was added to a methanol solution of **1b**, one band centered at 316 mμ replaced the characteristic long-wavelength bands of **1b** (323, 305, 294, 283 mμ). These latter reappeared when the solution was acidified. By contrast, **1a** was unaffected, even by 50% sodium hydroxide solution, and **1c** could not be recovered from basic solutions.

The close similarity between the spectra of **1a** and **1c** indicates very similar delocalized aromatic systems in these two molecules, and so one would expect similar stabilities. The observed instability of borathia system **1c** toward base can be accounted for in terms of steric effects postulated previously in discussing the stability of the boroxarophenanthrene system.[9] The strain in this system was thought to be relieved by the boron adopting a tetrahedral configuration in the presence of OH^-. The covalent radius of sulfur (1.02 Å) is considerably larger than that of oxygen (0.73 Å). The additional strain imposed by substituting sulfur for oxygen to give **1c** and **4b** could be relieved by cleavage of the B–S bond.

The problem of preparing substituted borazaro-, -oxaro-, or -thiarophenanthrenes now involves the synthesis of the related 2-iodoanilines, -phenols, and -thiophenols. This is much easier, in many cases, than preparing the corresponding biphenyl derivatives.

We are examining the scope of this type of photochemical synthesis of heterocyclic boron compounds. The present synthesis provides a convenient, simple route to a variety of substituted and complex multiring, boron-containing, heterocyclic compounds.

Experimental Section

General.—All melting points are corrected. Spectra were determined with a Cary Model 15 ultraviolet spectrometer and a Perkin-Elmer Infracord spectrometer. Analytical glpc was performed using an F & M Model 5750 gas chromatograph equipped

(9) M. J. S. Dewar and R. Dietz, *Tetrahedron*, **15**, 26 (1961).

with a 0.25 in. × 10 ft long column packed with 15% OV17 on Chromosorb W. Preparative glpc was performed using an F & M Model 776 gas chromatograph equipped with a 0.75 × 80 in. long column packed with 15% OV17 on Chromosorb W.

Materials.—Eastman Grade 2-iodoaniline and 2-iodophenol were used without further purification. Chlorodiphenylborane was prepared by the method of Niedenzu, Beyer, and Dawson.[10] 2-Iodobenzenesulfonyl chloride was prepared by the method of Schwarzenbach and Egli.[11]

2-Iodothiophenol.—A solution of 200 g (0.88 mol) of stannous chloride dihydrate in 250 ml of concentrated hydrochloric acid was treated over 10 min with a solution of 50 g (0.17 mol) of 2-iodobenzenesulfonyl chloride in 250 ml of acetic acid. The solution was stirred on a steam bath for 2 hr, then steam distilled. The distillate was extracted with dichloromethane, and the extract dried and evaporated to yield the crude thiol. Distillation yielded the pure thiol, 22 g, 56%, bp 117–120° (10 mm) [lit.[11] bp 119.5° (11 mm)]. It was stored at 0° over zinc dust under nitrogen.

Photocyclizations.—The horizontal thin-film photochemical reactor described earlier[12] was used for the preparation of the boron-containing compounds. The apparatus was thoroughly dried under vacuum for 1 hr and filled with dry nitrogen. The iodo compound was then introduced into the flask and the apparatus evacuated and filled with dry nitrogen several times. Approximately 600 ml of dry cyclohexane was then distilled directly from lithium aluminum hydride under nitrogen into the flask. The chlorodiphenylborane and the 2,6-lutidine were injected into the flask, and the contents mixed for 1 hr at room temperature by rotating the flask. The resulting solution was then irradiated using a Hanovia 100-W 608A-36 lamp in a quartz insert. The progress of the reaction was followed by withdrawing 100-μl samples of the photolysis solution. The sample was then diluted with 3 ml of solvent and examined by ultraviolet spectroscopy. Compound **1a** shows a characteristic band at 329 mμ (ε 10,600), **1b** shows a band at 323 mμ (ε 6300), and **1c** shows a band at 338 mμ (ε 7850). When no increase in the intensity of the long-wavelength band was observed, the contents of the flask were removed and washed in sequence with water, dilute hydrochloric acid, water, dilute sodium thiosulfate solution, and water. (Solutions of **1a** were also washed with dilute sodium hydroxide solution.) The organic layer was dried and evaporated to yield the crude product.

10-Phenyl-10,9-borazarophenanthrene (1a).—The crude product from run 5 (see Table I) crystallized as prisms from ligroin (bp 63–75°), 0.65 g, 51%, mp 106–108°, and was identical with an authentic sample.[4]

10-Phenyl-10,9-boroxarophenanthrene (1b).—The crude product (run 9, Table I) was purified by preparative glpc at 280° to yield the pure compound as a white solid, mp 80–82°, 0.35 g, 31%, identical with an authentic sample.[7]

10-Phenyl-10,9-borathiarophenanthrene (1c).—The crude product (run 12, Table I) crystallized from ligroin (bp 63–75°) in pale yellow prisms, 0.7 g, 50%, mp 129–130°.

Anal. Calcd for $C_{18}H_{13}BS$: C, 79.5; H, 4.8; B, 4.0; S, 11.8; mol wt, 272. Found: C, 79.2; H, 5.0; B, 4.0; S, 11.7; mol wt, 272 (mass spectrum).

Registry No.—**1a**, 19393-10-3; **1b**, 19374-73-3; **1c**, 19374-74-4.

(10) K. Niedenzu, H. Beyer, and J. W. Dawson, *Inorg. Chem.*, **1**, 738 (1962).
(11) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).
(12) J. L. R. Williams and P. J. Grisdale, *Chem. Ind.* (London), 1477 (1968).

Observations on the Mechanism of Addition of Iodine Isocyanate to Unsaturated Compounds[1,2]

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Addition of iodine isocyanate to unsaturated compounds has been studied under competitive reaction conditions with pairs of olefins using preformed solutions of iodine isocyanate and also generating it *in situ*. Reactivity series are obtained which not only differ from each other but also from a series derived from kinetic studies (single olefins used) with *in situ* generated iodine isocyanate. When preformed solutions of iodine isocyanate are used the rate depends primarily on its concentration and that of the unsaturated compound, and is approximated by second-order kinetics. When iodine isocyanate is generated *in situ* in the presence of the unsaturated compound, complexation with iodine can play a major role in the mechanism depending on the complexation ability of the unsaturated compound. With poorly complexing but reactive olefins, for example, 2,3-dimethyl-2-butene, the reaction approaches the limiting rate of formation of iodine isocyanate. Most unsaturated compounds, however, react in part with iodine isocyanate directly and in part as iodine–olefin complexes with silver cyanate to form the observed vicinal iodoisocyanates.

In previous articles[4,5] we discussed the relative rates of addition of iodine isocyanate, generated *in situ* from iodine and silver cyanate, to unsaturated compounds. These results showed that *in situ* addition of iodine isocyanate occurs in an electrophilic manner, confirming the same observation, based on stereochemical considerations, by Hassner and Heathcock[6] and Drefahl, Ponsold and Köllner.[7]

Studies by Rosen and Swern[8] have shown that homogeneous, preformed solutions of iodine isocyanate also react in an electrophilic manner. We have now extended these studies to include the competitive reaction of pairs of olefins with preformed and *in situ* generated iodine isocyanate.

(1) Pseudohalogens. VI. For V, see H. Hamann and D. Swern, *Tetrahedron Lett.*, No. 28, 3303 (1966).
(2) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966. The authors wish to acknowledge the partial support of this work by U. S. Public Health Service Research Grants CA-07803 and CA-07174 of the National Cancer Institute.
(3) Work submitted by C. G. G. in partial fulfillment of the requirements for the Ph.D. degree, and by S. R. for the Master's degree, Temple University, Feb 1967.
(4) C. G. Gebelein and D. Swern, *J. Org. Chem.*, **33**, 2758 (1968).
(5) C. G. Gebelein and D. Swern, *Chem. Ind.* (London), 1462 (1965).
(6) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964); *J. Org. Chem.*, **29**, 3640 (1964); **30**, 1748 (1965); *Tetrahedron Lett.*, 393 (1963); 1125 (1964).
(7) G. Drefahl and K. Ponsold, *Chem. Ber.*, **93**, 519 (1960); G. Drefahl, K. Ponsold, and G. Köllner, *J. Prakt. Chem.*, **28**, 136 (1964).
(8) S. Rosen and D. Swern, *Anal. Chem.*, **38**, 1392 (1966).

TABLE I

SUMMARY OF COMPETITIVE REACTIONS BETWEEN PAIRS OF OLEFINS AND *in situ* GENERATED IODINE ISOCYANATE (solvent, 100.0 ml of anhydrous ether)

Olefins used						Molar ratio of	Reactivity ratio
More reactive olefin	Amt, mol	Less reactive olefin	Amt, mol	AgOCN, mol	I_2, mol	total olefins/I_2	faster/slower
trans-3-Hexene[a]	0.01121	1-Octene	0.01110	0.01341	0.00689	3.24	2.89
Cyclohexene[b]	0.01635	1-Hexene	0.01274	0.01349	0.00671	4.34	100/0
Cyclohexene[b]	0.01607	*trans*-3-Hexene	0.01277	0.01334	0.00692	5.01	≥12.7
Cyclohexene[b]	0.01615	*trans*-3-Hexene	0.01282	0.01908	0.00985	2.94	2.59
Cyclohexene[b,c]	0.01604	*trans*-3-Hexene	0.01273	0.01336	0.00694	4.14	2.53
Cyclopentene[b]	0.01744	Cyclohexene	0.01593	0.01339	0.00690	4.84	6.85
Cyclopentene[b,d]	0.01715	Cyclohexene	0.01726	0.01346	0.00689	5.00	3.55

[a] Internal standard, *n*-heptane. [b] Internal standard, benzene. [c] In this experiment, the iodine was added last to start the reaction. [d] In this experiment, the iodine and cyclohexene were equilibrated for 24 hr at −20°. The cyclopentene was added 1 hr before the addition of AgOCN which started the reaction.

TABLE II

COMPOSITION AND REACTIVITY OF COMPETITIVE REACTIONS WITH PERFORMED IODINE ISOCYANATE SOLUTIONS

Olefins used				Iodine	Reactivity ratio
More reactive olefin	*M*	Less reactive olefin	*M*	isocyanate, *M*	faster/slower
trans-3-Hexene	0.097	1-Octene	0.088	0.057	4.1
trans-3-Hexene	0.136	Cyclohexene	0.171	0.075	1.8
2,3-Dimethyl-1-butene	0.143	Cyclohexene	0.139	0.040	1.4
2,3-Dimethyl-2-butene	0.163	2-Methyl-2-pentene	0.174	0.047	2.3
2-Methyl-2-pentene	0.154	2,3-Dimethyl-1-butene	0.142	0.043	≥10
Cyclopentene	0.189	Cyclohexene	0.165	0.060	≥10

Experimental Section

A. Competitive Reactions Using *in situ* Generated Iodine Isocyante.—The conditions and results of competitive reactions of *in situ* generated iodine isocyanate with pairs of olefins present in large excess are summarized in Table I. Reactions were run at −20 to −30°. The reaction vessel was a 100-ml four-necked flask fitted with an electrically driven Teflon-blade stirrer, a thermometer and a drying tube. The fourth opening was sealed with a rubber septum through which samples were removed for analysis by gas–liquid partition chromatography. All glpc analyses were obtained on a F & M Scientific Model 500 chromatograph using a 20-ft column of 15% Apiezon L on 70/80 mesh Anakrom ABS, with detection by thermal conductivity.

The accurately weighed amount of iodine was placed in the reaction flask, dissolved in ether and cooled to reaction temperature in a dewar flask. A known amount of a mixture of the two olefins and an internal standard for glpc calibration was then added and five to eight initial glpc determinations were made with 3–5 μl of solution. Silver cyanate was then added in one portion to start the reaction. Progress of the reaction was followed by periodic glpc analysis. These competitive *in situ* reactions were very slow and only the final results, after 24 hr, are summarized in Table I as the reactivity ratios. The results are the average of five to eight glpc determinations. In all cases, the concentrations of both olefins were determined by reference against a common internal standard. The reaction products could not be determined as they do not elute under the conditions used.

Since slightly different molarities of each olefin were used in these experiments, the reactivity ratios were computed as ratios of the percentages of each olefin that reacted.

B. Competitive Reactions Using Preformed Solutions of Iodine Isocyanate.—Preformed solutions were prepared in the usual manner.[8] After initial glpc measurements were made on the mixture of the two olefins with internal standard, a known amount of this mixture was added to the preformed iodine isocyanate solution. The composition of these homogeneous competitive experiments is shown in Table II.

Samples for glpc determination were removed periodically and the titer of iodine isocyanate was also determined.[8] Reactions with preformed iodine isocyanate were very rapid and essentially complete in less than 30 min. The method of calculation of the reactivity ratios in Table II was the same as with the *in situ* systems.

Results

The reactivity ratios of Table II for competitive reactions with preformed iodine isocyanate have been converted into a relative reactivity scale, shown in Table III, with the value for cyclohexene arbitrarily set at 100. The relative ranking of cyclopentene and 2-methyl-2-pentene can not be definitely established from the available data but 2,3-dimethyl-2-butene is 2.3 times as reactive as 2-methyl-2-pentene. These results constitute an electrophilic series similar to that determined previously from kinetic studies with *in situ* generated iodine isocyanate.[4,5]

TABLE III

COMPARISON OF THREE DIFFERENT RELATIVE REACTIVITY SERIES FOR THE ADDITION OF IODINE ISOCYANATE TO OLEFINS

	Reaction method		
Olefin	Competitive preformed[a]	Competitive *in situ*[b]	Kinetic *in situ*[d]
2,3-Dimethyl-2-butene	>3200		3800
2-Methyl-2-pentene	>1400		
Cyclopentene (C)	>1000	685	221
trans-3-Hexene (A)	180	≤7.9	571
2,3-Dimethyl-1-butene	140		
Cyclohexene (B)	100	100	100
1-Octene	44	≤2.7	50[c]

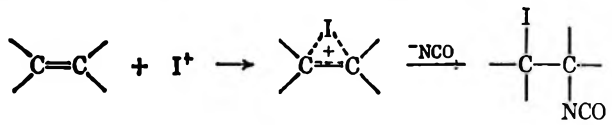
[a] From Table II. [b] From Table I. [c] 1-Hexene. [d] See ref 4 and 5.

An entirely different series results when the data from Table I for competitive reactions with *in situ* generated iodine isocyanate are compiled into a relative reactivity series shown in Table III. The series previously obtained in kinetic studies with *in situ* generated iodine isocyanate[4,5] is also shown in Table III.

Discussion

Comparison of the Different Iodine Isocyanate Series. Although each reactivity series is readily duplicated and generally conforms to an electrophilic pattern, the variation among them with the method of determining the series suggests differences in reaction mechanism. From a mechanistic standpoint, the simplest series is obtained from competitive studies of the addition of preformed solutions of iodine isocyanate to olefins. In the other cases, the iodine isocyanate is generated while the reaction is in progress and this might be expected to lead to complications. We have previously shown that generation of iodine isocyanate is a relatively slow process, in the absence of an olefin.[8]

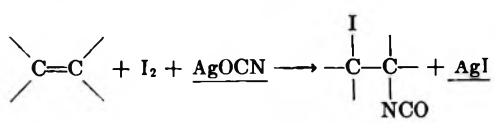
The reaction of preformed iodine isocyanate can be represented by the given sequence. Preliminary



kinetic data[8] on this system indicate that the reaction follows second-order kinetics. In general, rate of addition of preformed iodine isocyanate increases with the number of electron-donating alkyl groups attached to the double bond. Thus the reactivity increases with the ability to form more highly stabilized carbonium ions.

The competitive and kinetic *in situ* systems, however, give reactivity series that are different from each other and from that obtained with preformed iodine isocyanate. These differences are most apparent in the reactivity ranking (slowest to fastest) of *trans*-3-hexene (A), cyclohexene (B), and cyclopentene (C): competitive, preformed, B, A, C; competitive, *in situ*, A, B, C; kinetic, *in situ*, B, C, A.

The over-all equation for *in situ* reactions is given.



One of the steps is the generation of iodine isocyanate, but side reactions are also possible in this system. Olefins are known to form complexes with both silver and iodine, and complex formation would certainly result in differences in apparent reactivity.

The formation of diiodides from these complexes would introduce large errors into equilibrium constants and into any work on kinetics and competitive reactions. Diiodide formation can occur but is rapid only in the presence of light.[9-12] This problem was minimized in our studies by excluding light. Thus, we obtained yields of the iodine isocyanate adduct with cyclohexene in excess of 90% even though cyclohexene reacts relatively slowly in the *in situ* systems.

These considerations are consistent with the formation of an iodine–olefin complex as an important part of the reaction mechanisms. Numerous reactions can be visualized as important in the over-all reaction, including the formation and reaction of iodine–olefin complexes and the formation and reaction of iodine isocyanate, but the heterogeneous system is too complex for kinetic analysis.[13]

Rosen and Swern[8] have shown that *trans*-3-hexene reacts very rapidly with solutions of iodine isocyanate. The relative reactivities determined here show that 2,3-dimethyl-2-butene is at least 18 times more reactive than *trans*-3-hexene, and suggests that 2,3-dimethyl-2-butene reacts with iodine isocyanate as rapidly as it is generated. The rate of generation of iodine isocyanate is the limiting rate for the reaction in which *in situ* generated iodine isocyanate is added to this olefin.

Conclusions

The addition of iodine isocyanate, whether from preformed solutions or generated *in situ*, proceeds in an electrophilic manner. The reaction rate is much faster with preformed solutions. From a synthesis standpoint the use of preformed solutions of iodine isocyanate might prove advantageous when working with olefins that react slowly, such as 1 olefins. With relatively rapidly reacting olefins, such as *trans*-3-hexene, the *in situ* method is probably more convenient since the *total* time (generation of iodine isocyanate plus addition) is about the same.

Registry No.—Iodine isocyanate, 3607-48-5.

(9) G. S. Forbes and A. F. Nelson, *J. Amer. Chem. Soc.*, **59**, 693 (1937).
(10) J. E. Cline and G. B. Kistiakowsky, *J. Chem. Phys.*, **5**, 990 (1937).
(11) G. Sumrell, B. M. Wyman, R. G. Howell, and M. C. Harvey, *Can. J. Chem.*, **42**, 2710 (1964).
(12) P. S. Skell and R. R. Pavlis, *J. Amer. Chem. Soc.*, **86**, 2956 (1964).
(13) For details, see Ph.D. thesis of C. G. G., Temple University, 1967.

2-Oxazolidone Formation by Pyrolysis of β-Iodocarbamates. A Stereoselective Reaction[1]

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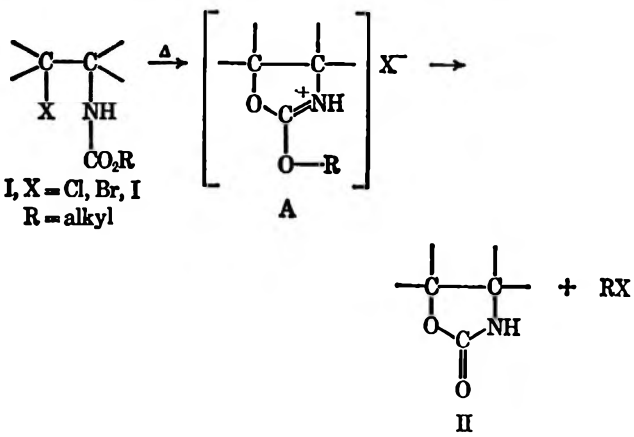
Received October 9, 1968

The pyrolytic cyclization of *threo*- and *erythro*-β-iodocarbamates from *cis*- and *trans*-2-butenes and -3-hexenes to 2-oxazolidones has been studied. The reaction is stereoselective, not stereospecific as with β-iodocarbamates from cyclic olefins. Selectivity of cyclization is greater with *erythro* than with *threo* isomers. The former yield 80–90% *trans*- and 10–20% *cis*-2-oxazolidones, the latter 70% *cis* and 30% *trans*. Ratios of isomers formed were determined by comparison of their nmr spectra with those of model 2-oxazolidones of known geometry.

The pyrolytic cyclization of β-halocarbamates (I) to 2-oxazolidones (II) has been the subject of a number of studies.[4-6] The mechanism of cyclization has been reported to involve intramolecular nucleophilic displacement of the halide ion by the carbonyl oxygen to yield an intermediate of type A.[5] Subsequent cleavage of the alkyl–oxygen bond by the departed halide ion yields II and alkyl halide. This process is similar to an



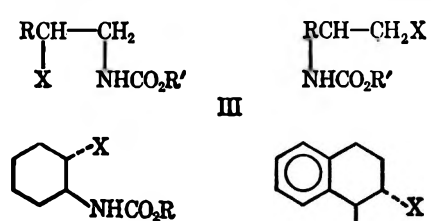
I, X = Cl, Br, I
R = alkyl

A

II

S_N2 displacement and has been regarded as a stereospecific reaction.[5]

In all examples reported to date, however, the starting β-halocarbamates (I) have been terminally substituted (III),[6] where stereochemistry is not involved, or the carbamate and halogen functions are attached to a cyclic system (IV, V).[5,6] In the last two



III

IV V

R′ = alkyl
X = Cl, Br, I
R = alkyl or aryl

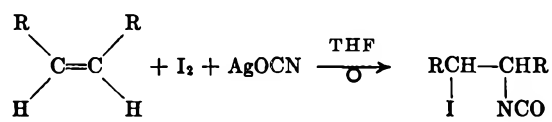
examples, stereospecific cyclization has indeed been observed (and confirmed by us) and is the basis for the above mechanism.[6]

In this paper we are reporting (a) the pyrolytic cyclization of internal acyclic β-iodocarbamates of known stereochemistry and (b) the stereoselectivity of the cyclization.

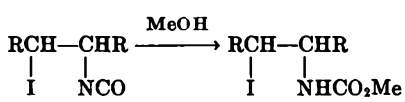
Results and Discussion

The model compounds selected for this study were the *erythro*- and *threo*-β-iodocarbamates (X–XIII). These were prepared by the addition of iodine isocyanate to *cis*- and *trans*-2-butene and *cis*- and *trans*-3-hexene followed by reaction with methanol as shown in Scheme I.

SCHEME I



VI, *erythro*, R = CH_3
VII, *threo*, R = CH_3
VIII, *erythro*, R = CH_2CH_3
IX, *threo*, R = CH_2CH_3



X, *erythro*, R = CH_3
XI, *threo*, R = CH_3
XII, *erythro*, R = CH_2CH_3
XIII, *threo*, R = CH_2CH_3

Addition of iodine isocyanate to olefins proceeds in a clean *trans* manner,[7,8] yielding *threo* adducts from *cis*-olefins and *erythro* adducts from *trans*-olefins. Conversion of the isocyanate group to the methyl carbamoyl group by reaction with methanol does not affect the stereochemistry.

The diastereoisomeric pair, VI and VII, as well as VIII and IX, are distinguishable by their nmr spectra, summarized in Table I. The spectra of iodoisocyanates VI and VII are interpretable on the basis of the preferred conformations in Figure 1a and not with those previously suggested.[9] The signal of H_a in conformer VIa, geminal to iodine,[10] appears at 4.24 ppm (TMS = 0), split into a quartet (J = 7 Hz) by the adjacent

(1) Pseudohalogens. XIV. For XIII, see D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968).

(2) To whom inquiries should be addressed.

(3) The authors acknowledge with thanks support of this investigation by U. S. Public Health Service, Grants No. CA-07803, CA-07174, and CA-10439 of the National Cancer Institute.

(4) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

(5) C. Heathcock and A. Hassner, *Angew. Chem. Intern. Ed. Engl.*, **2**, 213 (1963).

(6) T. A. Foglia and D. Swern, *J. Org. Chem.*, **32**, 75 (1967).

(7) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

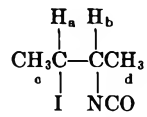
(8) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(9) A. Hassner and C. Heathcock, *Tetrahedron Lett.*, No. 19, 1125 (1964).

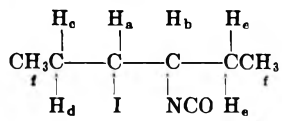
(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1963, p 84.

TABLE I

NMR SPECTRAL DATA FOR DIASTEREOMERIC IODOISOCYANATES



	H_a[a]	H_b	H_c	H_d
	δ			
threo VII	4.22 (octet), J_{ac} = 7.0, J_{ab} = 3.0 (double quartet)	3.15 (octet), J_{bd} = 7.0, J_{ba} = 3.0 (double quartet)	1.95 (d), J_{ac} = 7.0	1.40 (d), J_{bd} = 7.0
erythro VI	4.24 (octet), J_{ab} = 3.5, J_{ac} = 7.0 (double quartet)	3.45 (octet), J_{ba} = 3.5, J_{bd} = 7.0 (double quartet)	1.93 (d), J_{ac} = 7.0	1.42 (d), J_{bd} = 7.0



	H_a	H_b	H_{cde}	H_f
	δ			
threo IX	4.12 (septet), J_{ab} = 3.0, J_{ac} = 4.5, J_{ad} = 7.5 (double quartet)	2.84 (sextet), J_{ba} = 3.0, J_{be} = 7.0 (double triplet)	1.80 (m)	1.02 (m)
erythro VIII	4.14 (octet), J_{ab} = 8.5, J_{ac} = 5.5, J_{ad} = 4.5 (double quartet)	3.41 (sextet), J_{ba} = 8.5, J_{be} = 5.0, (double triplet)	1.72 (m)	1.06 (m), J_{ef} = 7

[a] J is given in cycles per second.

methyl group, each line of which is further split into a doublet (J = 3.5 Hz) by a proton H_b adjacent to the isocyanate group. H_a in conformer VIIa also appears as a double quartet centered at 4.22 ppm; J_{ab} is now 3 Hz while the coupling constant with the adjacent methyl group (J_{ac}) remains 7 Hz. This similarity in both chemical shift and coupling constant between H_a and H_b in both diastereomers indicates a similar magnetic environment and that the dihedral angle between H_a and H_b is very similar or the same. Accordingly, the nmr data are consistent with a *gauche* arrangement of H_a and H_b in both diastereomers, as in Figure 1a, and not the *gauche* and *anti* configurations previously assigned.[9] In both isomers, H_b also appears as a double quartet centered at 3.45 (VIa) and 3.15 ppm (VIIa), respectively. Thus, as previously noted, the iodine atom by nature of its magnetic anisotropy exerts unequal shielding on the nucleus of H_b in the two isomers.

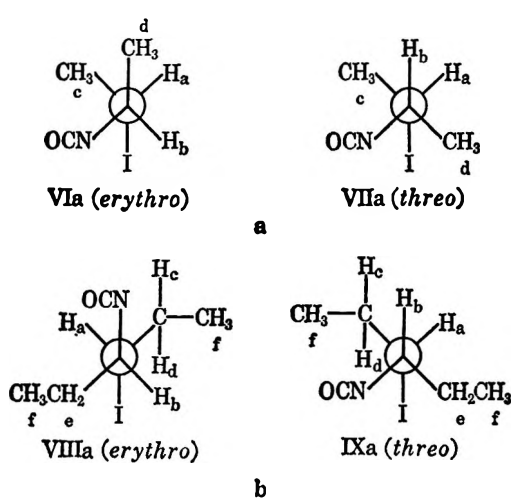


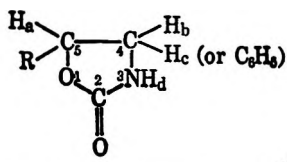
Figure 1

Interpretation of the nmr spectra of iodoisocyanates VIII and IX is based on conformations VIIIa and IXa in Figure 1b. In the *erythro* isomer (VIIIa) the *anti* conformation is assigned to H_a and H_b because of their large coupling constant (J_{ab} = 8.5 Hz) and the deshielding effect on H_b of the iodine atom as in VIa. H_a is seen at 4.14 ppm, split into an octet (two overlapping quartets) by H_b (J_{ba} = 8.5 Hz) and the two nonequivalent methylene protons[11] H_c and H_d (J_{ac} = 5.5; J_{ad} = 4.5 Hz). The signal of H_b appears at 3.41 ppm split into a triplet by the adjacent methylene group (J_{be} = 5 Hz) each line of which is further split by H_a (J_{ba} = 8.5 Hz). In the *threo isomer* (IXa) H_a and H_b are assigned the *gauche* conformation by the identity of their coupling constant with J_{ab} in *threo* isomer VIIa. H_a appears at 4.12 ppm as a septet (overlapping double quartet), split by the two nonequivalent methylene protons H_c (J_{ac} = 4.5 Hz) and H_d (J_{ad} = 7.5 Hz),[11] each line further split by H_b (J_{ab} = 3 Hz). H_b is seen at 2.84 ppm, split into a triplet by the adjacent methylene group (J_{be} = 7 Hz) each line of which is further split into a doublet by H_a (J_{ba} = 3 Hz). The alternate *gauche* conformation of IXa in which H_b is deshielded by the iodine atom (as in VIIIa) is eliminated in view of its chemical shift.

Conversion of iodoisocyanates VI–IX into the corresponding methyl iodocarbamates (X–XIII) does not alter the original stereochemistry. This was corroborated by their nmr spectra, which are very similar to those of the parent iodoisocyanates. The major differences in the spectra, aside from the expected methoxy signal at 3.70 ppm, is a general down-

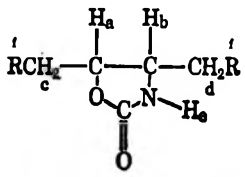
(11) L. M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, pp 99–103.

TABLE II
NMR SPECTRA
2-Oxazolidones



	δ			
	H_a	H_b[b]	H_c	H_d
4,5-Diphenyl				
cis XV	6.02 (d), J_{ab} = 8.5	5.28 (d), J_{ba} = 8.5		6.88 (s)
trans XVI	5.24 (d), J_{ab} = 7.5	4.76 (d), J_{ba} = 7.5		6.70 (s)
5-Phenyl[a]				
XVII	5.52 (dd), J_{ab} = 8.5, J_{ac} = 7.5	3.90 (t), J_{ba} = J_{bc} = 8.5	3.42 (dd), J_{cb} = 8.5, J_{ca} = 7.5	6.82 (s)

cis- and *trans*-Alkyl-2-oxazolidones



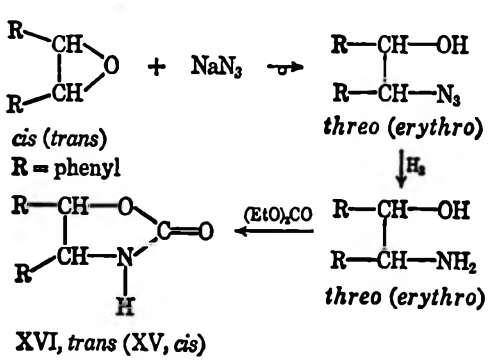
	δ			
	H_a	H_b[b]	$H_{c,d}$	H_e
4,5-Dimethyl, R = H				
cis XIX	4.80, J_{ab} = 8.5, J_{ac} = 7.0 (double quartet)	3.98, J_{ba} = 8.5, J_{bd} = 7.0 (double quartet)	1.34 (d), 1.20 (d), J = 7.0	6.82 (s)
trans XVIII	4.22 (quintet), J_{ab} = J_{ac} = 7.0	3.56 (quintet), J_{ba} = J_{bd} = 7.0	1.26 (d), 1.10 (d), J = 7.0	6.74 (s)
4,5-Diethyl, R = CH_3				
cis XXI	4.52, J_{ab} = 5.5, J_{ac} = 7.5, 1,1,2,2,1,1 sextet (double triplet)	3.70, J_{ba} = 5.5, J_{bd} = 7.5 (double triplet)	1.54 (m), 7.26 (s)	1.02 (m)
trans XX	4.12 (q), J_{ab} = J_{ac} = 5.5	3.40 (q), J_{ba} = J_{bd} = 5.5	1.58 (m), 6.98 (a)	0.98 (m)

[a] Coupling constants (cycles per second) obtained by treating with trifluoracetic acid and deuterium oxide to remove proton on nitrogen. [b] H_b always shows small splitting of <0.5 cps due to coupling with proton H_d.

field shift of H_b to approximately 3.2 ppm and the further splitting of H_b by the proton attached to nitrogen.

Before continuing with the investigation of the stereochemistry of pyrolysis of methyl β-iodocarbamates, it was necessary to be able to distinguish between *cis*- and *trans*-2-oxazolidones by nmr. Model 2-oxazolidones of known structure and stereochemistry were required for determination of coupling constants and chemical shifts. The compounds selected were the isomeric *cis*- and *trans*-4,5-diphenyl-2-oxazolidones (XV and XVI), prepared by the reaction sequences shown in Scheme II.

SCHEME II



The starting materials, *cis*- and *trans*-stilbene epoxides, were prepared in the conventional manner by epoxidation of *cis*- and *trans*-stilbene, respectively.[12] Nucleophilic attack on the epoxides by azide ion converted them into the *threo*- and *erythro*-azidohydrins, respectively. The stereochemistry of this reaction is known to proceed with inversion.[13] Hydrogenation of the azidohydrins gave the known *threo*- and *erythro*-amino alcohols which were then cyclized to the *cis*- and *trans*-2-oxazolidones by a modification of the Homeyer method.[14,15]

To obtain the geminal coupling constant of methylene protons on a 2-oxazolidone ring, 5-phenyl-2-oxazolidone (XVII) was prepared; its structure is well established.[6]

The nmr spectra of the model 2-oxazolidones are summarized in Table II. In the *cis* isomer (XV), H_a appears at 6.02 ppm (TMS = 0), split into a doublet (J_{ab} = 8.5 Hz) by H_b, also seen as a doublet upfield at 5.28 ppm.

In the *trans* isomer (XVI), H_a is seen at 5.24 ppm as a

(12) T. W. Findley, D. Swern, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **67**, 412 (1945).
(13) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963).
(14) A. H. Homeyer, U. S. Patent 2,399,118 (1946); R. J. Ludwig, W. A. West, and D. N. Farnsworth, *J. Amer. Chem. Soc.*, **76**, 2891 (1954).
(15) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951).

doublet (J_{ab} = 7.5 Hz), while H_b is a doublet at 4.76 ppm. The difference in the chemical shift of H_a and H_b in the two isomers is ascribed to the shielding effect of the benzene rings attached to the adjacent carbon atoms in the *trans* isomer. In 5-phenyl-2-oxazolidone (XVII), H_a is a double doublet at 5.52 ppm, coupled to the *cis* proton H_b (J_{ab} = 8.5 Hz) and the *trans* proton H_c (J_{ac} = 7.5 Hz). H_b appears at 3.90 ppm split into a triplet ($J_{ba,bc}$ = 8.5 Hz) by the *cis* proton H_a and the geminal proton H_c. H_c, shielded by the benzene ring, is seen at 3.42 ppm as a double doublet coupled to protons H_a and H_b.

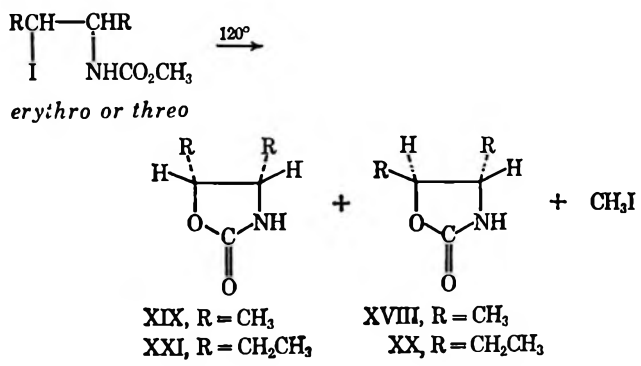
β-Iodocarbamates X–XIII were then pyrolyzed as neat liquids in a nitrogen atmosphere at 120°. The pyrolyses were monitored by disappearance of the methoxy signal in the nmr of the carbamates and by ir. The liberated methyl iodide was isolated in a cold trap usually in nearly quantitative yield; yields of 2-oxazolidones were essentially quantitative and the products were shown to be >97% pure by nmr.

Pyrolysis of methyl *erythro*-N-(3-iodo-2-butyl)carbamate (X) was complete after 1 hr. Examination of the reaction mixture by nmr and glpc showed it to be an 80:20 mixture of two compounds. After a cleanup distillation (no change in composition in the distillate), the two components were separated by preparative glpc and identified as the geometric isomers of 4,5-dimethyl-2-oxazolidone by elemental analysis, ir and nmr. The assignment of stereochemistry was made by analysis of their nmr spectra, listed in Table II. The major component, *trans*-4,5-dimethyl-2-oxazolidone (XVIII) showed H_a and H_b as quintets (J = 7.0 Hz) centered at 4.22 and 3.56 ppm, respectively. The methyl protons appeared as doublets (J = 7.0 Hz) at 1.26 and 1.10 ppm. The *trans* configuration is assigned since the coupling constant of H_a and H_b is of the same magnitude as that in the model *trans* compound XVI. Since all hydrogen–hydrogen coupling constants in the *trans* isomer are of the same magnitude the hydrogens appear as equivalent hydrogens. Accordingly, H_a and H_b are seen as quintets.

The minor component from the *erythro* isomer was identified as *cis*-4,5-dimethyl-2-oxazolidone (XIX) from its nmr spectrum (Table II). Assignment of the *cis* configuration is based on the magnitude of the coupling constant of H_a with H_b.

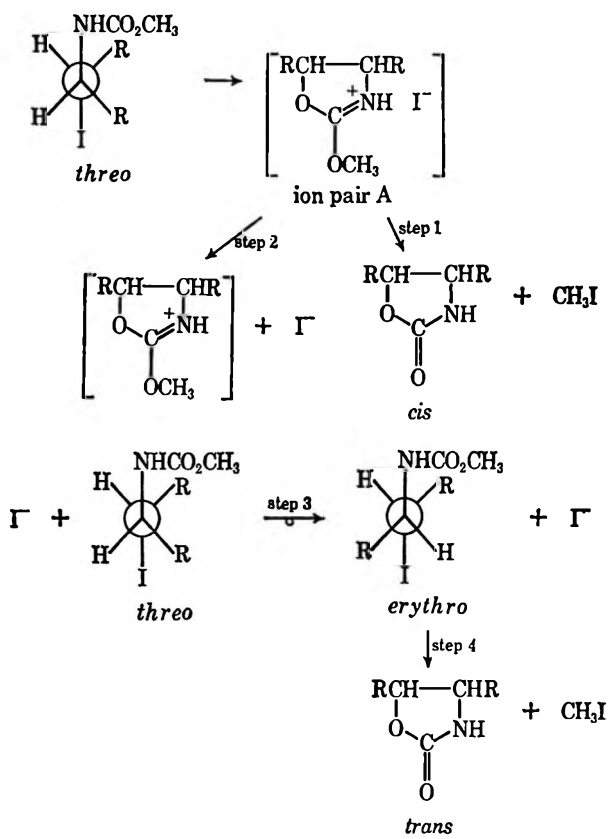
Pyrolysis of methyl *threo*-N-(3-iodo-2-butyl)carbamate (XI) also gave a mixture of isomeric 2-oxazolidones, the composition of which was 70% *cis* and 30% *trans*.

Pyrolysis of diastereomeric *erythro*- and *threo*-methyl N-(4-iodo-3-hexyl)carbamates XII and XIII also gave a mixture of *cis*- and *trans*-2-oxazolidones as shown by nmr. The isomer distribution from the *erythro* isomer was 90% of the expected *trans* (XX, Table II) and only 10% *cis* (XXI); from the *threo* isomer, the ratio was 70:30 with the expected *cis* isomer predominating. The assignment of stereochemistry was based on their nmr spectra, as in the dimethyl cases.



The pyrolytic cyclization of *erythro*- and *threo*-β-iodocarbamates, therefore, is a nonstereospecific cyclization although it is stereoselective. However, cyclization of *erythro* isomers, to yield predominantly *trans*-2-oxazolidones, is more stereoselective than pyrolysis of *threo* isomers that yield mainly *cis*-2-oxazolidones.

SCHEME III



A suggested mechanism to account for the lack of stereospecificity is shown in Scheme III using a *threo*-iodocarbamate as a prototype. The initial step involves formation of the previously proposed intermediate ion pair A from the β-iodocarbamate. This intimate ion pair can now proceed to the *cis*-2-oxazolidone (step 1) or dissociate to the free ions (step 2). The liberated iodide ion can undergo an identity reaction (SN2) with another molecule of *threo*-iodocarbamate to give the diastereomeric *erythro* isomer (step 3). The *erythro* isomer can then cyclize to *trans*-2-oxazolidone (step 4). Isomerization of *erythro* and *threo* isomers has been previously observed in the iodide ion-catalyzed conversion of acyl aziridines into oxazolines.[16]

The lower stereoselectivity observed in the pyrolytic cyclization of *threo*-iodocarbamates can be attributed to a higher degree of crowding of alkyl groups in approach-

(16) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).

ing the transition state for 2-oxazolidone formation (*trans*, antiparallel arrangement of the iodine and carbamoyl groups). Thus in *threo*-iodocarbamates the identity reaction suggested may become more competitive than in *erythro* isomers.

Experimental Section

Materials and Equipment.—The olefins used were the purest commercial reagents; glpc indicated >98%. Iodine isocyanate was prepared by the method of Rosen and Swern.[17] Infrared spectra were obtained on a Perkin-Elmer Infracord, Model 137. Nmr were obtained on a Varian A-60A spectrometer using TMS as internal standard. The samples were run as 10% solutions in chloroform. Glpc was carried out on a Wilkens Aerograph Autoprep, Model A-700. Refractive indices were taken on a Bausch and Lomb refractometer. Microanalyses were performed by Microanalysis Inc., Wilmington, Del.

Additions of INCO to Olefins. General Procedure. ***erythro*-4-Iodo-3-hexyl Isocyanate (VIII).**—Into a 500 ml three-necked flask equipped with a mechanical stirrer and condenser 25.0 g (0.15 mol) of freshly prepared silver cyanate and 200 ml of tetrahydrofuran (distilled from LAH) were placed. The stirred mixture was cooled to −35° and *trans*-3-hexene (10.0 g, 0.12 mol) was added followed by iodine (25.4 g, 0.10 mol) in one portion. The reaction temperature rose to −20° where it was held for 2 hr at which time the solution became colorless. The reaction mixture was allowed to come to room temperature, solids were filtered from the solution, washed with THF and the solvent was then removed from the filtrate at room temperature in a rotary vacuum evaporator. The residue was distilled to give VIII (20 g, 80% yield): bp 62–64° (0.30 mm); n^{25}D 1.5122; ir (neat) 3000, 2280 (-NCO), 1460, 1330, 1180, 950, 890, 820, and 800 cm^{-1}.

Anal. Calcd for $C_7H_{12}INO$: C, 33.1; H, 5.08; N, 5.52; I, 50.0. Found: C, 33.0; H, 5.01; N, 5.72; I, 49.8.

Methyl N-*erythro*-4-iodo-3-hexylcarbamate (XII) was prepared by adding VIII to 50 ml of anhydrous methanol and allowing the solution to stand for 18 hr in the dark. Vacuum evaporation of excess methanol gave a quantitative yield of XII as a viscous oil which solidified on cooling to −30°: mp 45–46°; ir ($CHCl_3$) 3500 (N–H), 3000, 1720 (C=O), 1520 (amide II), 1240, 1110, 990 and 870 cm^{-1}.

Anal. Calcd for $C_8H_{16}INO_2$: C, 33.7; H, 5.66; N, 4.91; I, 44.5. Found: C, 33.4; H, 5.91; N, 4.87; I, 44.0.

***threo*-4-Iodo-3-hexyl Isocyanate (IX)** was prepared from *cis*-3-hexene (10.0 g, 0.12 mol) in 75% yield by the described procedure: bp 66° (0.25 mm); n^{23}D 1.5125; ir (neat) 3000, 2260 (NCO), 1460, 1330, 1300, 1180, 1140, 1120, 920, 900, 840 and 790 cm^{-1}.

Methyl N-*threo*-4-iodo-3-hexylcarbamate (XIII) was prepared from IX as described for the *erythro* isomer. The crude residue was a viscous oil which could not be induced to crystallize. Its ir spectrum was similar to that of the *erythro*-iodocarbamate. Its nmr indicated it to be >98% pure.

***erythro*-3-Iodo-2-butyl isocyanate (VI)** was prepared from *trans*-2-butene in 70% yield: bp 49–50° (1.0 mm) [lit.[9] bp 57–59° (1.5 mm)]. The iodocarbamate, methyl *erythro*-N-(4-iodo-3-butyl)carbamate (X), was prepared as already described. The pure carbamate was a viscous oil obtained in quantitative yield: ir (neat) 3350 (NH), 2990, 1725 (C=O), 1510 (amide II), 1220, 1100 and 860 cm^{-1}.

Anal. Calcd for $C_6H_{12}INO_2$: C, 28.0; H, 4.71; N, 5.45; I, 49.4. Found: C, 28.7; H, 4.83; N, 5.50; I, 48.6.

***threo*-3-Iodo-2-butyl isocyanate (VII)** was prepared in 75% yield from *cis*-2-butene by the described procedure: bp 50–51° (1.0 mm) [lit.[9] bp 57–59° (1.5 mm)]. The iodocarbamate, methyl *threo*-N-(4-iodo-3-butyl)carbamate (XI), was prepared in 90% yield, mp 28–29°. Its ir spectrum was similar to that of the *erythro* isomer.

Anal. Calcd for $C_6H_{12}INO_2$: C, 28.0; H, 4.71; N, 5.45; I, 49.4. Found: C, 28.4; H, 4.77; N, 5.70; I, 48.5.

***cis*- (XIX) and *trans*-4,5-Dimethyl-2-oxazolidone (XVIII).**—*erythro*- or *threo*-methyl-N-(3-iodo-2-butyl)carbamate (X or XI) (12.65 g, 0.05 mol) was pyrolyzed at 120° until the evolution of methyl iodide ceased. The crude residue was cooled and examined by nmr and glpc. Both *cis* and *trans* isomers were present in the ratio of 20:80 from the *erythro*-iodocarbamate and 70:30 from the *threo*-iodocarbamate. Yields in both cases were quantitative and the residues were free of starting carbamate (nmr). The residues from the pyrolyses had identical boiling points [101–103° (0.15 mm)]. They were separated by preparative glpc employing a 5 ft × ⅜ in. column packed with 10% butanediol succinate on Anakrom 60 mesh at 185° with a helium flow of 200 ml/min.

Anal. Calcd for $C_5H_9NO_2$: C, 52.2; H, 7.88; N, 12.2. Found: C, 51.9; H, 8.19; N, 12.1.

***cis*- (XXI) and *trans*-4,5-Diethyl-2-oxazolidone (XX).** Pyrolysis of methyl *erythro*-N-(4-iodo-3-hexyl)carbamate (XII, 5.70 g, 0.02 mol) at 120° for 1 hr produced the theoretical amount of methyl iodide (2.8 g). The crude residue was cooled and examined by nmr, which indicated a 10:90 mixture of *cis*- and *trans*-2-oxazolidones of >98% purity. It was chromatographed on Florisil to give a colorless liquid of the same isomeric composition: ir (neat) 3320 (NH), 2980, 1750 (C=O), 1510 (amide II), 1220, 1150 and 970 cm^{-1}.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.15; N, 9.78. Found: C, 58.5; H, 9.26; N, 9.54.

Pyrolysis of methyl *threo*-N-(4-iodo-3-hexyl)carbamate (XIII, 5.70 g, 0.02 mol) at 120° for 1.5 hr gave the theoretical quantity of methyl iodide. The crude product partially crystallized on cooling. Examination by nmr indicated a 70:30 mixture of *cis*- and *trans*-isomeric 2-oxazolidones. The crude residue was dissolved in a minimum of ether and cooled to −30° to deposit white crystals, mp 79–80°, whose nmr spectrum indicated it to be pure *cis* isomer (XXI): ir ($CHCl_3$) 3540, 3350 (NH), 3000, 1760 (C=O), 1230 and 985 cm^{-1}.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.15; N, 9.78. Found: C, 58.8; H, 8.91; N, 9.76.

5-Phenyl-2-oxazolidone (XVII) was prepared in 55% yield by pyrolysis of neat ethyl N-(2-chloro-2-phenylethyl)carbamate, mp 87–88° (lit.[6] mp 87–87.5°).

***erthro*-1,2-Diphenylaminoethanol.**—*trans*-Stilbene oxide[18] (9.80 g, 0.05 mol) in ethanol (250 ml) was added in one portion to a solution of sodium azide (3.9 g, 0.06 mol) and ammonium chloride (3.3 g, 0.06 mol) in water (100 ml), and the solution was refluxed for 18 hr. The reaction mixture was poured into water (400 ml) and extracted with four 50-ml portions of ether. The ether solution was dried over anhydrous sodium sulfate and the solvent removed on a rotary evaporator. The crude residual azidohydrin was dissolved in ethanol (150 ml) and hydrogenated at room temperature in a stirring autoclave for 24 hr at 700 psi with platinum oxide catalyst (0.50 g). The solution was filtered and evaporated to dryness. The crude amino alcohol was recrystallized from aqueous alcohol, mp 163–165° (75% yield) (lit.[19] mp 165–166°).

***threo*-1,2-Diphenylaminoethanol** was prepared in 80% yield from *cis*-stilbene oxide[20] by the above procedure, mp 127–28° (lit.[19] mp 127–28°).

***cis*-4,5-Diphenyl-2-oxazolidone (XV)** was prepared from *erythro*-1,2-diphenylaminoethanol (4.25 g, 0.02 mol) and diethyl carbonate (40 g, 0.32 mol) by the method of Newman and Kutner.[15] The crude product was recrystallized from 80% aqueous methanol, mp 195–196° (55% yield) (lit.[15] mp 193.5–195.5°).

***trans*-4,5-Diphenyl-2-oxazolidone (XVI)** was prepared in 45% yield from *threo*-1,2-diphenylaminoethanol as described for the *cis* isomer, mp 161–163° (lit.[21] mp 161–162°).

Registry No.—VI, 19190-92-2; VII, 19190-93-3; VIII, 19202-65-4; IX, 19190-94-4; X, 19190-74-0; XI, 19190-75-1; XII, 19190-76-2; XV, 19202-66-5; XVI, 19190-95-5; XVII, 7693-77-8; XVIII, 19190-96-6; XIX, 19190-97-7; XX, 19190-98-8; XXI, 19190-99-9.

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The Determination of the Azo–Hydrazono Tautomerism of Some 2-Pyrazolin-5-one Dyes by Means of Nuclear Magnetic Resonance Spectroscopy and ^{15}N-Labeled Compounds[1]

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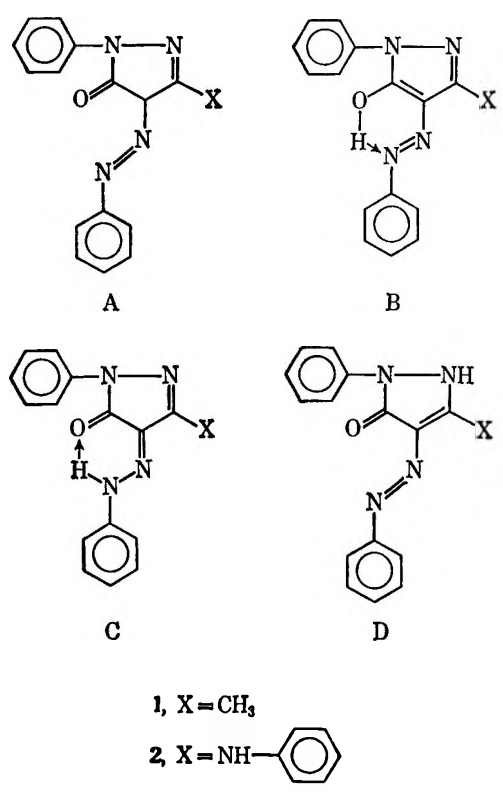
Through use of ^{15}N labeling and nmr spectroscopy we showed that 3-methyl-1-phenyl-4-phenylazo-2-pyrazolin-5-one (1) exists entirely in the hydrazone form in chloroform solution, in agreement with some of the earlier ir and nmr results with unlabeled compounds. In dimethyl sulfoxide (DMSO) and pyridine solutions a mixture of the hydrazono and the enol–azo forms is proposed. In a similar fashion we found that 3-anilino-1-phenyl-4-phenylazo-2-pyrazolin-5-one (2) exists entirely in the hydrazone form in chloroform and DMSO at 38° and in pyridine at −40°. At 38° in pyridine, however, a mixture of tautomeric forms is proposed.

The question of the tautomeric forms of 3-methyl-1-phenyl-4-phenylazo-2-pyrazolin-5-one (**1**) and of other 4-arylazo-2-pyrazolin-5-ones has stimulated much work in recent years.[2–7] The possible tautomeric forms of **1** and other 3-substituted 1-phenyl-4-arylazo-2-pyrazolin-5-ones are shown in Chart I. On the basis of spectroscopic studies, various authors have proposed **1** to exist in forms A,[2] B,[3] and C.[4–7] In our opinion the most persuasive arguments[5,6] have supported form C for compound **1** in chloroform.

CHART I
POSSIBLE TAUTOMERIC FORMS OF
3-SUBSTITUTED 1-PHENYL-4-PHENYLAZO-2-PYRAZOLIN-5-ONE



1, X = CH_3

2, X = NH—⬡

For our work we needed more conclusive proof and more extensive results than those reported in the literature. Since previous authors relied on similar spectroscopic techniques to arrive at quite varied conclusions, and since the tautomeric form of **1** could possibly change in going from chloroform to a more polar solvent such as DMSO, we reinvestigated the tautomerization of **1**.

In an earlier work[8] we observed marked differences in tautomeric ratios between 3-methyl-1-phenyl-2-pyrazolin-5-one and the 3-anilino analog in DMSO solution. In the current work compound **2** was included with **1** to see whether these differences in tautomeric ratios would persist in the 4-phenylazo derivatives of the 3-anilino-2-pyrazolin-5-ones.

The purpose of this work, then, was to (a) provide an unambiguous proof of the tautomeric form of **1** in chloroform and, if possible, in pyridine and DMSO; and (b) determine similarly the tautomeric form of **2**.

To do this we studied the tautomerization of **1** and **2** by using compounds labeled with ^{15}N adjacent to the 4-phenyl group. Since only the hydrazono form, form C, could exist with a hydrogen attached to the ^{15}N, a splitting of the proton resonance would be conclusive proof of the existence of the hydrazono form.

The labeled compounds, **1a** and **2a**, were prepared by diazotization of ^{15}N aniline followed by coupling with the appropriate pyrazolinone; the possibility of diazonium scrambling[9] under these mild conditions[10,11] is nil.

Table I summarizes the nmr data for **1a** and **2a**. In chloroform solution at 38 and 60° the unlabeled material **1** gave a broad singlet at 13.5 ppm, whereas compound **1a** showed a doublet with the center of gravity at 13.5 ppm, indicative of a proton attached to a ^{15}N. Since the ^{15}NH peak separation is so large[12] (96 Hz), and since the area of the ^{15}N proton peaks of **1a** relative to the aromatic protons was in a good 1:10 ratio, compound **1a** (and **1**) must exist entirely in the hydrazono form under these conditions. Furthermore, the high concentration of ^{15}N-bonded proton shows that little, if any, diazonium rearrangement[9] occurs during the synthesis of **1a**. The presence of only one ^{15}N-induced doublet in the spectrum of **1a** indicates that only one geometric isomer of the hydrazono form exists in this

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TABLE I

THE NMR SPECTRAL DATA FOR ^{15}N-LABELED 3-SUBSTITUTED 1-PHENYL-4-PHENYLAZO-2-PYRAZOLIN-5-ONE

Compound **1a**

Solvent	Temp, °C	NH, δ (ppm)[a]	Rel area[b] of ^{15}NH peak	J, ^{15}NH, Hz
$CDCl_3$	38	13.5[c]	1.1	96 ± 1
	60	13.5 (broad doublet)	*d*	96 ± 1
DMSO-d_6	38			
	60	13.5 (broad singlet)	*d*	
Pyridine-d_5	38	13 (very broad singlet)	*d*	
	−40	13.5 (broad singlet)	*d*	

Compound **2a**

Solvent	Temp, °C	NH, δ (ppm)[a]	Rel area[b] of ^{15}NH peak	J, ^{15}NH, Hz	N'H,[e] ppm[c]
$CDCl_3$	38	13.1[c]	1.1	97 ± 1	6.54
DMSO-d_6	38	13.1 (broad doublet)	0.8[d]	96 ± 1	9.08
Pyridine-d_5	38	13 (broad singlet)	*d*		9.86
	−40	13.7	1.0	97 ± 1	10.8

[a] δ is given in parts per million downfield from internal tetramethylsilane. [b] Relative to the area of the aromatic protons. [c] "Center of gravity" positions unless otherwise indicated. [d] Peaks were too broad for reliable area measurements. [e] ^{14}NH resonance from the 3-anilino moiety.

solvent, while the far-downfield position of the NH peak suggests that the proton is involved in a strong intramolecular hydrogen bond.

The above data indicate that form C represents the sole detectable tautomer of **1a** (and **1**) in chloroform. This conclusion is consistent with some of those[4-6] drawn from ir and nmr studies on unlabeled compounds. In the DMSO solution of **1a** no NH resonance was present at 38°; warming the solution to 60° gave only a broad singlet at 13.5 ppm. In pyridine at 38° no NH signal was observed but at −40° a broad absorption appeared at 13.5 ppm. The areas of these broad peaks ($W_{1/2} \cong 100$ Hz) are not a reliable measure of concentration; they are consistently low. Nevertheless, the chemical shift of this singlet indicates that the proton is in a magnetic environment similar to that of **1a** in chloroform. This suggests that the collapse of the ^{15}NH doublet and the peak broadening are both the result of proton exchange between the ^{15}N and the carbonyl oxygen. This means that **1a** probably consists of a mixture of forms B and C in these solvents.

Compound **2a** showed the sharp doublet (center of gravity at 13.1 ppm), characteristic of the ^{15}N-induced spin splitting, both in chloroform and DMSO solutions; in contrast, the unlabeled compound **2** showed only a broad singlet at 13.2 ppm in chloroform and 13.1 ppm in DMSO. The large coupling constant (96–97 Hz) for the ^{15}NH spin splitting is indicative[12b] of the sole existence of the hydrazono form (form C) for **2a** and is consistent with what has been observed with hydrazones.[10] Integration of the peak areas of **2a** gave a good 1:15 ratio for the NH peaks relative to the aromatic proton peaks for the chloroform solution and a slightly poorer ratio for the broader doublet of the DMSO example.

In pyridine at 38° compound **2a** gave a broad singlet at about 13 ppm; cooling to −40° gave the ^{15}NH doublet at 13.7 ppm (center of gravity position). Therefore, compound **2a** exists entirely in form C at −40° but at 38° probably consists of forms B and C for the same reasons as cited for compound **1a** in DMSO and pyridine solution.

In these three solvents the chemical shift of the ^{14}NH resonance of the 3-anilino group varied with solvent change whereas the "center of gravity" position of the ^{15}NH doublet remained relatively constant. This apparent solvent insensitivity of the ^{15}NH doublet further supports the claim that this proton is tied up in a strong intramolecular hydrogen bond.

Experimental Section

The nmr spectra were recorded on the Varian Model A-60 spectrometer; the solutions were *ca.* 10% (w/v) in chloroform, DMSO, and pyridine. All melting points are uncorrected. ^{15}N-Aniline (96.8% isotopic purity) was purchased from Merck Sharp & Dohme of Canada.

Preparation of 3-Methyl-1-phenyl-4-phenylazo-2-pyrazolin-5-one (1 and 1a).—These compounds were prepared by low temperature diazotization of the appropriate anilines followed by coupling of the diazonium salts with 3-methyl-1-phenyl-2-pyrazolin-5-one. The physical properties of **1a** were identical[13] with those of the unlabeled compound (1).

Preparation of 3-Anilino-1-phenyl-4-phenylazo-2-pyrazolin-5-one (2 and 2a).—These compounds were prepared by coupling the appropriate diazonium salts with 3-anilino-1-phenyl-2-pyrazolin-5-one (Eastman Organic Chemicals No. 8297) in the same manner as that described for **1** and **1a**. Recrystallization from carbon tetrachloride gave 0.8 g of red solid, mp 195–196°.

Anal. Calcd for $C_{21}H_{17}N_5O$: C, 71.0; H, 4.8; N, 19.7. Found: C, 70.8; H, 4.7; N, 20.0.

Registry No.—**1** (form C), 19374-75-5; **1a**, 19374-76-6; **2** (form C), 19374-77-7; **2b**, 19374-78-8.

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The Reaction of Ozone with a Pyrazolone Azomethine Dye

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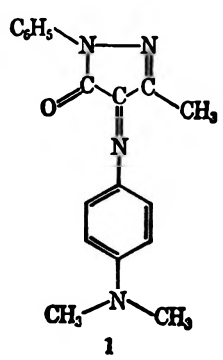
The reaction of the pyrazolone dye, 4-(4-N,N-dimethylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, **1**, with ozone is very rapid and proceeds *via* two paths. The major path produces oxaziridine **2** by adding an oxygen at the azomethine linkage. The second path involves attack at the dimethylamino moiety. Each path leads to a number of demethylated (**3** and **4**) and formylated (**5**, **6**, and **7**) products.

Bailey and coworkers[1] and Miller[2] have reported that ozonation of azomethine compounds, *e.g.*, Schiff bases, results in partial or complete cleavage of the azomethine linkage. Thus reaction of N-benzylidene-*t*-butylamine with ozone gives benzoic acid (40%), N-*t*-butylbenzamide (24%), and 2-*t*-butyl-3-phenyloxaziridine (15%). Emmons has shown that Schiff bases react with peracetic acid to give similar products,[3a] although certain

$$C_6H_5CH{=}NC(CH_3)_3 + O_3 \longrightarrow C_6H_5COOH + C_6H_5CONHC(CH_3)_3 + C_6H_5\underset{\displaystyle O}{\overset{\displaystyle H}{C}}{-}NC(CH_3)_3$$

oxaziridines were too subject to acid-catalyzed hydrolysis to isolate.[3b]

The present report identifies the products of the reaction of ozone with a pyrazolone azomethine dye, **1**,

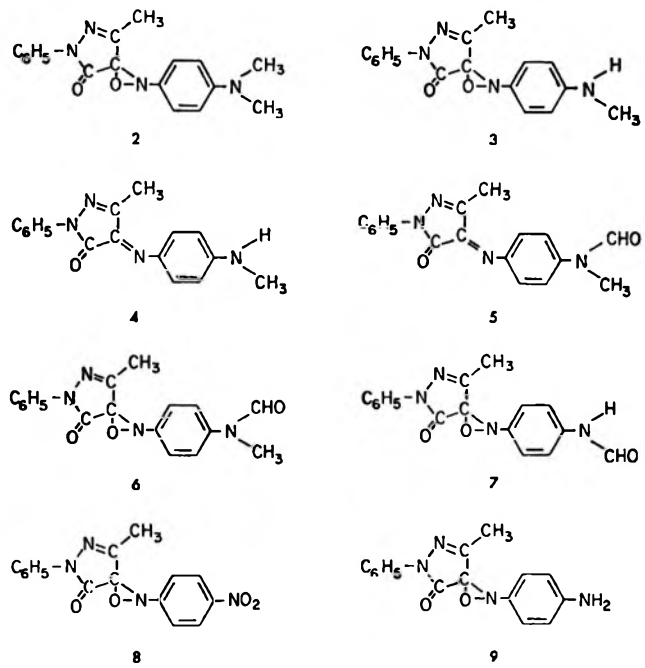


1

establishes the reactive sites in the molecule in regard to this particular reagent, and discusses possible mechanisms involved.

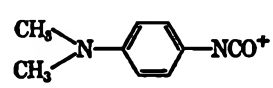
Results

Introduction of a dilute stream of ozone in oxygen (1:20) into a methylene chloride solution of **1** results in rapid reaction of the dye and the formation of the major reaction products, **2–4**, together with other minor products **5–8**. Compound **9** was detected (mass spectral data) in the reaction mixture, but resisted isolation and characterization. The reaction products obtained during the early stages of the reaction indicate that primary attack by ozone occurs at the azomethine and N,N-dimethylamino moieties, and leaves other points of unsaturation or high electron density untouched.



2 **3** **4** **5** **6** **7** **8** **9**

The products were isolated by thin layer (tlc) and adsorption chromatography.[4] Further purification was effected by recrystallization or by liquid–liquid partition chromatography.[5] Azomethine dyes **1** (unreacted) and **4** were identified by comparative tlc and by absorption spectroscopy. The structural proof of **2** is typical of that for the other oxaziridines **3**, **6**, **7**, and **8**. The elemental analysis of **2** indicates the addition of one oxygen atom per dye molecule. Compound **2** is colorless in solution (λ_{max} CH_3OH = 261, 287), thus excluding unsaturation at the 4 position of the pyrazolone ring and N-oxide formation. The parent mass spectrum peak corresponds to $C_{18}H_{18}N_4O_2$ (mol wt 322), which is in agreement with the assigned structure. The characteristic pyrazolone carbonyl stretching band of **1** (1670 cm^{-1} in KBr[6]) is shifted to higher frequencies in **2** (1725 cm^{-1}). This is further evidence of loss of unsaturation at the 4 position of the pyrazolone ring. Analysis of the principle fragment peak, mass 162, by high resolution mass spectroscopy shows the molecular ion to have an empirical formula corresponding to the following structure. The nmr spectrum shows δ values



(chemical shifts from tetramethylsilane reference) of 2.4 (s), 3.0 (s), and 6.7–7.7 (m), and integrated peak

(1) (a) A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Amer. Chem. Soc.*, **82**, 1801 (1960); (b) R. E. Erickson, A. H. Riebel, A. M. Reader and P. S. Bailey, *Ann.*, **653**, 129 (1962); (c) P. S. Bailey, A. M. Reader, P. Kolsaker, H. M. White, and J. C. Barborak, *J. Org. Chem.*, **30**, 3042 (1965).

(2) R. E. Miller, *ibid.*, **26**, 2327 (1961).

(3) (a) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957); (b) R. G. Pews, *J. Org. Chem.*, **32**, 1628 (1967).

(4) B. Loev and K. M. Snader, *Chem. Ind.* (London), 15 (1965); 2026 (1967).

(5) W. F. Smith and K. L. Eddy, *J. Chromatog.*, **22**, 296 (1966).

(6) (a) R. Jones, A. J. Ryan, S. Sternhill, and S. E. Wright, *Tetrahedron*, **19**, 1497 (1963); (b) B. W. Rossiter, unpublished results.

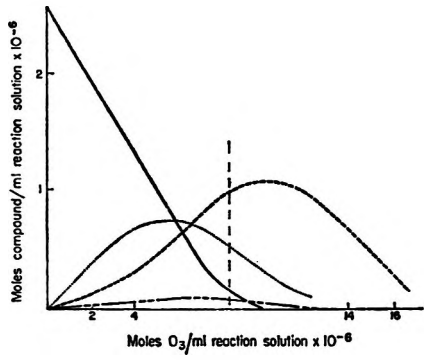


Figure 1.—Ozonation products of dye 1 as a function of the amount of ozone added: ——, 1; ···, 2; – – –, 3; — — —, 4 (solvent, dichloromethane; temperature, 0°).

ratios of 3.0, 6.0, and 9.4 corresponding to the CCH_3, $N(CH_3)_2$, and nine aromatic hydrogens, respectively. The aromatic hydrogen absorption of **2** is shifted upfield relative to that of **1**; thus the nmr spectrum is consistent with saturation of the azomethine linkage without loss or gain of hydrogens. Finally, **2** was independently prepared in 8% yield by the reaction of **1** with alkaline hydrogen peroxide.[7] Surprisingly, the oxaziridine ring of **2** and **3** is resistant to catalytic hydrogenation (15 psi, 25°), and to acid hydrolysis.

Figure 1 shows the concentrations of starting dye **1** and of the major products **2–4**, as a function of the amount of ozone added. It is apparent from the curve that (1) ozone reacts with some of the products in competition with reaction with **1**; (2) products **2** and **4** are formed by parallel reaction paths with the path to the former predominating; and (3) as the concentration of **2** decreases, that of **3** increases. If the reaction is stopped and products are isolated at the point designated by the dotted vertical line, the yields of **1**, **2**, **3**, and **4** are 5, 25, 38, and 2%, respectively.

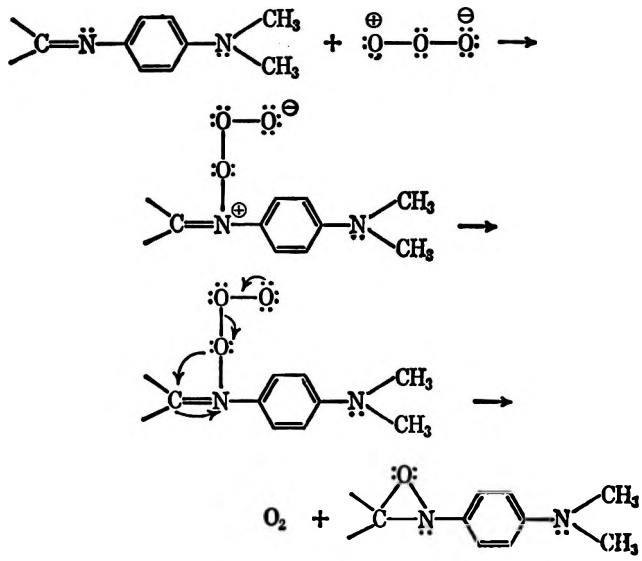
Treatment of the N′,N′-dimethylaminophenyloxaziridine, **2**, with ozone gives formyl derivatives **6** and **7**, desmethyloxaziridine **3**, and nitro derivative **8**. Similarly, ozonation of **3** gives **7** and **8**, and reaction of ozone with **5** produces **6** as the major product.

The ozonation of **1** is independent of the temperature over the range 0–25°. The products and their yields are influenced by the amount and rate of addition of ozone. Several solvents were used, dichloromethane, benzene, ethyl acetate, acetone, nitromethane, methanol, ethanol, isopropyl alcohol, and acetic acid. In general, the solvent does not enter into the reaction, although in the case of dichloromethane, there is mass spectral evidence that chlorinated derivatives of **2** and **8** are formed.

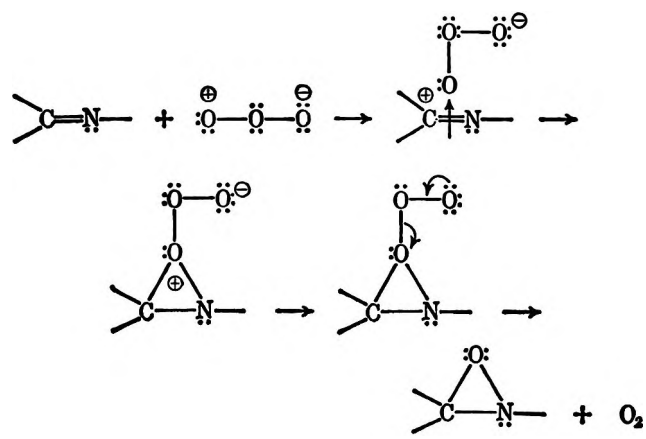
Discussion

Bailey and coworkers have proposed that ozonation of the azomethine linkage of Schiff bases[1a] and of 2,4-dinitrophenylhydrazones[1b] proceeds by nucleophilic attack at the azomethine carbon, which is in contrast to the proposal of electrophilic attack by ozone at carbon–carbon double bonds.[8] Erickson and Myszkiewicz have suggested that ozonation of nitrones involves electrophilic attack.[9] Our evidence suggests electrophilic attack, and is based on the relative rates of disappearance of dyes **1**, **4** and **5** (**1** > **4** > **5**, see Experimental Section). Smith has calculated that the azomethine nitrogen of **1** is considerably more negative than the azomethine carbon atom.[10] It is likely, therefore, that initial attack of ozone is at the azomethine nitrogen (Scheme I). An alternative mechanism involves electrophilic π complex formation of the type proposed for ozonation of carbon–carbon double bonds[8] (Scheme II).

SCHEME I



SCHEME II



No experimental evidence was found for a third possibility, namely, molozonide formation from ozone and the azomethine linkage. Breakdown of a hypothetical molozonide could give oxazirdiines *via* modified Criegee-type intermediates.[11a] Demethylation and oxidation of the dimethylamino moiety can be explained by a number of free radical or ionic reactions[11b,c,d] leading to an intermediate hydroxymethylamino deriva-

(7) (a) F. D. Gunestone, *Advan. Org. Chem.*, **1**, 132 (1960); (b) L. Fieser, *et al.*, *J. Amer. Chem. Soc.*, **61**, 3216 (1939); **62**, 2866 (1940).

(8) P. S. Bailey and A. G. Lane, *J. Amer. Chem. Soc.*, **89**, 4473 (1967).

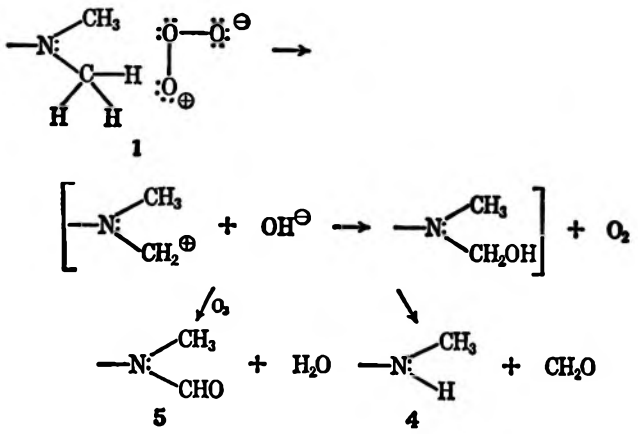
(9) R. E. Erickson and T. M. Myszkiewicz, *J. Org. Chem.*, **30**, 4326 (1965).

(10) W. F. Smith, Jr., *J. Phys. Chem.*, **68**, 1501 (1964).

(11) (a) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Amer. Chem. Soc.*, **90**, 1822 (1963); C. E. Bishop and P. R. Story, *ibid.*, **90**, 1905 (1968); P. R. Story, C. E. Bishop, and J. R. Burgess, *ibid.*, **90**, 1907 (1968); (b) P. S. Bailey, Robert A. Welch Foundation Annual Report, 1965–1966; (c) P. Kolsaker and O. Meth-Cohn, *Chem. Commun.*, 423 (1965); (d) P. S. Bailey, D. A. Mitchard, and A. Y. Khashab, *J. Org. Chem.*, **33**, 2675 (1968).

tive. One such sequence of reactions involving electrophilic attack at the hydrogens α to nitrogen is shown in Scheme III. The intermediate hydroxymethylamino

SCHEME III



derivative may eliminate formaldehyde, leading to demethylated derivatives,[11b] or be oxidized by ozone to the formyl derivative and other oxidation products. Reaction of **4** and **5** with ozone gives mainly **3** and **6**, respectively. A similar series of reactions is suggested for the ozonation of **2** and for the complete demethylations leading to **9**. Mass spectral evidence for the presence of **9** in the ozonation reaction mixture has been obtained, but **9** has not been isolated or fully characterized.

Conclusion

Ozone attacks pyrazolone dye **1** at the azomethine and dimethylamino moieties, reaction at the former site predominating. Other points of unsatuaration are left untouched in the initial reactions.

Experimental Section

Solvents were Eastman Grade. Precoated plates for thin layer chromatography were obtained from Brinkmann Instruments Inc. The ozone generator was essentially that described elsewhere.[12]

Ozonation Procedures. For Isolation of Products.—Ozone–oxygen gas (5% ozone) was bubbled into a gas wash bottle equipped with a sintered glass dispersing tube and charged with the solution (between 1 and 5 $\times 10^{-2}$ M) of the compound to be ozonized. Gas flow was held at a constant rate within the range of 400–1400 ml/min. The extent of decomposition was noted by the amount of ozone used or by the color of the reaction solution. After the desired amount of ozonation, the reaction solution was transferred to a round-bottom flask and the solvent was removed under reduced pressure. The residue was taken up in a minimum of solvent and separated into its components by adsorption chromatography.[4] The compounds were recovered from the adsorbent with a mixture of 15 volumes of methanol and 35 volumes of dichloromethane. Further purification was effected by tlc, liquid–liquid partition chromatography[5] or recrystallization. Table I lists the products obtained by ozonation. The physical data used for the identification of **2–8** are listed below with the specific compounds.

For Qualitative Identifications.—A solution (2.5 $\times 10^{-3}$ M) of the compound to be ozonized was treated in an open flask with an ozone–oxygen mixture containing about 5% ozone. The bubbling rate was 25–150 ml/min. Aliquots were removed at various time intervals and spotted onto the tlc plates. Authentic compounds were also spotted onto the tlc plates as references. The plates were developed with a mixture of 10 volumes of ethyl acetate and 90 volumes of dichloromethane. Compounds **1–8** showed the following R_f numbers for development in a glass chamber containing solvent saturated filter paper: 0.58, 0.51, 0.34, 0.52, 0.27, 0.12, 0.07, and 0.55, respectively; without the filter paper the values were 0.82, 0.69, 0.49, 0.74, 0.39, 0.16, 0.09, 0.78, respectively.

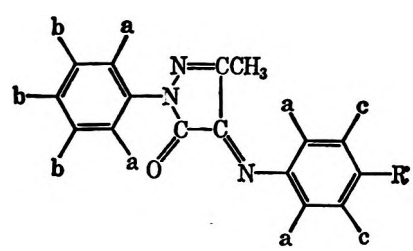
TABLE I

Compd ozonized	Major products isolated from the ozonation
1	2, 3, 4, 5, 6, 7, 8
2	3, 6, 7, 8
3	7, 8
4	3
5	6
6	6 (starting material)
7	7 (starting material)
8	8 (starting material)

TABLE II

Moles of $O_3 \times 10^{-6}$	Moles of dye 1 $\times 10^{-6}$	Moles of dye 4 $\times 10^{-6}$
0	1.45	1.25
1.1	1.34	1.17
2.2	1.14	1.01
3.3	0.92	0.81
4.4	0.75	0.63
5.5	0.54	0.50
6.6	0.37	0.41
8.8	0.09	0.18
9.9	0.03	0.12
11.0		0.06
12.1		0.03

The nmr spectra were recorded on a Varian Associates 60-MHz instrument. The chemical shifts (δ) are measured from the reference tetramethylsilane. The band intensities are relative to the pyrazolone ring methyl hydrogens taken as 3.0. The labeling of the aromatic ring hydrogens is illustrated. In the



oxaziridines, the aromatic hydrogen bands were bunched together, and were not identified individually. For reasons not clear to the authors, highly purified samples of compounds **1–6** all gave slightly higher values for the integrated peak ratios of the aromatic hydrogens than the expected 9.0.

For Quantitative Measurements.—The ozonation train was equipped with a three-way stopcock permitting the gas flow to be diverted either to the reaction solution or to a 2% KI trap (for analysis of ozone content). A flow meter (Ace Glass Co. Tru-Taper) was included in the train between the ozone generator and the three-way stopcock. The ozone concentration in the gas stream was determined before and after the ozonation of the desired compound. A solution (2.5 $\times 10^{-3}$ M) of the compound to be ozonized was placed in an erlenmeyer flask equipped with a magnetic stirrer, and the ozone–oxygen gas was then introduced through a sintered glass dispersing tube. Aliquots (1 ml) were removed at various time intervals *via* a pipet filler (Will Scientific Co.), and applied as a stripe to a 20 $\times$ 20 cm analytical thickness silica gel tlc plate. After development, the bands were removed individually and the compounds eluted from the adsorbent with EK S467 methanol. The eluates were diluted to volume in appropriate volumetric flasks, and the concentrations determined spectrophotometrically using the extinction coefficients for the compounds.

(12) L. I. Smith, *et al.*, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 673.

For Competitive Rate Measurements.—A mixture of dyes **1** (1.45×10^{-6} *M*) and **4** (1.25×10^{-6} *M*) in dichloromethane was treated with ozone in a quantitative manner as described above. Analysis of the aliquots gave the data in Table II showing dye **1** was lost slightly faster than dye **4**. As shown in Figure 1, dye **4** is found in the reaction mixtures after all of dye **1** is gone. Similarly, dye **5** is found, by tlc, after both dyes **1** and **4** are gone.

4-(4-N,N-Dimethylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 1, was prepared according to published procedures,[13] and recrystallized from acetone as deep purple plates: mp 187–188° (lit.[14] mp 188°); λ_{max} (MeOH) 440 nm (ϵ 12,300), 525 (30,000); mass spectrum (70 eV) *m/e* 306; nmr ($CDCl_3$) δ 8.4–7.9 (m, 4.1, aromatic H_a), 7.6–7.1 (m, 3.2, aromatic H_b), 6.7–6.5 (m, 2.1, aromatic H_c), 3.1 (s, 6.1, $>NCH_3$), 2.3 [s, 3.0, $-N=C(CH_3)-$].

4-[2-(4-N,N-Dimethylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 2, was isolated from the ozonation mixtures by adsorption chromatography, or was independently synthesized by treating a warm (70°) solution of **1** (0.5 g in 75 ml 95% ethanol) with 5 ml of hydrogen peroxide (25–35%), followed by the addition of six drops of sodium hydroxide (40%). After 3 hr, the reaction mixture was separated by tlc, giving an 8% yield of material identical with **2** (formed by ozonation of **1**) as shown by tlc and by mixture melting point. Compound **2** was recrystallized from alcohol as feathery, pale tan needles: mp 167–168°; uv max (MeOH) 261 nm (ϵ 23,000), 287 (9100); mass spectrum (70 eV) *m/e* 322, 162.0795; nmr ($CDCl_3$) δ 7.7–6.7 (m, 9.4, aromatic **H**), 3.0 (s, 6.0, $>NCH_3$), 2.4 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.1; H, 5.6; N, 17.4. Found: C, 66.8; H, 5.5; N, 17.5.

4-[2-(4-N-Methylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 3, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from cyclohexane–dichloromethane as a pale yellow powder: mp 213–214°; uv max (MeOH) 255 nm (ϵ 21,700), 287 (8700); mass spectrum (70 eV) *m/e* 308, 148; nmr ($CDCl_3$) δ 7.6–6.5 (m, 9.0, aromatic **H**), 3.9 (s, 1.0, >NH), 2.8 (s, 3.1, $>NCH_3$), 2.4 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.2; H, 5.2; N, 18.2. Found: C, 66.2; H, 5.5; N, 18.5.

4-(4-N-Methylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 4, was prepared according to the general procedures of Brown, *et al.*,[13] and recrystallized from chloroform–acetone as feathery red needles: mp 193–194°; λ_{max} (MeOH) 434 nm (ϵ 15,400), 511 (32,000); mass spectrum (70 eV) *m/e* 292; nmr ($CDCl_3$) δ 8.3–7.9 (m, 4.1, aromatic H_a), 7.6–7.1 (m, 3.6, aromatic H_b), 6.6–6.5 (m, 1.8, aromatic H_c), 4.7 (s, 1.0, >NH), 2.9 (s, 3.1, $>NCH_3$), 2.3 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.9; H, 5.5; N, 19.2. Found: C, 69.7; H, 5.6; N, 19.2.

4-(4-N-Formyl-N-methylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 5, was isolated from the ozonation mixtures by adsorption chromatography, and was synthesized by each of the following procedures.

Procedure A.—A poor yield of **5** was obtained by treating a solution of **2** with sufficient formic acid (EK P139) to obtain a color change of the solution (magenta to purple), removing the water by azeotropic distillation, and separating the remaining mixture by adsorption chromatography.

Procedure B.—Compound **5** was obtained in better yield by dissolving 0.3 g of compound **2** in a mixture of 40 ml of ethyl formate (EK P439) and 40 ml of toluene. A small amount of sodium methylate was added. The mixture was heated to boiling and the solvent removed by slow distillation. When the temperature of the distillate had risen to 104° (3–4 hr), the mixture was cooled and separated by adsorption chromatography. The band corresponding to compound **5** was purified further by liquid–liquid partition chromatography, and recrystallized from cyclohexane as a red powder: mp 120–121°; uv max (MeOH) 246 nm (ϵ 26,900), 357 (5600), 493 (1200); mass spectrum (70 eV) 320; nmr ($CDCl_3$) δ 8.6 [s, 0.6, $HC(=O)-$], 8.0–6.9 (m, 9.9, aromatic **H**), 3.3 (s, 2.6, $>NCH_3$), 2.3 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.6; H, 5.2; N, 17.7.

4-[2-(4-N-Formyl-N-methylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 6, was isolated from the ozonation mixtures by adsorption chromatography and was synthesized by treating compound **3** according to procedure B used to prepare compound **5**. Compound **6** was recrystallized from alcohol as a light tan powder: mp 150–152°; uv max (MeOH) 246 nm (ϵ 23,600), 280 (10,200); mass spectrum (70 eV) 336.1222, 176.0587; nmr ($CDCl_3$) δ 8.6 [s, 1.1, $HC(=O)-$], 7.7–7.3 (m, 9.6, aromatic **H**), 3.3 (s, 2.8, $>NCH_3$), 2.4 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.3; H, 4.8; N, 16.7. Found: C, 64.0; H, 4.7; N, 16.4.

4-[2-(4-N-Formylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 7, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from dichloromethane–cyclohexane as a white powder: mp 250–252°; uv max (MeOH) 241 nm (ϵ 20,400), 280 (8600); mass spectrum (70 eV) 322.1068, 162; nmr ($CDCl_3$) δ 10.3 [s, 1.0, $-NHC(=O)-$], 8.6 [s, 0.8, $HC(=O)-$], 7.9–7.2 (m, 9.1, aromatic **H**), 2.4 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.3; H, 4.4; N, 17.4. Found: C, 62.8; H, 4.7; N, 17.3.

4-[2-(4-Nitrophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 8, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from cyclohexane as colorless plates: mp 195–196°; uv max (MeOH) 238 nm (ϵ 12,900), 268 (15,700); mass spectrum (70 eV) 324.0843, 164; nmr ($CDCl_3$) δ 7.6–7.4 (m, 6.8, aromatic **H**), 8.4 (m, 2.0, aromatic H_c), 2.4 [s, 3.0, $-N=C(CH_3)-$].

Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.4; H, 3.3; N, 17.5.

Registry No.—Ozone, 10028-15-6; **1**, 1456-89-9; **2**, 19362-39-1; **3**, 19362-40-4; **4**, 13617-66-8; **5**, 19362-42-6; **6**, 19362-43-7; **7**, 19362-44-8; **8**, 19362-45-9.

Acknowledgments.—The authors gratefully acknowledge the assistance of the following colleagues in obtaining and interpreting spectral data: D. P. Maier and G. P. Happ (mass spectra); T. H. Regan (nmr); and Miss T. J. Davis (infrared spectra). We thank Miss M. P. O'Grady and Mr. J. R. Abbott of these laboratories for some of the dye samples.

(13) (a) G. Brown, *et al.*, *J. Amer. Chem. Soc.*, **73**, 919 (1951); **79**, 2919 (1957); (b) A. Weissberger and H. D. Porter, *ibid.*, **65**, 732 (1943).

(14) F. Sachs and H. Barschell, *Ber.*, **35**, 1437 (1902).

The Reaction of 12H-Benzo[a]phenothiazine and 12H-Benzo[b]phenoxazine with Certain Heterocyclic Azides

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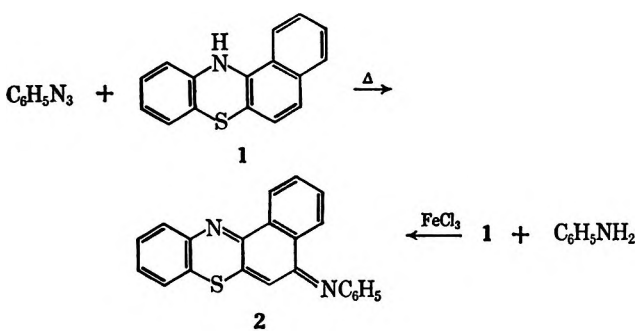
Received October 1, 1968

12H-Benzo[a]phenothiazine (1) reacts with certain heterocyclic azides under the influence of heat or light to give azomethine dyes in which the coupling occurs at the 5 position of 1. 12H-Benzo[b]phenoxazine under the same conditions yields a dimer of the azacarbon, and in the case of one class of heterocyclic azides, azomethine dyes derived from the dimer are obtained.

The formation of nitrene intermediates by the thermal or photochemical elimination of nitrogen from aryl azides is well known.[1] Aryl nitrenes undergo a variety of reactions including insertion into a C–H bond.[2] The present paper describes an intermolecular insertion reaction of heterocyclic nitrenes into benzo[a]-phenothiazine to give azomethine dyes, and the dimerization of benzo[b]phenoxazine by these nitrenes.

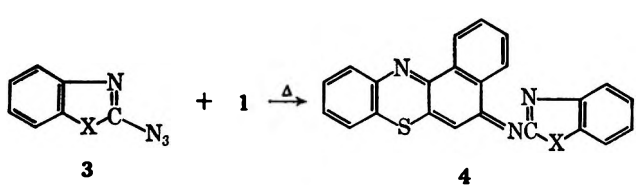
Phenyl azide was thermally decomposed in the presence of 12H-benzo[a]phenothiazine (1) in 1,2,4-trichlorobenzene to give dye **2**, which has been prepared previously by the oxidative coupling of aniline with **1**.[3]



This reaction has been extended to a wide variety of heteroxyclic azides with phenothiazine, phenazine, and phenoxazine derivative, but only a few representative examples will be included in this paper.

The heterocyclic azides **3a–3d**[4] were thermally decomposed in 1,2,4-trichlorobenzene in the presence of **1** to give dyes **4a–4d** (Scheme I). We were unable to obtain satisfactory elemental analyses for **4b** prepared by thermal decomposition, so the dye **4d** was saponified with methanolic potassium hydroxide to give a sample of **4b**, for which we did obtain a correct analysis.

Scheme I



a, X=S
b, X=NH
c, X=O
d, X=NCONHCH$_2$CO$_2$C$_4$H$_9$

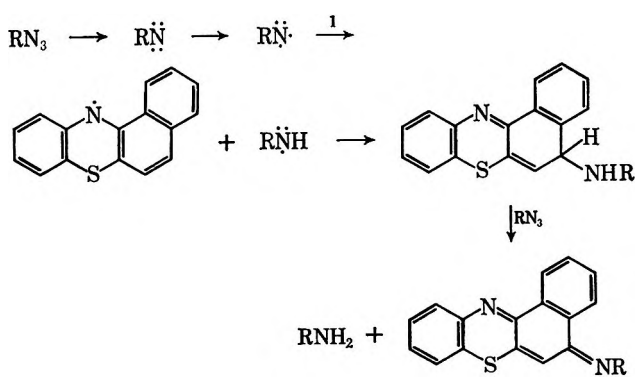
The thermolysis procedure, in the case of **3d**, gave a mixture of **4b** and **4d**. Dye **4d** was prepared by the reaction of **3d** with **1** at room temperature with cupric acetate in acetone or tetrahydrofuran. Copper salts are effective catalysts for dye formation only with N-carbonyl-substituted azides, such as **3d**.

Dyes **4a–4d** are the same as those produced by the photolysis of the corresponding azide and **1**,[5] as shown by comparison of their electronic spectra.

The reaction of a nitrene with **1** to give dyes **4a–4d** requires that an oxidation take place. For the investigation of this facet of the reaction, equal molar quantities of **3a** and **1** were heated in trichlorobenzene in a nitrogen atmosphere. Dye **4a** was isolated in 47% yield. A similar run was made bubbling air through the solution and **4a** was obtained in the same yield. The reaction was then carried out with 2 equiv of azide per mol of **1**, resulting in a quantitative yield of **4a**.

A plausible reaction sequence which leads to dye formation is shown in Scheme II. This mechanism is similar to that proposed for the formation of N-alkyl-amines from phenyl azide and alkanes.[2]

Scheme II



The dye **4c**, on mass spectrometric analysis, gives a molecular ion at *m/e* 379 for the proposed structure and a peak at 381 corresponding to a dihydro derivative of **4c**. The relative intensity of the peak at *m/e* 381 was approximately half that observed at *m/e* 379. This ratio is subject to a number of variables, in addition to differences in the actual amount of each component which may be present. The variables include different yields of the molecular ion under electron impact for

(1) L. Horner and A. Christmann, *Angew. Chem. Intern. Ed. Engl.*, **2**, 599 (1963).

(2) J. H. Hall, J. W. Hill, and J. M. Fargher, *J. Amer. Chem. Soc.*, **90**, 5313 (1968).

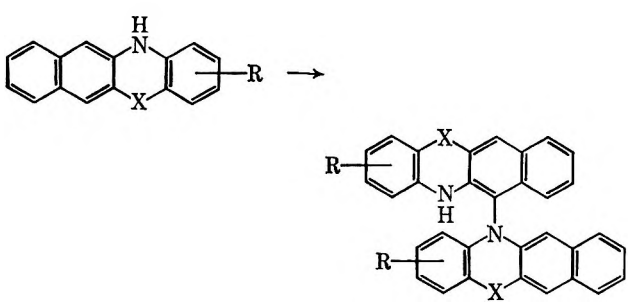
(3) F. Kehrmann, *Ann.*, **322**, 45 (1902).

(4) It has been shown [G. A. Reynolds, J. A. VanAllan, and J. F. Tinker, *J. Org. Chem.*, **24**, 1205 (1959)] that **3b** is a tetrazole. We have used the azide structure in the present paper for convenience and because it is probably the representative structure in heated solutions.

(5) J. J. Sagura and J. A. VanAllan, U. S. Patent 3,282, 693 (1966).

different structures, and differences in volatility of two components at a given temperature. The mass spectrum of **4d** does not show the intact molecule (molecular weight 535) but does show two peaks at 378 and 380. These may be rationalized on the basis of a thermal decomposition of the parent compound to compounds **4b** and its dihydro derivative, with the loss of $CONHCH_2COOC_4H_9$. This type of thermal reaction also occurs with **3d,** which decomposes to **3b** (*m/e* 159), 2-aminobenzimidazole (*m/e* 133), and $(C_4H_9O_2CCH_2NH)_2CO$ (*m/e* 288). In the case of **4d,** the ratio observed for mass spectral peaks at *m/e* 378 and *m/e* 380 varied from 1:2 to 2:1 from one analysis to another. Since the samples were examined in the direct inlet probe with the temperature programmed from 200 to 230°, this variation might be connected with the actual temperature at the time the paricular peaks were recorded. Since it is possible that the dihydro derivatives may be formed in the heated inlet of the mass spectrometer, compound **2,** which is of known structure, was examined under the same conditions as **4b, 4c** and **4d** (*i.e.*, in a direct inlet system but at temperatures of 140–160° rather than from 200 to 230°) and produced only a very small amount (<5%) of the dihydro compound. The spectra on this known showed that the intensity of the *m/e* 340 peak, relative to the molecular ion at *m/e* 338, was greatest at 140° (where it was about 20%) and that it decreased to about 5% at 160°, where the volatility of the *m/e* 338 material was about 80 times as great. From this evidence, we believe that a dihydro form of **4a–4d** may be present in the original samples and that the dihydro form and the dye may occur as a molecular complex, possibly of a quinhydrone type.[6]

The reaction of heterocyclic azides has been extended to 12H-benzo[*b*]phenoxazine (**5**), yielding products that were more complicated than those from the corresponding reactions with **1.** The thermal decomposition of 1 equiv of **3a–3d** in the presence of 1 eqiv of **5** gave a dimer of **5** (parent peak *m/e* 464) to which we have assigned the structure **6.** It was found that **5** dimerizes with a variety of oxidizing agents, such as cupric acetate, hydrogen peroxide, benzoquinone, cobaltic acetate and potassium permanganate. A convenient method for the preparation of **6** in 75–80% yield consists in aerating a solution of **5** in pyridine in the presence of a catalytic amount of cupric acetate at room temperature. In a similar fashion, 2-phenyl-12H-benzo[*b*]phenoxazine (**7**), 3-pentadecyl-12H-benzo[*b*]phenoxazine (**8**), and 12H-benzo[*b*]phenothiazine (**9**) give dimers **10, 11,** and **12,** respectively. Phenoxazine, 12H-benzo[*a*]phenothiazine, 7H-benzo[*c*]phenoxazine, and phenothiazine give oxidation products but no dimer by this procedure, and 12-methylbenzo[*b*]phenoxazine was recovered unchanged. From these data it appears that the essential requirements for dimer formation under these conditions are the presence of at least four linear fused rings in an azacarbon containing an NH group.



5, X = O; R = H
7, X = O; R = 2-phenyl
8, X = O; R = 3-pentadecyl
9, X = S; R = H

6, X = O; R = H
10, X = O; R = 2-phenyl
11, X = O; R = 3-pentadecyl
12, X = S; R = H

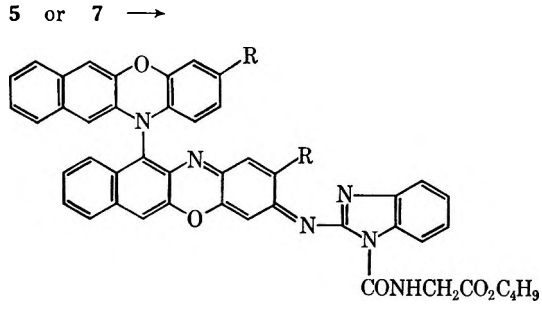
It seems reasonable to assume that the dimers are not bonded through a 2 or 3 position, since **7** and **8** give dimers. We have shown previously[7] that the 6 and 11 positions of **5** have enhanced reactivity in a variety of reactions, and we have assigned the 11 position as the point of fusion of one of the benzophenoxazine moieties of the dimer. There is precedent for the choice of this position since Musso[8] has shown that phenoxazine gives dimers and polymers in which some of the coupling occurs in a position adjacent to a heteronitrogen atom.

The infrared spectra of the dimers show a well-defined absorption at 3380 cm^{-1} for the NH group. The intensity of this NH absorption for the dimers is approximately one-half the intensity of the corresponding absorption for the monomers, which is evidence that one of the fusion points in the dimers is a nitrogen atom. We were unable to prepare an acetyl derivative of **6,** but this is probably the result of steric hindrance. The nmr spectrum of **6** could not be determined because of solubility difficulties.

The electronic spectra of **5** and its dimer **6** are almost identical with respect to the position of peak absorptions, and the extinction coefficients are higher by a factor of 2 for the dimers. This is consistent with the postulate that the two monomeric units are not in the same plane, and the π systems do not interact.

More rigorous conditions of oxidation of **5,** for instance, heating **5** in pyridine at 95–100° for 16 hr in the presence of cupric acetate, give a trimer of **5** (parent peak *m/e* 923) and other higher "mers" which are not volatile in the mass spectrometer.

The reaction of excess **3d** with **5** or **7** and cupric acetate in acetone or tetrahydrofuran gives the dyes **13** and **14.** The dimer **6** also reacts with **3d** under similar conditions (pyridine was used as solvent because of the limited solubility of **6**) to give **13.** Other azides of the same type as **3d** have also given dyes derived from the dimer. It appears that for the dye formation, the



13, R = H
14, R = phenyl

(6) Heterocyclic compounds such as phenazines are known to form quinhydrones. See G. Swan and D. Felton, "The Chemistry of Heterocyclic Compounds," Vol. 11, Interscience Publishers, New York, N. Y., 1957, p 48.

(7) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27,** 1659, 2873 (1962); **28,** 520 (1963).

(8) H. Musso, *Chem. Ber.*, **92,** 2862, 2873 (1959).

Table I

Physical Constants of Compounds

Compd no.	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Method of prepn	Yield, %	Solvent of recrystn	Absorption spectra λ_{max} mμ (× 10^{-3})	Solvent
2	178–179	$C_{22}H_{14}N_2S$	78.3	3.9	8.3	78.2	4.2	8.1	A	45	Chlorobenzene	230 (27.6) 360 (11.3) 268 (23.6) 470 (11.3) 318 (19.7)	Acetonitrile
4a	230–231	$C_{22}H_{13}N_3S_2$	69.9	3.3	10.6	70.0	3.6	10.3	A	96	*o*-Dichlorobenzene	218 (23.7) 370 (8.5) 263 (11.9) 519 (9.4) 340 (9.2)	Dimethylformamide
4b	330–332	$C_{22}H_{14}N_4S$	73.0	3.7	14.8	72.9	3.4	14.7		62	Pyridine	283 (20.4) 374 (16.7) 348 (15.0) 535 (19.5)	Dimethylformamide
4c	229–230	$C_{22}H_{13}N_3OS$	72.8	3.5	11.1	73.2	3.2	11.2	A	91	*o*-Dichlorobenzene	280 (10.5) 560 (10.0) 365 (6.0)	Dimethylformamide
4d	208–209	$C_{30}H_{25}N_5O_3S$	67.3	4.7	13.1	67.3	4.8	12.7	B	66	Tetrahydrofuran + methyl alcohol	240 (28.2) 388 (14.5) 277 (18.8) 560 (18.7) 355 (14.0)	Chloroform
6	356–357	$C_{32}H_{20}N_2O_2$	82.7	4.3	6.0	82.4	4.5	5.8	C	78	Dimethylformamide	236 (79.5) 310 (19.8) 260 (55.4) 368 (19.4)	Acetonitrile
10	327–329	$C_{44}H_{28}N_2O_2$	85.7	4.6	4.5	85.3	4.7	4.5	C	68	Dimethylformamide		
11	155–156	$C_{62}H_{80}N_2O_2$	84.1	9.1	3.2	84.1	9.4	3.3	C	48	Tetrahydrofuran + methyl alcohol		
12	140–142	$C_{32}H_{20}N_2S_2 + C_4H_8O$	76.0	5.0	4.9	76.1	4.9	4.8	C	52	Tetrahydrofuran		
13	226–228	$C_{46}H_{34}N_6O_5$	73.6	4.6	11.2	73.6	4.8	10.9	D	93	Tetrahydrofuran	460 (20.4) 597 (27.6) 548 (28.0) 650 (16.0)	Chloroform
14	219–220	$C_{58}H_{42}N_6O_5$	77.1	4.7	9.3	76.8	4.8	9.3	D	83	Tetrahydrofuran	279 (88.5) 540 (32.2) 310 (25.2) 580 (26.4) 478 (22.8) 630 (15.0)	Chloroform

initial step is the dimerization of **5** followed by the reaction of the dimer with azide. The mechanism outlined in Scheme II is also applicable in this case if it is assumed that the benzophenoxazine radical dimerizes more rapidly than it couples with RNH. The 100-mμ shift in the absorption spectrum of **13**, compared with that of the dyes derived from **1**, suggests that the benzimidazole substituent enters a position which permits increased conjugation, and this condition is satisfied by placing this substituent in a position *para* to the heteronitrogen atom. Compound **7** reacts with **3d** to give dye **14**, whereas **8**, on reaction with **3d**, gives a dimer of **8**, and not the expected dye.

Experimental Section

The methods of preparation for most of the compounds described in this paper are recorded as general procedures and the physical constants and analytical data are collected in Table I.

12H-Benzo[*a*]phenothiazine (1) was prepared as previously described.[7]

Azides **3a–3d** were prepared as previously described.[9]

12H-Benzo[*b*]phenoxazine (5).—A mixture of 165 g of 2,3-dihydroxynaphthalene and 113 g of *o*-aminophenol was heated overnight at 200°. The temperature was reduced to 160–170° and 430 ml of acetic anhydride was added. Heating was then continued until a clear solution formed (about 2 hr). The reaction mixture was cooled to 15° and the precipitate was collected and washed first with acetic acid and then with alcohol. The yield of the N-acetyl derivative of **5** was 163 g (59%), mp 140–144°. This material was dissolved in 600 ml of hot ethoxyethanol, followed by slow addition of 140 ml of concentrated hydrochloric acid. A vigorous reaction ensued, and the reaction mixture solidified. The solid was collected and washed with methyl alcohol to give 118 g (51%) of white **5**: mp 298°; absorption spectrum in acetonitrile, λ_{max} mμ ($\epsilon \times 10^{-3}$) 237 (33.2), 262 (30.8), 315 (9.9), 360 (8.5).

Phenoxazines **7** (mp 284–285°) and **8** (mp 194–195°) were prepared in a similar manner from the appropriate o-aminophenol derivative.

General Procedure A.—A mixture of 0.02 mol of the azide, 0.01 mol of **1** and 10 ml of 1,2,4-trichlorobenzene was heated under reflux for 10 min, cooled, and the solid was collected and recrystallized.

General Procedure B.—A suspension of 0.01 mol of **1**, 0.011 mol of the azide, 0.5 g of cupric acetate hydrate, and 50 ml of acetone was stirred for 2 hr at room temperature and then heated under reflux for 5 min. The solid was collected and recrystallized.

General Procedure C.—A mixture of 0.01 mol of **5**, **7**, **8** or **9** and 0.01 mol of azides **3a–3d** in 100 ml of 2-ethoxyethanol or toluene was refluxed for 1 hr, cooled, and the gray solid was collected.

General Procedure D.—The preparations were carried out as in procedure B, with 3 equiv of **3d** and 1 equiv of **5**.

5-(2-Benzimidazolylimino)-5H-benzo[*a*]phenothiazine (4b).—A suspension of 2 g of **4d** in 12 ml of pyridine was heated on the steam bath, 12 ml of 10% methanolic potassium hydroxide was added, and heating was continued for 2 hr. The reaction mixture was filtered, the filtrate diluted with water, and the precipitate collected and washed with alcohol.

11-(Benzo[*b*]phenoxazinyl-12)-12H-benzo[*b*]phenoxazine (6).—In addition to procedure C, the following methods were used to prepare **6**.

(1) A fast stream of air was passed through a solution of 22 g of **5** and 0.5 g of cupric acetate monohydrate in 450 ml of pyridine for 7 hr. The dimer began to precipitate during the first half-hour. The solid was collected, washed with methyl alcohol, and recrystallized, yield 17 g.

(2) A suspension of 3 g of **5** and 3 g of potassium permanganate in 100 ml of acetone was stirred for 3 hr, decolorized with aqueous sodium bisulfite, and the precipitated solid was collected and recrystallized, yield 2.1 g.

(3) A solution of 75 g of **5** in 1.5 l. of 1,2,3-trichloropropane was heated on a steam bath and 22.5 ml of 30% hydrogen peroxide was added with stirring. The mixture was cooled and the solid was collected, yield 65 g.

(4) A solution of 2.3 g of **5** and 1 g of benzoquinone in 25 ml of chlorobenzene was refluxed 1 hr and cooled, yield 1.6 g of solid.

(5) A solution of 3 g of **5** and 0.5 g of cobaltic acetate in 50 ml of 1,2,3-trichloropropane was heated to reflux while air was bubbled in. The solution was cooled and 2.1 g of **6** was collected.

Dimers **10–12** were also prepared by these procedures.

Trimer from Benzo[*b*]phenoxazine.—A solution of 10 g of **5** and 0.25 g of cupric acetate in 400 ml of pyridine was aerated for 16 hr, the temperature being kept at 90–95°. The solution was diluted with water, chilled, and the solid was collected. The solid was boiled with 150 ml of toluene and the insoluble material collected, yield 5 g, mp >400°.

Registry No.—**1**, 225-83-2; **2**, 19359-56-9; **4a**, 19359-57-0; **4b**, 19359-58-1; **4c**, 19359-06-9; **4d**, 19359-07-0; **5**, 258-04-8; **6**, 19359-09-2; **10**, 19359-10-5; **11**, 19359-11-6; **12**, 19359-12-7; **13**, 19359-13-8; **14**, 19588-11-5.

(9) J. A. VanAllan and G. A. Reynolds, *J. Heterocycl. Chem.*, **5**, 471 (1968).

1-Methylazepine-2,7-dione. Synthesis and Reactions

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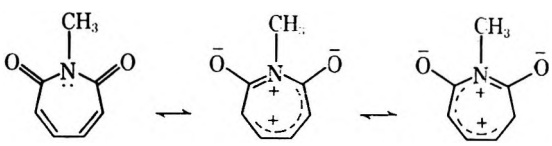
Received October 9, 1968

1-Methylazepine-2,7-dione (1), the first simple derivative of the azepine-2,7-dione system, has been synthesized. This was accomplished by dehydrohalogenation of *trans*-3,6-dibromo-1-methyladipimide (4), prepared by the reaction of cupric bromide with 1-methyladipimide (3). Three reactions of 1 were investigated. Bromination yielded 5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione. The Diels–Alder reaction of 1 with cyclopentadiene gave both an *exo* and *endo* adduct. Ethanolysis of 1 yielded ethyl N-methyl-*cis*,*cis*-muconamate (7). The saturated analog of 1, compound 3, did not react under identical conditions. Hydrogenation of 7 gave ethyl N-methyladipamate which was also synthesized by a different route. The properties of 1 are compared to several aromatic analogs and the results are discussed.

We have been interested in the properties of unsaturated heterocyclic systems, particularly with respect to their chemical reactivity and aromaticity. The azepinedione system is of interest because of its resemblance to the resonance-stabilized systems, 2-pyridone and tropone. The preparation of derivatives of 1H-azepine-2,5-dione has been reported,[2-4] but only the dibenzo derivative of azepine-2,7-dione is known.[5,6] We desired to prepare 1-methylazepine-2,7-dione (1) (N-methyl-*cis*,*cis*-muconimide) because, as a simple derivative of the parent system, it would afford unambiguous measurement of the properties we sought to investigate. If this 6π-electron system is stabilized by resonance of the aromatic type, the resonance hybrid would contain appreciable contributions of the canonical structures indicated. These structures are similar to those postulated for tropone.



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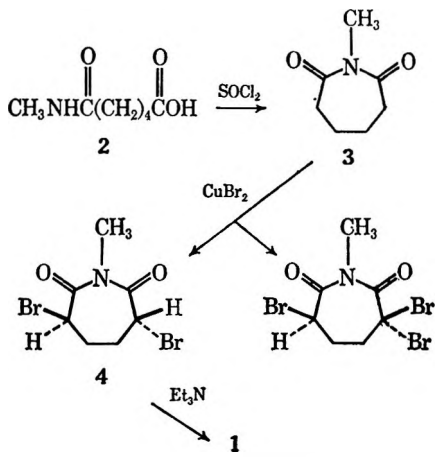
Results and Discussion

Our synthetic scheme first involved the synthesis of the saturated analog, 1-methyladipimide (3). Although Flitsch had reported the synthesis of this compound in 30–40% yields by the pyrolysis of N-methyladipamic acid (2),[7] our yields upon repetition of his work were much lower and not acceptable. We succeeded in the synthesis of 3 by treating 2 with thionyl chloride and cyclization of the thionyl chloride–acid amide complex to the imide by vacuum pyrolysis (Scheme I). The properties of this compound were identical with those reported by Flitsch.[7] Imide 3 was brominated with cupric bromide[8] to yield two products which were separated by column chromatography on

SCHEME I



silica and identified as *trans*-3,6-dibromo-1-methyladipimide (4) and 3,3,6-tribromo-1-methyladipimide (5) from their elemental analyses, nmr and ir spectra. The chemical shifts and relative intensities of 5 in the nmr spectrum unambiguously placed all the three bromines α to the imide carbonyls.[9] The ir spectrum of 5 showed two intense carbonyl bands which were each shifted *ca.* $+28$ cm^{-1} relative to 3. In 2-bromocyclohexanone, an equatorial bromine exerts a marked effect on the carbonyl stretching absorbance, $+15$–22 cm^{-1}, because of the inhibition of resonance stabilization. An axial bromine exerts a minor effect, -3 to $+3$ cm^{-1}.[10] In all of the possible conformers of 5, there is always a bromine in a quasi-equatorial (parallel to carbonyl) postion.[11] This accounts for the observed shift. In the nmr spectrum of dibromoimide 4, the bromines were assigned to C_3 and C_6 upon inspection of the two-proton multiplet at τ 4.90, (C_3, C_6), and the four-proton multiplet at 7.08–8.00. (C_4, C_5). The splitting patterns for both absorbances were very complex, having a total of 48 observed transitions. This complexity was due in part to virtual coupling[12] and conformational effects. The melting point and chromatographic behavior[13] of 4 appeared to indicate that we were dealing

(1) New York University Special Predoctoral Fellow 1966–1967.

(2) (a) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Lett.*, 1071 (1965); (b) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron*, **22**, 1201 (1966).

(3) R. W. Rickards and R. M. Smith, *Tetrahedron Lett.*, 2361 (1966).

(4) G. R. Bedford and G. Jones, *ibid.*, 2367 (1966).

(5) H. W. Underwood, Jr., and E. L. Kochman, *J. Amer. Chem. Soc.*, **46**, 2069 (1924).

(6) The preparation of a trihydroxyiminoazepine derivative has been reported briefly: A. H. Rees, *Chem. Ind.* (London), 1298 (1965). This compound could exist as several tautomers, including azepine-2,4-dione and an azepine-2,7-dione. No full characterization or study of the tautomerism of this compound has as yet appeared.

(7) W. Flitsch, *Chem. Ber.*, **97**, 1542 (1964).

(8) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).

(9) The lone hydrogen α to the imide was represented by a quartet, indicating that a potential AMNXY system had simplified to an AMN system. For a discussion of this type of simplification, see ref 18, p 94.

(10) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

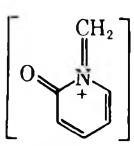
(11) The terms quasi-axial and quasi-equatorial are used in this paper to describe the stereochemical positions found in a seven-membered ring. These, of course, are approximations of the true axial and equatorial positions as found in cyclohexane.

(12) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

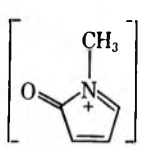
(13) Compound 4 was found to be chromatographically pure on silica in the following systems: chloroform, benzene, chloroform–hexane 80:20, hexane–ethyl acetate 80:20, 50:50.

with a single isomer, *cis* or *trans*. Attempts to assign the stereochemistry of **4** by hydrolysis of it to a known α,α'-dibromoadipic acid were unsuccessful. The ir spectrum did provide useful information, however. The carbonyl stretching absorbances in **4** are shifted *ca.* +7 cm^{-1} relative to **3**. In light of the previous discussion, this would indicate that the predominant conformer of **4** has no quasi-equatorial bromines. Examination of models reveal that *trans* **4** has such a conformer, while *cis* **4** has not. The *trans* structure was therefore assigned to **4**.

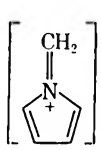
1-Methylazepine-2,7-dione (**1**) was formed by dehydrohalogenation of **4** with triethylamine. The product was separated by preparative thin layer chromatography on silica gel. The mass spectrum of **1** was consistent with its structure. Fragments of *m/e* 109 and 81 corresponded to the loss of one and two C=O units, and are postulated to represent radical ions derived from N-methyl-2-pyridone and N-methylpyrrole. Loss of C=O from systems of this type is well known.[14a,b] Although the exact electronic structure of the daughter ion formed in the M—C=O decomposition is still in question,[14c,d] it is likely that the suggested structures do comprise some portion of this ion. Postulated structures for other major fragments (*m/e* >60, relative abundance >15%, 70 eV) are shown (**6a, b, c**). The loss of hydrogen radical from



6a, *m/e* 108



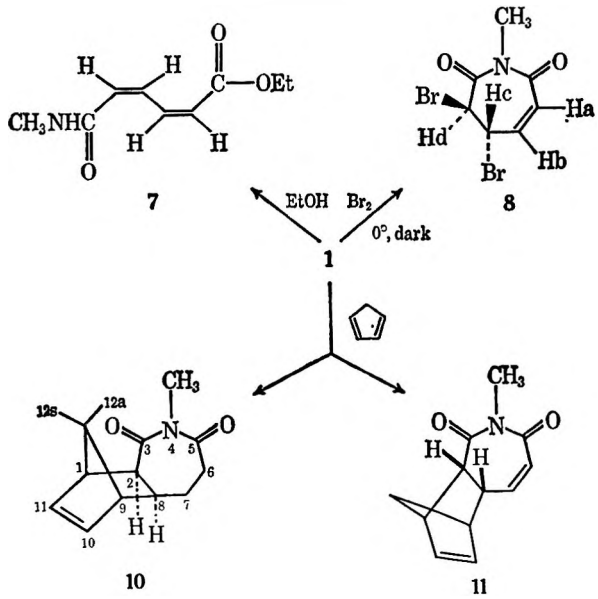
6b, *m/e* 96



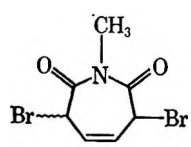
6c, *m/e* 80

1-methyl-2-pyridones to give fragments corresponding to **6a** has been reported.[14e] It is interesting to note that the mass spectrum of **1** contains every major peak found in the spectrum of 1-methyl-2-pyridone.[14e] The nmr spectrum of **1** shows a striking case of solvent effect. In deuteriochloroform, **1** exhibited two singlets (τ 3.37, 4 H; 6.64, 3 H). In deuteriobenzene, however, the low-field singlet is expanded into an AA'BB' spin pattern, similar in shape to that observed for phenazine.[15] The coupling contants and chemical shifts were calculated[16] by computer using a modified version of the LAOCN3 program[17] and were found to be $J_{aa'} = 7.72 \pm 0.16$; $J_{bb'} = 0.58 \pm 0.14$; $J_{ab} = 12.33 \pm 0.16$; $J_{ab'} = 1.56 \pm 0.15$; $\nu_a = 382.1 \pm 0.10$; $\nu_b = 346.4 \pm 0.10$ Hz. The infrared spectrum of **1** suggested a conjugated imide: the two carbonyls were shifted to lower wave number (*ca.* 60 cm^{-1}) relative to **3**. The ultraviolet spectrum showed a strong band at 220 mμ (ϵ 15,200) and a moderate one at 287 mμ (ϵ 3620) indicative of a conjugated system. The azepine-2,5-dione system shows two absorbances quite similar to these but in addition another maximum above 300 mμ.[3] The first reaction of **1** to be investigated was bromination (Scheme II). Although bromination of **1** in chloro-

SCHEME II



form at ambient temperature gave a mixture of products, bromination conducted in ice-cold hexane in the dark yielded only one product identified as *trans*-5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione (**8**). The assignment of structure was based on interpretation of its ir and nmr spectra. There are two normal modes of addition that can occur in this system—1, 2 and 1,4 addition. These would yield products **8** and **9**,



9

respectively. The ir carbonyl stretching absorptions fit structure **8** better than **9**; **9** should have relatively the same values as **4** because they are similar in structure. The carbonyl frequencies observed were much lower, indicating that the unsaturation was conjugated with the carbonyl group. The nmr spectrum taken in deuteriobenzene was definitely a first-order spectrum. It obeyed the condition for first-order approximations, *i.e.*, $\Delta\nu > 6J$.[18,19] Multiplets were observed for four distinctly different kinds of protons. This eliminated the possibility of 1,4 addition, **9**, because it should have exhibited an AA'XX' or possibly an AA'BB' pattern, both of which have specific symmetry elements not found in this spectrum. We assign in **8**: τ 4.00 to H_a;

(14) (a) H. Budzikiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 359, 571; (b) C. Nolde, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 1051 (1968); (c) W. T. Pike and F. W. McLafferty, *J. Amer. Chem. Soc.*, **89**, 5954 (1967); (d) M. M. Bursey and L. Dusold, *Chem. Commun.*, 712 (1967); (e) R. Lawrence and E. S. Waight, *J. Chem. Soc., B*, 1 (1968).

(15) T. K. Lim, A. Taurins, and M. A. Whitehead, *Can. J. Chem.*, **44**, 1211 (1966).

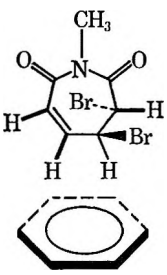
(16) The root mean square error in line fitting was 0.414.

(17) LAOCN3 is the recently revised version of the LAOCOON II program described in S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(18) R. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 48.

(19) The only value below this ratio is $\Delta\nu_{ab}/J_{ab} = 2.75$. This intermediate value seems to affect only the relative line intensities of both patterns, decreasing the outer lines and increasing the inner ones; *cf.* the spectrum of 4-vinylpyridine: N. S. Bhacca, L. F. Johnson, J. N. Schoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, No. 155.

4.55 to H_b; 5.32 to H_d; 6.35 to H_c; and J_{ab} = 12.1 Hz; J_{bc} = 7.0 Hz; J_{bd} = 1.4 Hz; J_{cd} = 5.0 Hz. This assignment of chemical shifts was supported by the observed selective solvent shifts of **8** in deuteriobenzene, as compared to carbon tetrachloride.[20-23] H_b and H_c were shifted 63 cps upfield, and H_a and H_d 20–21 cps upfield. These results can be pictured in terms of the given solvent–solute collision complex. This is consistent with the observation that the benzene molecule aligns itself away from the negative and close to the positive end of the solute dipole.[20-23] A model similar to the above can be found in phthalic anhydride where the α protons are shifted +49 Hz and the β protons +68 Hz.[20]



The magnitudes of J_{ab} and J_{cd} are reasonable for the structures involves.[24] It is unlikely that H_c and H_d are in quasi-diaxial positions, as a larger J_{cd} value might be expected. The value of J_{bc} also suggests that H_c is quasi-equatorial. 3,4-Dibromobicyclo[3.2.1]octa-2-ene, a molecule of fixed geometry, has an allylic coupling constant of 6.6. Hz.[25] The dihedral angle of the protons involved is close to that for H_b and H_c in models of **8** in which H_c is quasi-equatorial. The H_b to H_d coupling observed is an example of the W effect.[26]

In Diels–Alder reactions **1** did not act as a diene, *i.e.*, it did not react with maleic anhydride or tetracyanoethylene. It did act as a dieneophile by reacting with cyclopentadiene at room temperature to form two products which were separated by preparative thin layer chromatography. Both products had identical molecular formulas and very similar ir and uv spectra. The nmr taken in deuteriochloroform showed absorbances at chemical shifts consistent with the formulas, *exo*-4-methyl-4-azatricyclo[7.2.1.$0^{2,8}$]dodeca-6,10-diene-3,5-dione (**10**) and *endo*-4-azatricyclo[7.2.1.$0^{2,8}$]dodeca-6,10-diene-3,5-dione (**11**). The splitting patterns were very complex, probably due to the fact that protons H_6, H_7, H_8, H_2 are strongly coupled with each other. This additional multiplicity hinders assignment of the *exo* or *endo* isomers on coupling constant grounds,[27-29] however, this assignment can be made upon interpretation of the chemical shifts of the bridge protons (H_{12a}, H_{12s}). Models of the isomers show that in the *exo* case the bridge protons could absorb at chemical shifts different from the corresponding protons in *exo*- or *endo*-5-substituted 2-norbornenes (τ 8.44–8.78).[27] The direction of this shift cannot be unequivocally predicted. The chemical shifts of the same protons in the *endo* isomer should be quite close to those of the norbornenes. Indeed in the two nmr spectra, the bridge protons appear in considerably different regions. One isomer exhibited absorbances of τ 7.30 and 7.95 and was assigned the *exo* configuration. The other isomer exhibited an absorbance at τ 8.50 and was assigned the *endo* configuration. Since it is known that in this reversible reaction the *endo* isomer is the kinetic product while the *exo* isomer is the thermodynamic product, we measured the product ratio at a lower temperature. When the reaction was conducted at 0°, the ratio of *exo*/*endo* was 1.37. When compared with a value of 11.70 obtained at 30°, we see that a higher temperature favors the *exo* product. In addition, the *endo* product isomerized to the *exo* one after standing 6 weeks at ambient temperature protected from light. These facts add further support to our assignment. Additional evidence which reinforced this assignment was found in the mass spectra. The mass spectra of the two isomers showed nearly identical *m/e* positions, but very different relative abundances. It would seem that the relative stabilities of the parent and daughter ions in a fragmentation play an important part in determining the probability of such fragmentation. This probability would manifest itself in the rate constant of this fragmentation.[30,31] In our case the *endo* isomer, being more highly strained, would undergo a fragmentation to a less strained ion faster than the *exo* isomer. A good vehicle for this analysis is the $M^{\cdot+}-C_5H_5\cdot$ fragmentation. We are assuming that this retro-Diels–Alder reaction is purely an electron impact phenomenon and not thermally initiated.[32] Following Bursey and McLafferty's[33] kinetic approach to mass spectra, we have derived a similar expression which allows us to calculate the ratio of the two fragmentations: $M^{\cdot+}_{endo} - C_5H_5\cdot$, $M^{\cdot+}_{exo} - C_5H_5\cdot$. By

$$M^{\cdot+}_{endo} \xrightarrow[k_{endo}]{-C_5H_5\cdot} A^+_{endo}$$

$$M^{\cdot+}_{exo} \xrightarrow[k_{exo}]{-C_5H_5\cdot} A^+_{exo}$$

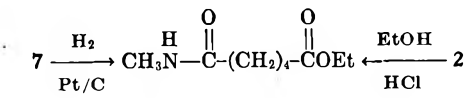
$$\frac{A^+_{endo}/M^{\cdot+}_{endo}}{A^+_{exo}/M^{\cdot+}_{exo}} = \frac{k_{endo}}{k_{exo}}$$

substituting the appropriate values we arrive at k_{endo}/k_{exo} = 1.50. This value again supports our assignment of isomers.

Azepinedione **1** reacted with ethanol at ambient temperature in the dark. No catalyst was needed, although catalytic amounts of sodium hydroxide increased the rate of reaction. The product of this reaction was ethyl N-methyl-*cis*,*cis*-muconate (**7**). Conclusive proof of this structure was obtained upon

(20) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).
(21) R. M. Moriarty and J. M. Kleigman, *J. Org. Chem.*, **31**, 3007 (1966).
(22) K. M. Baker and B. R. Davis, *J. Chem. Soc., B*, 251 (1968).
(23) J. Ronayne and D. H. Williams, *ibid.*, **540** (1967).
(24) R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 144.
(25) C. W. Jefford, *Proc. Chem. Soc.*, (London), 64 (1963).
(26) (a) J. Feeney, *Ann. Rept. Progr. Chem.*, **63**, 247 (1966); (b) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964); (c) S. Sternhell, *Rev. Pure App. Chem.*, **14**, 15 (1964).
(27) J. C. Davis Jr. and T. V. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965).
(28) P. Laszlo and P. von R. Schleyer, *ibid.*, **86**, 1171 (1965).
(29) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).
(30) D. C. DeJongh and S. R. Shrader, *ibid.*, **88**, 3881 (1966).
(31) P. Natalis, *Bull. Soc. Chim. Belges*, **75**, 668 (1966).
(32) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).
(33) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).

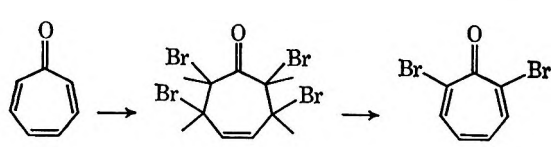
catalytic hydrogenation of **7** on Pt/C which yielded ethyl N-methyladipamate (**12**). Compound **12** was prepared by the reaction of **2** with dry hydrogen chloride in ethanol. The product from the hydrogenation and from the esterification were identical. A point to note



12

is that the ethanolysis and subsequent hydrogenation confirmed that the synthesis of **1** had proceeded without rearrangement. As the conditions of the ethanolysis reaction and work-up were not sufficient to cause isomerization in related systems,[34a] it was assumed that **7** had retained the *cis–cis* stereochemistry of **1**. Examination of the nmr, uv, and ir spectra of **7**, and a comparison of these to similar systems, did not refute or support this assignment.[34,35] The kinetics of the ethanolysis were found to be pseudo first order, $k_{47°} = 9.97 \pm 0.45 \times 10^{-5}$ min^{-1}, by ultraviolet spectroscopy. No reaction was observed when the saturated analog, **3**, was subjected to identical reaction conditions, although the hydrolysis of **3** in alkali has been reported.[36]

It is of interest to consider the physical and chemical properties of **1** with reference to the possible aromaticity of the system. One of the methods of evaluating the extent of aromaticity of a new compound is to compare it with known compounds considered to have aromatic character. Some of the criteria of aromaticity are manifested in the uv and nmr spectra and in the chemical reactivity. Two compounds which are similar to **1** and possess aromatic properties are tropone[37–39] and 1-methyl-2-pyridone.[38–40a] The uv spectra of the compounds, a measure of π electron conjugation, are similar: tropone,[37a] $\lambda_{max}^{H_2O}$ 228 mμ (log ϵ = 4.34), 312.5 (3.92); 1-methyl-2-pyridone,[41] λ_{max}^{MeOH} 227 mμ (log ϵ = 3.64), 300 (3.64); 1-methylazepine-2,7-dione, λ_{max}^{MeOH} 220 mμ (log ϵ = 4.18), 287 (3.56). The nmr spectra, a measure of diamagnetic anisotropy, has also been used in estimating aromatic character.[40] A chemical shift of a ring proton downfield from the expected position has been considered to indicate the existance of an appreciable diamagnetic ring current. The following chemical shifts are for $CDCl_3$ solution. Tropone exhibits an absorption at τ 2.92.[37a] The C_4 and C_6 ring protons of 1-methyl-2-pyridone absorb at τ 2.74 and 2.69, respectively.[40a] 1-Methylazepine-2,7-dione shows absorption at τ 3.37. This greater shielding suggests the existance of a lesser diamagnetic ring current in **1** than in tropone or 1-methyl-2-pyridone. A comparison of chemical properties shows that tropone undergoes addition of bromine to yield 2,3,6,7-tetrabromo-4-cycloheptenone, which loses hydrogen bromide upon heating to give 2,7-dibromotropone.[42] 1-Methyl-2-pyridone reacts with bromine to give the substituted product, 3,5-dibromo-1-methyl-2-pyridone.[43] Although an addition–elimination sequence cannot be excluded for this reaction, no intermediate was reported. Tropone reacts both as diene (with maleic anhydride) and as dienophile (with 1,3-cyclohexadiene)[42] while 1-methyl-2-pyridone was found not to react with maleic anhydride.[40a] Although 1-methyl-2-pyridone does not undergo ring opening with alkali[40a] 2-halotropones undergo a facile ring contraction to benzoic acid derivatives in an alkali-catalyzed reaction.[37] We conclude that both the chemical and physical properties show that 1-methyl-2-pyridone seems to be more aromatic than tropone which in turn is slightly more aromatic than 1-methylazepine-2,7-dione (**1**).



Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 spectrophotometer or Beckman DU, infrared spectra with a Perkin-Elmer Model 137 or Baird-Atomic Model 1455, nmr with a Varian A-60 using tetramethylsilane as internal reference (τ 10). Analyses were performed by Mr. George Robertson Jr., Florham Park, N.J., Spang Microanalytical Laboratory, Ann Arbor, Mich., or by an F & M Elemental Analyzer, Model 185. Mass spectra were determined with a Varian M-66 employing a direct inlet system. Thin layer chromatography was performed on plates prepared with Adsorbosil-1 (Applied Science Laboratories, State College, Pa.) to which approximately 5% Radelin phosphor GS-115 had been incorporated. Plates were visualized with an ultraviolet lamp equipped with a short wave filter. Gas chromatography was performed on a Varian-Aerograph Model 90P-3.

1-Methyladipimide (3).—N-Methyladipamic acid (**2**,[44] 324 g, 2.04 mol) was added in small portions to 375 ml (5.19 mol) of ice-cold, stirred thionyl chloride. The clear solution was stirred for 48 hr at 4.0°. The unreacted thionyl chloride was removed by vacuum distillation at 5 mm, employing a liquid nitrogen trap and an ice bath around the distillation flask to moderate the distillation. When distillation at ambient temperature ceased (thionyl chloride removed), the liquid nitrogen trap was removed and large KOH traps were connected between the vacuum pump and distillation apparatus. A glass helices column was fitted to the distillation flask and a heating mantle was attached. The pyrolysis–distillation was begun and the fraction with bp 86–95° (5 mm) was collected. This material was redistilled to yield 100 g (35%), bp 96–100° (6 mm) [lit.[7] bp 119° (18 mm)], of 1-methyladipimide. Gas chromatography[45] showed the product to be 99.4% pure: λ_{max}^{MeOH} 235 mμ (ϵ 1580); ir (neat) 1721, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.96 (singlet, 3 H), 7.16 (distorted triplet,[46] 4 H), 8.10 (distorted triplet,[46] 4 H).

(34) (a) J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 1793 (1953); (b) J. A. Elvidge and P. Sims, *ibid.*, *C*, 385 (1966).

(35) J. A. Elvidge and P. D. Ralph, *ibid.*, *C*, 387 (1966).

(36) W. Flitsch, *Chem. Ber.*, **97**, 1548 (1964).

(37) (a) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, New York, N. Y., 1959, Chapter VII; (b) P. Paulson, *Chem. Rev.*, **55**, 9 (1955).

(38) It has been estimated that tropone[39] and 1-methyl-2-pyridone[40a] have resonance energies of 16–24 and 12–15 kcal/mol, respectively.

(39) W. N. Hubbard, C. Katz, G. B. Guthrie, Jr., and G. Waddington, *J. Amer. Chem. Soc.*, **74**, 4456 (1952).

(40) (a) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961); (b) R. J. Abraham and W. H. Thomas, *ibid.*, *B*, 127 (1966); (c) H. P. Figeys, *Tetrahedron Lett.*, 4625 (1966).

(41) H. Specker and H. Gawrosch, *Chem. Ber.*, **75**, 1338 (1942).

(42) T. Nozoe, *Proc. Jap. Acad.*, **28**, 477 (1952).

(43) (a) H. Decker, A. Kaufmann, M. Sassu, and W. Wisloki, *J. Prakt. Chem.*, **84**, 432 (1911); (b) S. H. Babcock and R. C. Fuson, *J. Amer. Chem. Soc.*, **55**, 2946 (1933).

(44) (a) See ref 7; (b) G. T. Morgan and E. Walton, *J. Chem. Soc.*, 91 (1933).

(45) Glpc analyses were carried out employing a 5-ft 20% FFAP on Chromosorb W column. Injection port and detector temperature were maintained at 290°. The column temperature was 240° and the flow rate 25 ml/min. The imide had a retention time of 5.4 min.

(46) This is a very good example of virtual coupling: see R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 130.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92; mol wt, 141. Found: C, 59.50; H, 7.73; N, 9.75; mol ion, 141.

Bromination of 1-Methyladipimide.—Imide **3** was brominated using the method of King and Ostrum.[3] Cupric bromide (25.7 g, 115 mmol) was ground in a mortar and pestle and placed in a 250-ml round-bottomed flask. Ethyl acetate (90 ml) was added, and the flask fitted with a condenser and magnetic stirring bar. The mixture was heated, with stirring, to reflux. The imide (3.69 g, 26.2 mmol) was dissolved in 80 ml of chloroform and also heated. The solution of the imide was added to the stirred mixture of cupric bromide. The reaction was continued at reflux for 24 hr. The reaction mixture was cooled and filtered to remove the copper salts, and the filtrate evaporated to yield a viscous black oil. The oil was dissolved in a small amount of ethyl acetate and chromatographed on 280 g of Mallinckrodt SilicAR CC-7, 100/200 mesh. Initially a solvent system of hexane–ethyl acetate 99:1 was employed, with a gradual change to 95:5 during the addition of the first liters of solvent. The remainder of the elution was done with a 95:5 solvent mixture. Two major products were collected. The fast fraction was collected, concentrated and recrystallized from hexane to yield 285 mg (3%) of colorless cubes, mp 108.5–110°, of 3,3,6-tribromo-1-methyladipimide (**5**): λ_{max}^{MeOH} 252 mμ (ε 638); ir (KBr) 1748 1692 cm^{-1} (C=O); nmr ($CDCl_3$) τ 5.18 (four lines, 1 H), 6.68, (singlet, 3 H), 6.90 (multiplet, 2 H), 7.11–7.92 (multiplet, 2 H).

Anal. Calcd for $C_7H_8NO_2Br_3$: C, 22.19; H, 2.11; N, 3.70; Br, 63.42. Found: C, 22.03; H, 2.14; N, 3.78; Br, 62.92.

The more slowly moving fraction was collected, concentrated and recrystallized slowly from hexane to yield 1.562 g (19%), colorless plates, mp 58.2–9.5°, of *trans*-3,6-dibromo-1-methyladipimide (**4**): λ_{max}^{MeOH} 245 mμ (ε 576); ir (KBr) 1727, 1672 cm^{-1} (C=O); nmr ($CDCl_3$) τ 4.90 (multiplet, 2 H), 6.73 (singlet, 3 H), 7.08–8.00 (multiplet, 4 H).

Anal. Calcd for $C_7H_9NO_2Br_2$: C, 28.09; H, 3.01; N, 4.68; Br, 53.50; mol wt, 298.898. Found: C, 28.17; H, 3.03; N, 4.68; Br, 53.62; mol ion, 298.895.

1-Methylazepine-2,7-dione (1)—Dibromoimide **4** (500 mg, 1.67 mmol) was refluxed with 200 ml of triethylamine for 6 hr. The reflux apparatus was placed in an oil bath maintained at 120°. After completion of the reaction, the reaction mixture was cooled to ambient temperature, filtered to remove the triethylamine hydrobromide and the filtrate evaporated to yield a light yellow oil. This oil was chromatographed on five 0.5-mm silica plates, employing a solvent system of hexane–ethyl acetate 60:40. These plates exhibited two major bands, R_f 0.58 and 0.95, corresponding to the azepinedione and unreacted dibromoimide, respectively. The band at R_f 0.58 was collected and stirred for 1 hr with a mixture of ethyl acetate–chloroform 75:25. The silica was filtered off and the filtrate evaporated. The evaporate was recrystallized from hexane to yield 60 mg (26%, colorless needles, mp 76–77.8°) of 1-methylazepine-2,7-dione: λ_{max}^{MeOH} 220 mμ (ε 15,200), 287 (3620); ir (KBr) 1658, 1595 cm^{-1} (C=O); nmr (C_6D_6) τ 3.65, 4.21 (AA'BB', 4 H), 6.58 (singlet, 3 H). Mass spectrum (70 eV) *m/e* (relative intensity) 137 (35), 109 (38), 108 (100), 96 (22), 82 (11), 81 (82), 80 (60), 55 (13), 54 (13), 53 (22), 52 (76), 51 (70), 50 (30), (only absorbances with relative intensities greater than 10% are listed).

Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21; mol wt, 137. Found: C, 61.00; H, 4.81; N, 9.95; mol ion, 137.

Reaction of 1-Methylazepine-2,7-dione with Bromine.—Azepinedione **1** (65 mg, 0.474 mmol) was dissolved in 250 ml of hexane (Baker, Chromatography Grade) and the flask containing the solution covered with aluminum foil and immersed in an ice bath. Freshly prepared 10% (v/v) bromine (6 ml) in hexane solution was added, and the resulting solution stirred for 64 hr at 0°. The reaction mixture was rotary evaporated at 0° under 1 mm pressure. The crystalline residue was recrystallized from petroleum ether. All operations except for the recrystallization were carried out in the dark to prevent decomposition of the product to the starting material. This reaction yielded 90 mg (64%), colorless plates, mp 78–79°, of *trans*-5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione (**8**): λ_{max}^{MeOH} 215 mμ (ε 10,400), 245 (6500); ir (KBr) 1706, 1635 cm^{-1} (C=O); nmr (C_6D_6) τ 4.00 (doublet, J = 12.1 Hz, 1 H), 4.55 (doublet of doublet of doublets, J = 12.1, 7.0, 1.4 Hz, 1 H), 5.32 (doublet of doublets, J = 5.0, 1.4 Hz, 1 H), 6.25 (doublet of doublets, J = 7.0, 5.0 Hz, 1 H), 6.90 (singlet, 3 H).

Anal. Calcd for $C_7H_7NO_2Br_2$: C, 28.30; H, 2.36; N, 4.72; Br, 53.87; mol wt, 297. Found: C, 28.36; H, 2.64; N, 4.62; Br, 54.46; mol ion, 297.

Reaction of 1-Methylazepine-2,7-dione with Cyclopentadiene.—To 52 mg (0.38 mmol) of **1** was added 3 ml (37.2 mmol) of freshly prepared cyclopentadiene. The colorless solution was stirred for 3 hr. Thin layer chromatography on 0.75-mm silica plates, employing a solvent system of hexane–ethyl acetate, 70:30, revealed three major bands: R_f 0.60, 0.40, 0.20. The band at R_f 0.20 corresponded to unreacted azepinedione. The reaction mixture was separated on five 0.75 mm plates, the bands collected, extracted with ethyl acetate–chloroform, filtered and the filtrate evaporated. Band R_f 0.60 was recrystallized from petroleum ether to yield 40 mg (52%), colorless plates, mp 70.5–71.5°, of *exo*-4-methyl-4-azatricyclo[7.2.1.0^{2,8}]dodeca-6,10-diene-3,5-dione (**10**): λ_{max}^{MeOH} 220 mμ (ε 6960); ir (KBr) 1712, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.63 (multiplet, H_6,H_7, 2 H), 4.29 (multiplet, H_{10},H_{11}, 2 H), 6.16 (multiplet, H_1,H_9, 2 H), 6.40–6.97 (multiplet, H_2,H_8, 2 H), 6.87 (singlet, 3 H), 7.30 (multiplet, H_{12s}, 1 H), 7.95 (multiplet, H_{12a}, 1 H).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; mol wt, 203. Found: C, 71.09; H, 6.36; N, 6.89; mol ion, 203.

After extraction, the slower band was dried over Linde Molecular Seive 4X. After drying there remained 3.4 mg (4.4%), colorless liquid, of *endo*-4-methyl-4-azatricyclo[7.2.1.0^{2,8}]dodeca-6,10-diene-3,5-dione (**11**): λ_{max}^{MeOH} 220 mμ (ε 6500); ir ($CHCl_3$) 1712, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.49–4.50 (multiplet, H_6,H_7,H_{10},H_{11}, 4 H), 6.20–7.00 (multiplet, H_1,H_9,H_2,H_8, N-CH_3, 7H), 8.50 (multiplet, H_{12a}, H_{12s}, 2H).

Anal. Calcd for $C_{12}H_{13}NO_2$: mol wt. 203.094. Found: mol ion, 203.097.

Ethanolysis of 1-Methylazepine-2,7-dione.—Azepinedione **1**, 50 mg (0.36 mmol), was stirred in the dark, with 150 ml of absolute ethanol and 9 ml of a 1 × 10^{-5} *M* NaOH/EtOH solution for 3 weeks at ambient temperature. The reaction mixture was evaporated and chromatographed on six 0.75-mm silica plates employing a solvent system of ethyl acetate–hexane 55:45. The plates exhibited only two bands, R_f 0.60 and 0.40, corresponding to the unreacted azepinedione and the ethanolic product, respectively. The band at R_f 0.40 was collected, extracted with ethyl acetate–chloroform and the extract was recrystallized from hexane to yield 20 mg (30%), colorless needles, mp 80.5–82.0°, of ethyl N-methyl-*cis*,*cis*-muconamate (**7**): λ_{max}^{EtOH} 267 mμ (ε 24,700); ir (KBr) 3311 (N–H), 1718 (C=O, ester), 1645 (C=O, amide), 1592 (C=C), 1555 cm^{-1} (NH); nmr (C_6D_6) τ 1.57 (six-line multiplet, Hβ, 2 H), 4.30 (four-line multiplet, Hα, 2 H), 6.00 (quartet, J = 7.1 Hz, 2 H), 7.59 (doublet, J = 4.5 Hz, 3 H), 9.04 (triplet, J = 7.1 Hz, 3 H).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; mol wt, 183. Found: C, 59.07; H, 7.16; N, 7.52; mol ion, 183.

Ethyl N-Methyladipamate (12).—N-Methyladipamic acid (**2**, 10 g, 63 mmol) was stirred with 350 ml of absolute ethanol while dry HCl was bubbled into the reaction flask. After 28 hr the reaction mixture was evaporated to an oil, dissolved in water and neutralized with solid $NaHCO_3$. The aqueous solution was extracted with ether, and the extracts were combined and dried over anhydrous Na_2SO_4. The ether was distilled off and the liquid distilled under vacuum to yield 4.53 g (39%), colorless liquid, bp 140° (0.7 mm), of ethyl N-methyl adipamate: ir ($CHCl_3$) 3279 (NH) 1736 (C=O, ester), 1675 (C=O, amide), 1538 cm^{-1} (NH); nmr ($CDCl_3$) τ 2.30 (broad singlet, 1 H), 5.83 (quartet, J = 7.4 Hz, 2 H), 7.21 (doublet, J = 4.9 Hz, 3 H), 7.66 (multiplet, 4 H), 8.28 (multiplet, 4 H), 8.74 (triplet, J = 7.4 Hz, 3 H).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; mol wt, 187. Found: C, 58.17; H, 9.43; N, 7.73; mol ion, 187.

Hydrogenation of Ethyl N-Methyl-*cis*,*cis*-muconamate (7).—Hydrogenation was accomplished with a (Brown)[2] Micro Hydro-Analyzer[47a] which generated a very active platinum on carbon catalyst *in situ*. Muconamate **7** (8 mg, 0.043 mmol) was hydrogenated according to the normal procedure,[47b] except that the quantities for catalyst generation were doubled, and those for hydrogen generation were tripled. The reaction mixture was filtered, evaporated, and triturated with chloroform and the chloroform solution reduced to about 1 ml. The mixture was separated by preparative gas chromatography.[48] The chromato-

(47) (a) Delmar Scientific Laboratories, Maywood, Ill. (b) "Operating Instructions for the (Brown)[2] Micro Hydro-Analyzer," Delmar Scientific Laboratories, Maywood, Ill., 1964.

(48) A 10-ft silicon grease on Haloport F column was employed at a temperature of 210° and a flow rate of 30 ml/min. Ethyl N-methyladipamate had a retention time of 4.4 min.

gram exhibited two peaks, retention times 1.2 and 4.4 min, corresponding to the solvents and the hydrogenation product, respectively. The peak at 4.4 min was collected and rechromatographed to yield a small amount of a colorless liquid. This liquid had an infrared spectra ($CHCl_3$) identical with that of previously prepared ethyl N-methyl adipamate (12).

Registry No.—**1**, 19519-85-8; **3**, 19519-86-9; **4**, 19519-87-0; **5**, 19519-88-1; **7**, 19519-89-2; **8**, 19519-90-5; **10**, 19519-91-6; **11**, 19519-92-7; **12**, 19519-93-8.

Acknowledgment.—The authors wish to thank Dr. Sungzong Kang for his help and the use of his program in the calculation of the kinetic data.

Addition of Dienophiles to the Acridizinium Ion. III.[1] Evidence for a Two-Step Reaction

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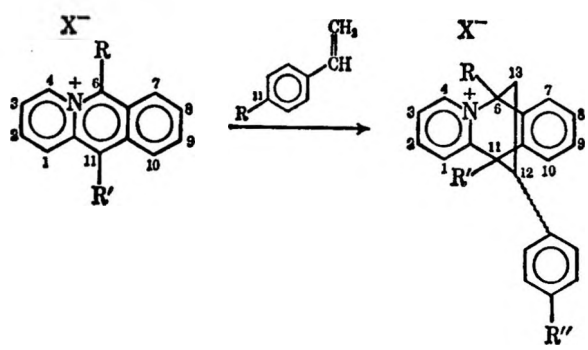
The introduction of a methyl group into the two *meso* positions of the acridizinium ion has opposite effects, at position 6 *decreasing* and at position 11 *increasing* the rate of reaction. Even in the presence of sodium acetate (hence in the absence of any traces of perchloric acid) diethyl maleate adds to acridizinium ion to give a rearranged (*anti, syn*) product (12). It is believed that these observations can best be explained in terms of a two-step mechanism.

The discovery several years ago[3] that the acridizinium (benzo[*b*]quinolizinium) ion (1) will undergo 1,4 cycloaddition with some common dienophiles was rationalized by the recent evidence[4,5] that the reaction is an example of what Sauer and Wiest have designated as a Diels–Alder reaction with inverse electron demand

SCHEME I



1, R = R′ = H
2, R = CH_3; R′ = H
3, R = H; R′ = CH_3
4, R = R′ = CH_3
5, R = R′ = H
6, R = CH_3; R′ = H
7, R = H; R′ = CH_3
8, R = R′ = CH_3

(Scheme I).[6] The great ease with which acridizinium derivatives can be prepared[7–9] makes the system of unique promise in the study of the factors affecting the Sauer and Wiest type of cycloaddition.

For the classical Diels–Alder reaction, it has been reported that introduction of methyl groups into the *meso* (9,10) positions of anthracene results in a very significant enhancement of the reaction rate.[10] Difficulty in assessing the relative importance of steric and electronic factors might have made prediction of the net effect of *meso* substitution difficult, but the observed rate enhancement is readily understood in terms of the predominant effect of the electron release of the methyl groups.

If one introduces one or two methyl groups into the *meso* (6, 11) positions of the acridizinium ion, it would appear, at least at first glance, that both steric and electronic effects would cooperate to reduce the speed of the reaction. With 6-methylacridizinium (2) perchlorate, the rate of addition of styrene to form adduct 6, as measured by the disappearance of the long-wavelength absorption of the 6-methylacridizinium ion, is in fact about one-half the rate at which the acridizinium ion undergoes the same reaction (Table I). The nmr of styrene adduct 6 showed the signal for the C-11 proton as a doublet, indicating that the phenyl group was at the 12 rather than the 13 position. The adducts from the reaction of 6-methylacridizinium ion with the *substituted* styrenes were not isolated, but it was observed that the effect of the *para* substituent in the styrene ring on the rate parallels that observed[5] earlier for the acridizinium ion.

If the methyl group is introduced at position 11 instead of position 6 there is no decrease in the observed rate of addition to styrene, but instead a 13-fold *increase* in reaction rate over that for the unsubstituted acridizinium ion. A similar but smaller increase in rate was observed when methyl groups were introduced in both the 6 and 11 positions of the acridizinium ion. The adducts of styrene with 11-methyl- and 6,11-dimethylacridizinium ion (7 and 8) cannot be characterized as 12-phenyl (rather than 13-phenyl) derivatives with the same certainty as the adduct which possesses a hydrogen at position 11[11]; however, all indirect

(1) For the preceding papers of this series, see ref 3 and 5.

(2) NASA Trainee. This work was supported in part by Public Health Grant No. HE-02170 of the National Heart Institute of the National Institutes of Health.

(3) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **80**, 933 (1958).

(4) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(5) C. K. Bradsher and J. A. Stone, *ibid.*, **33**, 519 (1968).

(6) J. Sauer and H. Wiest, *Angew. Chem.*, **74**, 353 (1962).

(7) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).

(8) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

(9) C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.*, **1**, 121 (1964).

(10) Preparative experiments carried out by W. E. Bachmann and M. C. Kloetzel [*J. Amer. Chem. Soc.*, **60**, 481 (1938)] indicated that 9,10-dimethylanthracene might react as much as 90 times as fast as anthracene.

(11) Even in the cases in which there is a hydrogen at position 6, it is so strongly deshielded by the adjacent positive charge that the signal from it becomes indistinguishable from the signals from the aromatic protons.

TABLE I

RATE OF CYCLOADDITION OF *para*-SUBSTITUTED STYRENES WITH ACRIDIZINIUM PERCHLORATE AT 65°

meso substituent		Rate[a] k, $min^{-1} \times 10^{-2}$			
R (6)[b]	R′ (11)[b]	R″=CH_3O	R″=CH_3	R″=H	R″=NO_2
H	H	18 ± 1	8.1 ± 0.2	5.0 ± 0.1	2.3 ± 0.3
CH_3	H	5.7 ± 0.2	3.2 ± 0.2	2.5 ± 0.2	1.8 ± 0.3
H	CH_3	180 ± 10	94 ± 2	68 ± 3	36 ± 5
CH_3	CH_3	93 ± 6	57 ± 4	43 ± 1	30 ± 2

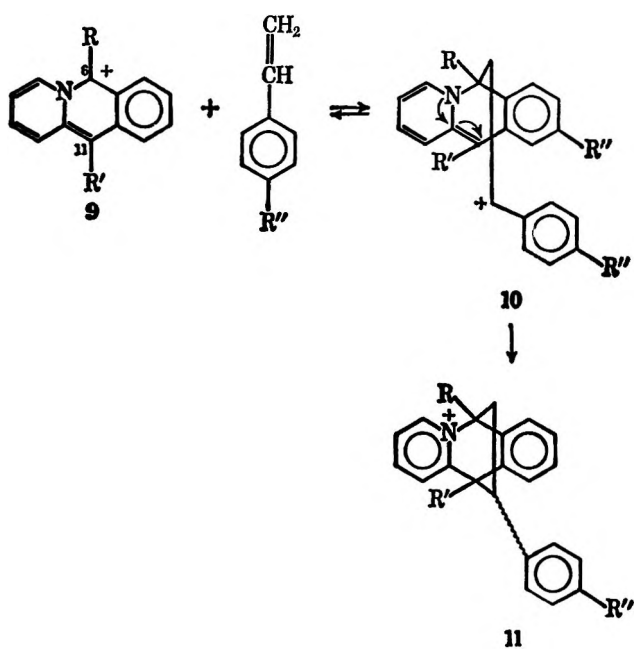
[a] A tenfold excess of the styrenes was used in order to obtain pseudo-first-order kinetics. [b] 6 and 11 position.

evidence such as similarities in ir and nmr spectra point to the assigned structures. The rates of disappearance of 11-methyl- (**3**) and 6,11-dimethylacridizinium ion (**4**) with substituted styrenes parallels the inverse electron demand pattern seen with the parent compound (**1**) and its 6-methyl derivative (**2**).

It appears that the reaction rate studies can best be rationalized by the assumption that the reaction of the acridizinium ion with substituted olefins occurs through a regiospecific[12] two-step reaction.

It has been shown[13] that in reaction with nucleophiles the acridizinium ion is attacked at position 6, suggesting that the resonance hybrid can react as the carbonium ion **9**. If such an ion reacts with styrene to form the most stable (benzylic) carbonium ion (**10**), this could then cyclize by attack of the electrons at position 11 (Scheme II). The divergent effects of the

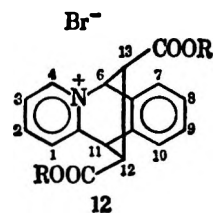
SCHEME II



substitution of methyl groups at the two *meso* positions is understandable in terms of this mechanism. A methyl group at position 6 for steric[14] and electronic reasons should adversely affect the concentration of intermediate **10** at equilibrium and hence the observed rate. A methyl group at position 11 could make electrons more readily available at that position and increase the tendency of the benzylic carbonium ion (**10**) to undergo cyclization. In each case it is the second step in the reaction which must be rate determining.

In the preceding publication of this series an effort was made to rationalize the reaction of diethylmaleate with acridizinium bromide to yield *anti,syn*-12,13-dicarboethoxy-6,11-dihydro-6,11-ethanoacridizinium ion **12**.

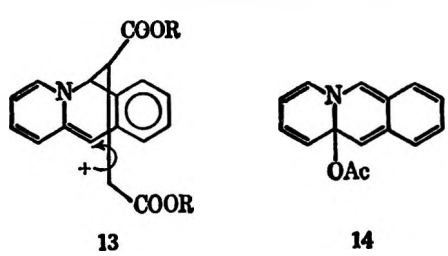
diethyl maleate + acridizinium bromide →



12

It was demonstrated that hydrogen bromide was formed during the reaction and that the excess ester, recovered after 7.5 hr, was essentially pure diethyl fumarate. The evidence which we have discussed in the preceding paragraphs made it important to establish whether the diethyl maleate reaction could be taking place by a two-step process. A preliminary test showed that the reaction of diethylmaleate with acridizinium perchlorate would take place in acetic acid in the presence of 2 equiv (excess) of anhydrous sodium acetate. The excess ester recovered from such a reaction was *unrearranged* diethylmaleate. Although a lower yield was obtained in the presence of excess sodium acetate, the only adduct obtained (41% yield) was the *anti,syn* product (**12**, R = C_2H_5).

It now appears most likely that the addition of maleate esters can likewise take place as a two-step reaction and that the carbonium ion first formed (**13**) rotates through 180° before cyclization. In harmony with this theory is the observation made earlier[5] that the



13 **14**

addition of dimethyl maleate to acridizinium perchlorate yielded a mixture containing chiefly the *syn,syn* sterioisomer (to be expected if there had been no rotation about the C-12–C-13 bond in **13**) and the *anti,syn* isomer (to be expected if rotation about the bond occurred).

(12) A. Hassner [*J. Amer. Chem. Soc.*, **90**, 216 (1968)] has introduced the useful term regiospecific to describe orientation in the addition to multiple bonds.

(13) C. K. Bradsher and J. P. Sherer, *J. Org. Chem.*, **32**, 733 (1967).

(14) Under the conditions used for the reaction of 6-methylacridizinium, the 6-propylacridizinium ion[8] had a rate constant of 1.0 ± 0.2 $min^{-1} \times 10^{-2}$ with styrene.

TABLE II

REACTION RATES[a] OF ACRIDIZINIUM PERCHLORATE WITH MALEATE AND FUMARATE ESTERS AT 100°

Ester	Medium	k, min^{-1} × 10^{-4}
Dimethyl maleate	$MeNO_2$	1.1 ± 0.1
Dimethyl fumarate	$MeNO_2$	8.9 ± 0.1
Diethyl maleate	$MeNO_2$	1.7 ± 0.0[b]
Diethyl maleate	HOAc	1.6 ± 0.0[b]
Diethyl maleate	HOAc + NaOAc[c]	1.5 ± 0.1[b,d]
Diethyl fumarate	$MeNO_2$	13 ± 1[b]
Diethyl fumarate	HOAc	12 ± 0.5
Diethyl fumarate	HOAc + NaOAc[c]	9.6 ± 0.8[d]

[a] Except as noted all values are the average of at least three determinations. [b] Average of only two values. [c] Sodium acetate (2 equiv) added. [d] Darkening of solution prevented measurements after 10 hr.

Rates for the reaction of maleate and fumarate esters are shown in Table II. As in the case of the classical Diels–Alder reaction,[15] the rate of addition of fumarate esters exceeds that of the maleate isomers. This difference in rate would appear to be a steric rather than an electronic effect, otherwise the order of reactivity should be reversed in going from a classical to an inverse electron demand type of 1,4-cycloaddition. The reaction rate of methyl esters seems to be slightly less than that of the ethyl homologs. No very great rate difference was observed in going from acetic acid to nitromethane as a reaction medium nor was the rate change observed when sodium acetate was added to the acetic acid used as a solvent great enough to suggest that the nature of the reaction was significantly altered. It is now clear that acetic acid does not participate in the addition reaction and that an uncharged molecule such as **14** cannot be an intermediate in the cycloaddition reaction.

Experimental Section[16]

6-Methyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium (6) Perchlorate.—A solution containing 0.6 g of 6-methylacridizinium (**2**) perchlorate[9] and 1 ml of styrene in 50 ml of acetonitrile was refluxed for 16 hr. The volume of the solution was reduced to about 25 ml and poured into 100 ml of cold anhydrous ether. The resulting precipitate was recrystallized from ethanol affording 0.4 g of a colorless powder, mp 238–240°. The analytical sample consisted of colorless prisms: mp 264–266°; uv λ_{max} 272 mμ (log ε = 3.76), 265 sh (3.74); nmr[17] (CF_3COOH) τ 7.5–8.0 (m, 2, CH_2), 7.39 (s, 3, 6-Me), 6.60–6.11 (m, 1, C-12 proton); 5.06 (d, 1, J = 2 Hz, C-11 proton).

Anal. Calcd for $C_{22}H_{20}ClNO_4$: C, 66.33; H, 5.03; N, 3.52. Found: C, 66.21; H, 5.11; N, 3.50.

11-Methyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium (7) Perchlorate.—Starting with 1.5 g of 11-methylacridizinium perchlorate and following the procedure used in the preparation of isomer **6**, 1.7 g (84%) of colorless needles were obtained: mp 235–237°; uv λ_{max} 270 mμ (log ε 3.73), 266 sh (3.71); nmr (CF_3COOH) τ 8.25 (s, 3, CH_3), 8.13–6.76 (m, 3, C-12 and C-13 protons).

Anal. Calcd for $C_{22}H_{20}ClNO_4$: C, 66.33; H, 5.03; N, 3.52. Found: C, 66.17; H, 5.17; N, 3.52.

6,11-Dimethyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium (8) Perchlorate.—Following the procedure used in the preparation of lower homologs **6** and **7**, except that the starting material was 6,11-dimethylacridizinium (**4**) perchlorate, the title compound (**8**) was obtained in 55% yield and crystallized from acetone as colorless needles: mp 223–224°; uv λ_{max} 273 mμ (log ε 3.74), 266 sh (3.71); nmr (CF_3COOH) τ 8.25 (s, 3, 11-CH_3), 7.47 (s, 3, 6-CH_3); 8.08–6.03 (complex, 3, CH_2, CH).

Anal. Calcd for $C_{23}H_{22}ClNO_4$: C, 66.99; H, 5.34; N, 3.40. Found: C, 66.93; H, 5.65; N, 3.11.

Reaction Rates for Cycloaddition Reactions of Acridizinium Derivatives.—The reaction rates in Table I were determined exactly as described in ref 5 except that pure dimethyl sulfoxide rather than a mixture with acetic acid was used as the solvent, and that for each substituted acridizinium salt the progress of the reaction was followed by measuring the absorption at the long wavelength maximum (corresponding to 397 mμ for the acridizinium ion).

The measurements described in Table II likewise were carried out as in ref 5 except that pure solvents rather than a mixture of acetic acid and dimethyl sulfoxide were used, and water rather than methanol was used in the vapor bath.

Reaction of Acridizinium Perchlorate with Diethyl Maleate in the Presence of Sodium Acetate.—A solution of 0.6 g (0.00215 mol) of acridizinium (**1**) perchlorate, 0.35 g (0.0043 mol) of sodium acetate and 1.5 ml (0.0093 mol) of diethyl maleate in 15 ml of acetic acid was heated on the steam bath for 3 days and the cooled mixture poured into cold anhydrous ether. The precipitate crystallized from ethanol as colorless needles: mp 182–183°, yield 0.4 g (41%). This material was shown by ir to be *anti,syn*-12,13-dicarbethoxy-6,11-dihydro-6,11-ethanoacridizinium (**5**) perchlorate.

If the reaction was interrupted after 6 hr, poured into water and the excess ester recovered by ether extraction, it was found by vapor phase chromatography[5] that no isomerization to diethyl fumarate had occurred. In a similar experiment *without* sodium acetate, it had been shown[5] that nearly complete isomerization of the excess ester had occurred.

Registry No.—**1** perchlorate, 18507-95-4; **6** perchlorate, 19190-65-9; **7** perchlorate, 19202-63-2; **8** perchlorate, 19190-66-0; **12** (R = C_2H_5), perchlorate, 15259-87-7.

(15) J. Sauer, H. Wiest, and M. Mielert, *Z. Naturforsch.*, *B*, **17**, 203 (1962); J. Sauer, D. Lang, and H. Wiest, *ibid.*, *B*, **17**, 206 (1962).

(16) General details concerning the experimental technique will be found in the first paragraph of the Experimental Section of ref 5.

(17) In this and in subsequent nmr reports signals in the aromatic proton region have been omitted.

Arylsuccinimides. I. Alkylation and Acylation Studies

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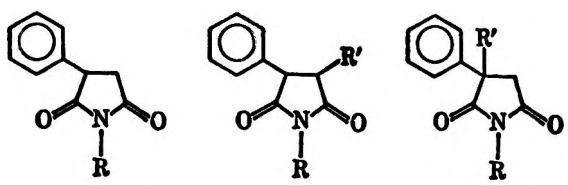
Received February 28, 1968

Alkylation of a series of phenylsuccinimides has been studied with several base–solvent combinations. Substitution at the 4 position in preference to the 3 position was observed in several cases when excess $NaNH_2$–NH_3 or Li-*i*-Pr_2N–Et_2O was employed. Acylations and dialkylations of 3,3-disubstituted succinimides were carried out using NaH–THF.

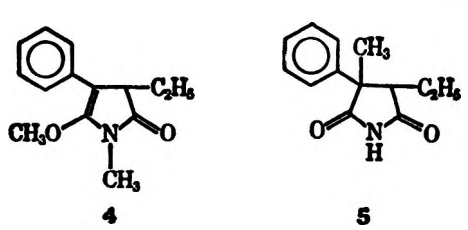
A wide variety of synthetic methods have been used for the preparation of arylsuccinimides.[1b] The ready availability of such systems and the ubiquity of the pyrrolidine ring system to which they are easily reduced[2] prompted us to investigate some of their reactions. This paper describes some alkylations and acylations of compounds of types **1**, **2**, and **3**.



1 **2** **3**

It would certainly be expected that alkylation in any of these systems in which R = H would occur first on nitrogen, although Hauser[3] has shown that succinimide itself will undergo C rather than N alkylation with 2 equiv of potassium amide in liquid ammonia. Excellent yields of N-substitution products can be obtained from succinimides using sodium amide in xylene or even potassium hydroxide in alcohol. Indeed N-acyl derivatives are formed using an acyl halide in pyridine.[4]

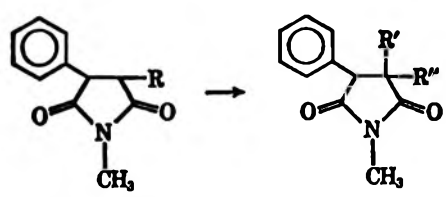
For systems carrying a substituent on nitrogen, substitution would be expected to occur at the ring position bearing the phenyl group in **1** and **2** since this is activated by two groups. When **2** (R = CH_3; R′ = C_2H_5) was treated with methyl iodide and sodium hydride in DMF, an 85% yield of the 3-methyl derivative was obtained, contaminated with about 10% of what is probably enol ether **4**. In like fashion, N-



4 **5**

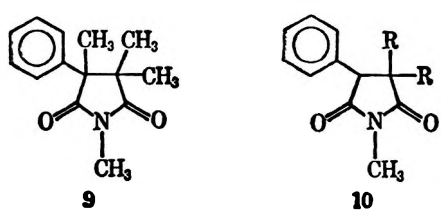
benzoyl derivative **2** (R = COC_6H_5; R′ = C_2H_5) was converted in moderate yield into **5** after hydrolysis.

When alkylation was carried out on these systems with excess sodium amide in liquid ammonia or excess lithium diisopropylamide (LDIPA) in ether, however, quite different results were obtained. With these base–solvent combinations, alkylation occurred at the 4 position of the ring instead of the expected 3 position. In each case, a yellow precipitate formed on addition of **1** or **2** to the solution of the base, and the precipitate dissolved gradually on addition of alkyl halide. Subsequent work-up yielded the 4,4-disubstitution product. For 1-methyl-3-phenylsuccinimide (**1**, R = CH_3) at least 3 mol of base and 2 mol of halide were used to produce the disubstitution product, while lesser proportions gave mixtures of products and starting material, probably because the monoalkylation product in solution competed successfully for the halide with the starting material which was present at least partially as a precipitate. With type **2** compounds, at least 2 mol of base and 1 mol of halide gave good yields of mixtures of isomers of the 4-substitution product. Table I summarizes the 4 alkylations carried out in this way (eq 1).



(1)

Starting materials of type **2** already carrying one 4 substituent gave almost exclusively 4 alkylation and very little 3 alkylation except for the case of **2** (R′ = CH_3) where a small amount of 3 alkylation was detectable (by nmr, see below). 1-Methyl-3-phenylsuccinimide (**1**, R = CH_3), on the other hand, gave mixtures of products depending on base–solvent and halide used. With excess methyl iodide and $NaNH_2$–NH_3, the product was chiefly the completely alkylated **9**, while with excess ethyl iodide and LDIPA–ether the



9 **10**

product was largely the 4,4-disubstitution product (**10**, R = C_2H_5). Methyl iodide with LDIPA–ether and ethyl iodide with $NaNH_2$–NH_3 gave mixtures of reaction types. Type **3** (R′ = CH_3) was not 4 substituted by ethyl iodide with $NaNH_2$–NH_3 under these conditions, although such an alkylation was realized with a different base–solvent (see below).

(1) (a) To whom all correspondence should be addressed at E. R. Squibb & Sons, New Brunswick, N. J. (b) C. A. Miller and L. M. Long, *J. Amer. Chem. Soc.*, **75**, 6256 (1953); R. Robbin, *Bull. Soc. Chim. Fr.*, 2275 (1965); R. Carrie, *C. R. Acad. Sci., Paris*, **251**, 2981 (1960); A. Foucaud, *ibid.*, **246**, 3257 (1958); G. Poulain, *Bull. Soc. Chim. Fr.*, 913 (1964).

(2) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y., 1956, pp 634 ff.

(3) D. R. Bryant and C. R. Hauser, *J. Amer. Chem. Soc.*, **83**, 3468 (1961).

(4) British Patent 844,267 (Aug 10, 1960).

TABLE I

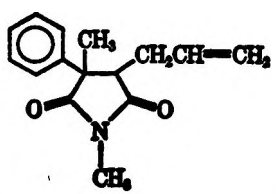
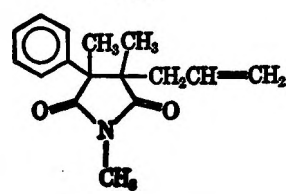
4 ALKYLATIONS OF 3-ARYLSUCCINIMIDES (EQ 1)

R	R′	R″	Base–solvent	Halide	Bp (mm) or mp, °C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
H	CH_3	CH_3	LDIPA–Et_2O	CH_3I	118–119 (0.03)	*a*					
H	CH_3	CH_3	$NaNH_2$–NH_3	CH_3I	128–131 (0.1)	*b*					
H	C_2H_5	C_2H_5	LDIPA–Et_2O	C_2H_5I	126–134 (0.1)	*c*					
H	C_2H_5	C_2H_5	$NaNH_2$–NH_3	C_2H_5I	131–134 (0.1)	*d*					
H			Either	$Br(CH_2)_4Br$		0[e]					
H			Either	$Br(CH_2)_5Br$		0[e]					
CH_3	CH_3	CH_3	$NaNH_2$–NH_3	CH_3I	129–134 (0.3)[f] 68–69	58	$C_{13}H_{15}NO_2$	71.87	72.07	6.96	7.15
C_2H_5	CH_3	C_2H_5[g]	$NaNH_2$–NH_3	CH_3I	126–127 (0.3)	95	$C_{14}H_{17}NO_2$	72.70	72.54	7.41	7.29
C_2H_5	CH_3	C_2H_5	LDIPA–Et_2O	CH_3I	120–122 (0.05)	83					
C_2H_5	C_2H_5	C_2H_5	$NaNH_2$–NH_3	C_2H_5Br	134–136 (0.3)	95[h]	$C_{15}H_{19}NO_2$	73.44	73.65	7.81	8.00
C_2H_5	CH_2=$CHCH_2$	C_2H_5	LDIPA–Et_2O[i]	CH_2=CH_2CH_2Br	135–138 (0.3)	73	$C_{16}H_{19}NO_2$	74.68	74.80	7.44	7.74
$CH_2C_6H_5$	C_2H_5	$CH_2C_6H_5$	LDIPA–Et_2O	C_2H_5I	180–185 (0.3)[j]	81	$C_{20}H_{21}NO_2$	78.14	78.14	6.89	6.86

[a] A 0.25-mol run gave 29 g of product whose nmr spectrum indicated that 58% of the 3 proton remained. [b] A 0.25-mol run gave 57 g of product whose nmr spectrum showed it to be impure 9. [c] A 0.25-mol run gave 44 g of product whose nmr spectrum indicated that 73% of the 3 proton remained. [d] A 0.25-mol run gave 51 g of product whose nmr spectrum indicated that 62% of the 3 proton remained. In another run using only 1.1 equiv of C_2H_5I, nmr indicated a complex mixture of starting material and substitution products. [e] Starting imide recovered. Nmr on crude product showed that some 3 alkylation had occurred. [f] Nmr indicates slight difference in isomer content from previous run. [g] Same result obtained when either only 1.1 equiv of halide or 4 equiv used. [h] Less satisfactory results obtained with $NaNH_2$–NH_3. [i] Nmr indicated that some O alkylation had occurred.

TABLE II

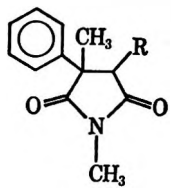
ALKYLATION OF 3-PHENYL-1,3-DIMETHYLSUCCINIMIDE WITH SODIUM HYDRIDE–TETRAHYDROFURAN (EQ 2)

Halide	Product(s)	Bp (mm) or mp, °C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
CH_3I	c, R = CH_3	99–101[a]	26	$C_{14}H_{17}NO_2$	72.70	72.50	7.41	7.42
C_2H_5I	c, R = C_2H_5	90–92[b]	40[c]	$C_{15}H_{21}NO_2$	74.09	73.97	8.16	8.21
n-C_3H_7I	c, R = *n*-C_3H_7	66–67[d]	38	$C_{18}H_{25}NO_2$	75.22	75.30	8.77	8.98
i-C_3H_7Br	b, R = *i*-C_3H_7	115–117[a]	10[e]	$C_{15}H_{19}NO_2$	73.44	73.65	7.81	8.08
CH_2=$CHCH_2Br$	c, R = CH_2CH=CH_2	135–138 (0.3)	46	$C_{18}H_{21}NO_2$	76.29	76.29	7.47	7.57
$HOCH_2CH_2Br$	b, R = CH_2CH_2OH	155–160 (0.3)	32[f]	$C_{14}H_{17}NO_3$	68.00	68.15	6.93	7.23
$Br(CH_2)_4Br$	c, R + R = $-(CH_2)_4-$	108–110[a]	56	$C_{16}H_{19}NO_2$	74.68	74.70	7.44	7.51
$Br(CH_2)_5Br$	c, R + R = $-(CH_2)_5-$	80–81[g]	82	$C_{17}H_{21}NO_2$	75.24	75.02	7.80	7.99
trans-$BrCH_2CH$=$CHCH_2Br$	c, R + R = $-CHCH$=CH_2 (with $-CH_2$)	140–142 (0.3)	26[e,f]	$C_{15}H_{17}NO_2$	75.27	75.40	6.71	7.01
CH_3I on 		125–135 (0.4)	79	$C_{16}H_{19}NO_2$	74.68	74.60	7.44	7.35
CH_3I on 1	c, R = CH_3	*h*	77					

[a] From benzene–petroleum ether. [b] From ethanol. [c] A run with equivalent quantities of halide and imide gave a mixture of a + b + c. [d] From methanol–water. [e] Purified by chromatography on neutral alumina. [f] 1.301.0 halide–imide used. [g] From ethanol–water. [h] Identical with material prepared above.

TABLE III

ACYLATIONS OF 3-PHENYL-1,3-DIMETHYLSUCCINIMIDE WITH SODIUM HYDRIDE–TETRAHYDROFURAN



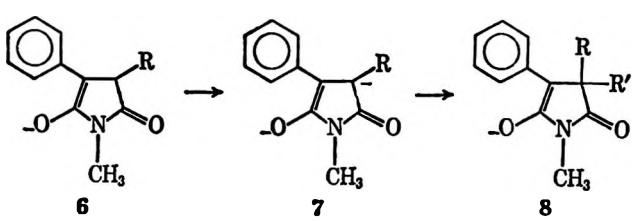
Acylating agent	Product, R	Bp (mm) or mp, C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
Diethyl carbonate	$CO_2C_2H_5$	148–150 (0.2)	90	$C_{15}H_{17}NO_4$	65.44	65.14	6.22	6.12
Ethyl formate	=CHOH	188–189[a]	75	$C_{12}H_{13}NO_3$	67.52	67.23	5.67	5.83
Ethyl acetate	=COHCH$_3$	139–140 (0.3) 67–68	80	$C_{14}H_{15}NO_3$	68.55	68.37	6.16	6.08
Ethyl oxalate	=COHCO$_2$C$_2$H$_5$	98–99[c]	66	$C_{16}H_{17}NO_5$	63.35	63.08	5.65	5.66
Ethyl benzoate	—COC$_6$H$_5$	109–113[c] Softens 86	62	$C_{19}H_{17}NO_3$	74.25	73.95	5.57	5.69

[a] From EtOH–H_2O. [b] From MeOH–H_2O. [c] From benzene–petroleum ether.

Gassman[5] has recently reported the successful alkylation of the related N-methylpyrrolidone using $NaNH_2$–NH_3.

We postulate that these 4 alkylations proceed through a dianion (7) as shown in Scheme I, reminiscent of the dianions studied by Hauser.[6] This alkylates at the more nucleophilic 4 position to give monoanion **8.** This can then form a second dianion when R = H and undergo a second alkylation at the 4 position to give **8** (R = R′). That **8** does not alkylate further is explicable on steric grounds. The geminal alkyl groups interacting with the phenyl group would be expected to stabilize the enol form of monosalt **8,** since this staggers

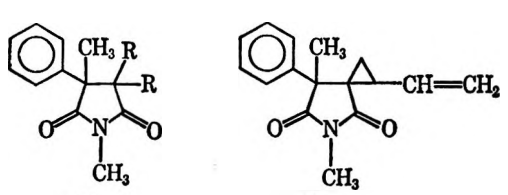
SCHEME I



6 **7** **8**

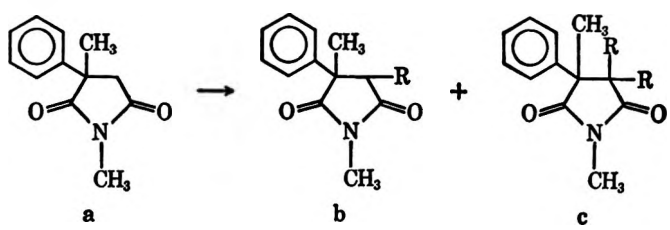
the phenyl group with respect to the alkyl groups, and this effectively blocks the 3 position. Alkylation on oxygen is hindered by the N-methyl group as well as the phenyl group.

Alkylation of type **3** imides was successful using sodium hydride in tetrahydrofuran. This base–solvent combination readily introduced two groups into the 4 position of 1,3-dimethyl-3-phenylsuccinimide (**3,** R = R′ = CH_3) to give products of type **11** with excess



11 **12**

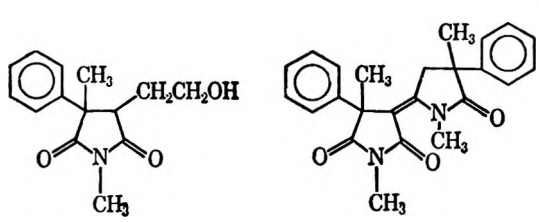
halide. Lesser proportions of halides gave difficult mixtures of products and starting material. Table II lists the alkylations of this type (eq 2) that were carried out.



a **b** **c**

(2)

Needles and Whitfield[7] have reported recently that the related N,N-dimethylacetamides gave mixtures of starting material, mono- and dialkylation products with $NaNH_2$ in refluxing benzene or toluene. We have found that NaH–THF worked well with a variety of bromides and iodides including dihalides and some functional halides but not with chlorides. 1,4-Dibromobutane and 1,5-dibromopentane formed the corresponding spiro derivatives even when excess halide was employed. 1,3-Dibromopropane gave intractable mixtures of products and 1,2-dibromoethane failed to alkylate at all. *trans*-1,4-Dibromo-2-butene yielded cyclopropane derivative **12.** Kierstead,[8] Nickl,[9] and Korte[10] have shown that such *trans*-1-4-dihalobutenes yield vinylcyclopropanes on reaction with active methylene compounds. Only monoalkylation in low yield occurred with isopropylbromide, and bromoethanol gave **13** and some of the self-condensation product **14.**



13 **14**

When 3-bromopropanol was used, only **14** was obtained, no normal alkylation being observed. The preparation

(5) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **31,** 982 (1966).

(6) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **30,** 61 (1965), and earlier references cited therein.

(7) H. L. Needles and R. E. Whitfield, *ibid.*, **31,** 989 (1966).

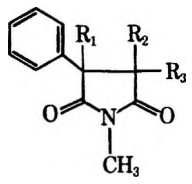
(8) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610, 3616 (1952); 1799, 1803 (1953).

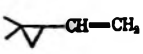
(9) J. Nickl, *Ber.*, **91,** 553 (1958).

(10) F. Korte, D. Scharf, and K.-H. Büchel, *Ann.*, **664,** 97 (1963).

TABLE IV

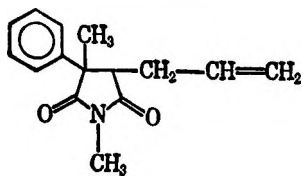
PERTINENT NMR DATA[a] (IN CARBON TETRACHLORIDE, δ)



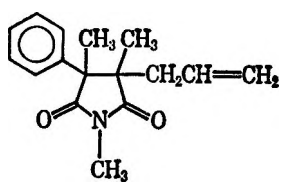
R_1	Registry no.		R_2		R_3	
H	86-34-0	3.87 ABX q[b]	H	*ABX*[c]	H	
H	19362-47-1	4.0 d, J = 7[d]	H	2.66[c]	CH_3	1.29 d, J = 7
		3.43 d, J = 7				0.73 d, J = 7
H	19362-48-2	3.70	CH_3	1.35	CH_3	0.76
CH_3	77-41-8	1.60	H	AB 3.00 d, J = 18	H	
				2.73 d, J = 18		
CH_3	19362-50-6	1.55	CH_3	1.28	CH_3	0.70
H	19362-51-7	3.53 d, J = 6	H	2.73[e]	C_2H_5	0.95 t, J = 7
H[f,g]	19362-52-8	3.88 d, J = 6	H	3.10[e]	C_2H_5	1.08 t, J = 6
H	19362-53-9	3.78 s[d]	CH_3	1.37	C_2H_5	c
		3.83 s		0.73		
H	19362-54-0	3.89	C_2H_5	0.63 t, J = 6	C_2H_5	0.95 t, J = 6
H	19362-55-1	4.13 s[d]	C_2H_5	c	$CH_2CH{=}CH_2$	4.5–6.1 c
		3.97 s				
H	19362-56-2	3.53 d[h]	H	Obscured	$CH_2C_7H_5$	3.02 d?[h]
H[g]	19362-57-3	4.00	C_2H_5	1.45 q, J = 7	$CH_2C_6H_5$	3.49 d, J = 23, 1 H
				0.74 t, J = 7		2.69 d, J = 23, 1 H
CH_3[d,g]	19362-58-4	1.76 s	C_2H_5	c	H	Obscured
		1.67 s				
CH_3[d,i,j]	60-45-7	1.67 s	C_2H_5	0.97 t, J = 6	H	2.87 t, J = 6
		1.52 s		0.80 t, J = 6		2.64 t, J = 6
CH_3	19362-60-8	1.64	C_2H_5	c	C_2H_5	c
CH_3	19362-61-9	1.63	C_3H_7	0.3–1.9 c	C_3H_7	0.3–1.9 c
CH_3	19362-62-0	1.64	$CH_2CH{=}CH_2$	2.58	$CH_2CH{=}CH_2$	2.46
CH_3	19362-63-1	1.57	$-(CH_2)_4-$[k]			
CH_3	19362-64-2	1.53	$-(CH_2)_5-$[k]			
CH_3[d]	19362-65-3	1.57 s				5.73–6.35 c, 1 H
		1.47 s				4.65–5.40 c, 2 H
						0.75 q[l]
CH_3	19362-66-4	1.65	i-C_3H_7	1.60 broad, 1 H	H	2.50 d, J = 5
				0.91 d, J = 7, 3 H		
				0.62 d, J = 7, 3 H		
CH_3[d]	19362-67-5	1.66 s	C_2H_4OH broad		H	Obscured
		1.47 s				
CH_3[d]	19362-68-6	1.67 s	$CH_2CH{=}CH_2$	6.1–4.4	H	2.6[m]
		1.52 s				
CH_3[d]	19362-69-7	1.67 s	$CH_2CH{=}CH_2$	5.8–4.4	CH_3	1.28 s, 0.74 s } 3 H
		1.55 s				
CH_3[d]	19362-70-0	1.73 s	$CO_2C_2H_5$	1.28 t, 0.75 t, J = 7, 3 H	H	3.90 s } 1 H
		1.53 s		4.23 q, 3.54 q, J = 7, 2 H		3.60 s } 1 H
CH_3[n]	19362-71-1	2.09 s	=CHOH			
CH_3[g]	19362-72-2	1.78 s	$=COCH_3$	1.69 s, 3 H		
				11.85, 1 H		
CH_3[g]	19362-73-3	1.95	$=COHCO_2C_2H_5$	4.05 s, J = 7, 2 H		
				1.04 t, J = 7, 3 H		
				12.2 broad, 1 H		
CH_3	19362-74-4	1.47 s	$COC_6H_5 \rightleftharpoons$	4.84 s ~ 0.5 H		
			$COHC_6H_5$	~12.0 broad, ~0.5 H		

[a] s = singlet, d = doublet, t = triplet, q = quartet, c = complex, H = proton. Aromatic in range 7.20–7.36; NCH_3 in range 2.89–3.08. [b] 3.77, 3.83, 3.91, 3.97. [c] Partially obscured by NCH_3. [d] Mixture of diastereomers indicated. [e] Six-line pattern for M of AMX_2 partially obscured by NCH_3. [f] N-Benzoyl compound. [g] Run in $CDCl_3$. [h] Poorly resolved. [i] NH compound. [j] Aromatic shows as two singlets. [k] Broad envelope. [l] Only clearly resolved X part of ABX pattern; 0.85, 0.75, 0.70, 0.60; rest is obscured. [m] Obscured by $CH_2C{=}$. [n] Run in pyridine.

of **16** by the alkylation of **15** illustrates the utility of this procedure for the preparation of imides with different 4 substituents. Alkylation of **1** (R = CH_3) under these conditions produced a good yield of the completely methylated derivative **9**.



15



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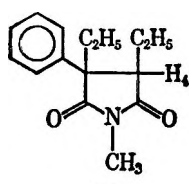
The use of NaH in THF also led to successful acylations with **3** (R = R′ = CH_3) and a variety of esters as shown in Table III. Winterfeld[11] reported that N-methylsuccinimide condensed with ethyl picolinate using sodium in benzene to gixe 90% yield of the acylation product. Seidel[12] has recently reported the acylation of N-arylpyrrolidones using alkoxides in DMF, and Zimmer[13] has used NaH in THF for the aldol condensation of aldehydes with 1-acetyl-2-pyrrolidone. Earlier, Meyer and Vaughan[14] had condensed ethyl formate with 1-phenyl-2-pyrrolidone to obtain the hydroxymethylene derivative, while Korte[15] and coworkers have studied a variety of similar condensations with pyrrolidones and piperidones. The interesting carboxylation using magnesium methyl carbonate that Finkbeiner[16] applied to 3-phenyl-2,4-oxazolidinedione was unsuccessful with **3** (R = R′ = CH_3) while condensation with diethyl carbonate gave the ester in excellent yield.

Since the structural assignments for many of the products obtained in these studies as well as the analysis of mixtures of products depended heavily on nmr data, these are tabulated in Table IV along with data for some pertinent known compounds. The marked difference in chemical shift for 3 and 4 protons in this series is immediately apparent. The highest field peak position noted for a 3 proton was 3.43 and the lowest field peak position for a 4 proton was 3.03 for only alkyl-substituted compounds. This difference along with the lack of spin–spin splittings made the assignment of structures for the 4-alkylation products relatively simple. Thus in the spectrum of the product of alkylation of **2** (R′ = C_2H_5) with ethyl bromide a sharp singlet at 3.89 was observed. Had the product been **17**, a triplet due to splitting by the adjacent



17

methylene would have been expected near 2.6–2.8 and a second triplet due to the other possible stereoisomer would have been likely. The nmr spectrum for the derivative without the N-methyl group prepared by an unambiguous route, has been reported recently[17] and shows a singlet at 4.1. All of the succinimides prepared in this study showed typical[18] infrared absorption for such functionality except for those acylation products which existed at least partially in their enol forms (see Experimental Section). The structures of the products thus rests on a combination of elemental analysis, nmr and ir spectra and, in at least some cases, nonidentity with known compounds. The completely alkylated products (**11**) revealed a complete absence of ring protons by their nmr spectra and normal succinimide functionality by their ir spectra.

Experimental Section[19]

Starting Materials.—The phenylsuccinimides used in these studies were prepared by known methods: 4-allyl-1,3-dimethyl-3-phenylsuccinimide,[20] 4-benzyl-1-methyl-3-phenylsuccinimide,[20] 1,3-dimethyl-3-phenylsuccinimide,[21] 1,4-dimethyl-3-phenylsuccinimide,[22] 4-ethyl-3-phenylsuccinimide,[22] 4-ethyl-1-methyl-3-phenylsuccinimide,[22] 4-ethyl-3-methyl-3-phenylsuccinimide,[23] and 1-methyl-3-phenylsuccinimide.[21]

Alkylation at the 3 Position. 1,3-Dimethyl-4-ethyl-3-phenylsuccinimide.—A solution of 21.7 g (0.10 mol) of 4-ethyl-1-methyl-3-phenylsueeinimide in 100 ml of DMF was treated portionwise under nitrogen with 5 g (0.11 mol) of 50% NaH in mineral oil. After stirring for 3 hr at 50°, the mixture was cooled and treated dropwise with 15 ml of methyl iodide (excess). After the exothermic reaction subsided, the mixture was held at 60–80° for 2 hr. After cooling, filtration and removal of solvent, the residue was dissolved in benzene and washed thrice with water. Distillation afforded 19.3 g (85%) of crude product collected at 125–130° (0.1 mm). The ir (film) and nmr ($CDCl_3$) spectra of this material were identical with those of a sample of authentic material[23] except for a small band at 1650 cm^{-1}, and a peak at 3.68 s (OCH_3) that integrated for 0.33 proton (*ca.* 10% enol ether present).

N-Benzoyl-4-ethyl-3-phenylsuccinimide.—To a solution of 101.5 g (0.50 mol) of 4-ethyl-3-phenylsuccinimide in 300 ml of pyridine was added dropwise 77.2 g (0.55 mol) of benzoyl chloride at 25–30° and the mixture stirred 1 hr longer before being heated to 55–65° for 1 additional hr. The mixture was diluted with ether, filtered, and freed of solvent. The crystalline residue recrystallized from benzene–petroleum ether (bp 30–60°) had mp 125–126° and amounted to 134 g (87%): ir (KBr) 1794 (m), 1730 (s), and 1695 cm^{-1} (m); nmr data are given in Table IV.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.57. Found: C, 74.20; H, 5.61.

4-Ethyl-3-methyl-3-phenylsuccinimide.—A solution of 76.8 g (0.25 mol) of the above benzoyl derivative in 500 ml of DMF was treated portionwise with 14 g (20% excess) of 50% NaH in mineral oil at 20–25°. The dark red solution was stirred 2 hr then treated dropwise with 45 g (excess) of methyl iodide at 25–28° (intermittent cooling). After 1 hr, the mixture was heated to 55–70° for 1 additional hr, then cooled, filtered, and freed of solvent, leaving 78 g of crude product. This was dissolved in 300 ml of EtOH plus 30 ml of H_2O and treated all at once with 33 g of KOH. The solution was heated under reflux for 1.5 hr, cooled, filtered, diluted with an equal volume of water, and washed thrice with benzene. After acidification,

(11) K. Winterfeld and F. W. Holschneider, *Arch. Pharm.*, **273**, 305 (1935).
(12) M. C. Seidel and R. S. Cook, *J. Heterocycl. Chem.*, **3**, 311 (1966).
(13) H. Zimmer, D. C. Armbruster, and L. J. Trauth, *ibid.*, **2**, 171 (1965).
(14) W. Meyer and W. Vaughan, *J. Org. Chem.*, **22**, 1554 (1957).
(15) K. H. Büchel and F. Korte, *Ber.*, **95**, 2460 (1962), and earlier papers cited therein.
(16) H. Finkbeiner, *J. Amer. Chem. Soc.*, **87**, 4588 (1965).
(17) K. Tamaribuchi, Ph.D. Thesis, Stanford, 1964.
(18) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958.
(19) Melting points were taken in open glass capillaries using a Thomas–Hoover unimelt apparatus and are uncorrected. Infrared spectra were recorded on Bechman IR-7 and IR-9 spectrophotometers. Nmr spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are quoted in parts per million downfield from tetramethylsilane (δ), and coupling constants in cycles per second.
(20) F. P. Hauck, J. Demick and J. T. Fan, *J. Med. Chem.*, **10**, 611 (1967).
(21) C. A. Miller and L. M. Long, *J. Amer. Chem. Soc.*, **73**, 4895 (1951).
(22) C. A. Miller, H. I. Scholl, and L. M. Long, *ibid.*, **73**, 5608 (1951).
(23) C. A. Miller and R. L. Hull, U. S. Patent 3,183,245 (1965).

the product was extracted with benzene, washed with bicarbonate solution, dried over $MgSO_4$ and freed of solvent. The 26 g of crude product was distilled to yield 21 g (39%) of product collected at 160–165° (0.5 mm). The ir and nmr spectra were identical with those of an authentic sample.[23]

General Procedure for Alkylation at the 4 Position of 1 and 2 Types. In Liquid Ammonia.—To a suspension of 2.0 mol of $NaNH_2$ in 2 l. of NH_3 was added a solution of 0.25 mol of the imide in 250 ml of toluene rapidly but dropwise. A yellow precipitate formed. After 10 min, the mixture was treated with 2.0 mol of halide in 500 ml of ether dropwise. After 1 hr the mixture was treated with excess NH_4Cl to decompose any remaining base, the ammonia evaporated, the inorganics removed by filtration. After removal of solvents, the products were distilled twice for analysis.

In Ether–LDIPA.—To a solution of 2.0 mol of lithium diisopropylamide in 2 l. of ether was added rapidly but dropwise a solution (0.25 mol) of the imide in 250 ml of toluene. After 10 min the dark solution containing a yellow precipitate was treated rapidly dropwise with 2.0 mol of halide in 500 ml of ether. After 0.5 hr under reflux, the mixture was cooled and treated with water. The organic layer was separated, washed with water, dried and distilled as above.

General Procedure for Dialkylations at the 4 Position of 3 with THF–NaH.—A stirred solution of 0.5 mol of the imide and at least 1.0 mol of the appropriate halide in 1 l. of THF was treated portionwise with at least 1.0 mol of NaH (mineral oil suspension). If gas evolution did not commence immediately, the mixture was heated at the beginning of the addition, before much hydride was added, until reaction had definitely started. The mixture was gradually brought to reflux and held there for 12–36 hr depending upon the reactivity of the halide employed. The mixture was then cooled, treated dropwise with 20 ml of water followed by 100 ml of acetic acid, and filtered. After removal of solvent, the residue was taken up in benzene, washed thrice with water, and again freed of solvent. When possible, the residue was triturated with petroleum ether to remove mineral oil before fractionation. In some cases, chromatography on neutral alumina was used to finish the separation from starting material when fractional distillation did not accomplish this.

Preparation of the Self-Condensation Product 14.—A solution of 203 g (1.0 mol) of **3** ($R = R' = CH_3$) and 181 g (1.3 mol) of 3-bromopropanol in 2 l. of THF was treated portionwise with 120 g of 57% NaH in mineral oil. The reaction was quite vigorous causing the temperature to rise gradually to 48° then fall slowly to *ca.* 40° during the addition. The mixture was then heated under reflux for 24 hr, cooled, and treated dropwise with 200 g of acetic acid. After filtration, the solids were washed with benzene and the combined filtrates freed of solvent. The residue was taken up in benzene, washed twice with water and again freed of solvent. Mineral oil was removed by repetitive trituration with petroleum ether, and the residue then distilled. After starting material and a small forerun, 68 g of product (35%) was collected at 255–260° (0.3 mm) and soon solidified. A sample recrystallized from acetic acid–water had mp 245–248°; ir (KBr) 1755, 1735 and 1680 cm^{-1}; nmr ($CDCl_3$) 3.56 s, 3.05 (3 H, NCH_3), 2.81 (J = 17 and 2.67, J = 17, AB pattern,[24] 2 H, ring CH_2), 1.88 (3 H), and 1.52 (3 H, CH_3).

Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.23. Found: C, 74.27; H, 6.24.

General Procedure for Acylation of 3.—A solution of 1.0 mol of the imide and at least 2.0 mol of the appropriate ester in 1 l. of THF was stirred and treated with a small portion of NaH–mineral oil plus a few drops of absolute EtOH, then heated under reflux until gas evolution definitely started. Heating was stopped and the rest of 2.0 mol of NaH added portionwise at a rate to maintain vigorous but controlled refluxing. Heating was resumed and continued overnight. The mixture was cooled, treated dropwise with acetic acid, diluted with benzene, and filtered. The filtrate was taken to dryness and the residue dissolved in benzene, washed twice with water and again freed of solvent. Trituration with petroleum ether removed the mineral oil. Those products not solids at this point were distilled.

Registry No.—**14**, 19362-75-5.

Acknowledgment.—The authors wish to thank Mr. Charles Childs and staff for microanalytical work and Dr. John Vandenbelt and staff for physical measurements.

(24) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 83.

Conversion of 2,2-Dichloroacetoacetanilides into 4-Hydroxymethyl-2(1H)-quinolones

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A novel sulfuric acid catalyzed transformation of 2,2-dichloroacetoacetanilides into 4-hydroxymethyl-2(1H)-quinolones is described; 2,2-dichlorobenzoylacetanilides gave rise to products tentatively regarded as indeno-[1,2,3-*d,e*]-2(3H)-quinolones.

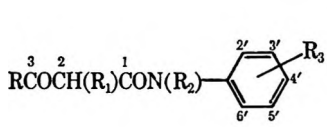
In the Knorr reaction, anilides of type **1** possessing one or two H atoms in the 2 position are converted by concentrated sulfuric acid into the corresponding 2(1H)-quinolone **2** (Chart I).[1] We now report on the cyclization of those anilides having no H atom in the 2 position, in particular, the little-known dichloro derivatives of type **3**. These substances and monochloroanilides **1** (R_1 = Cl) were readily obtained by the action of a 3:1 *M* proportion, respectively, of sulfuryl chloride on the appropriate anilide in ether.[2] Under different conditions nuclear chlorination of some substrates occurred as well. Thus, although N-ethylbenzoylacetanilide when heated with excess of sulfuryl chloride gave 2,2-dichloro-N-ethylbenzoylacetanilide (**3j**) as the final product, benzoylacetanilide on similar treatment afforded 2,2,4′-trichlorobenzoylacetanilide (**3g**). 2′,5′-Dimethylbenzoylacetanilide formed the trichloro derivative **3i** even at room temperature. Elemental and infrared analysis, supplemented on occasion by nmr spectra, served to confirm the structure of the products.

In contrast to anilides **1** (R_1 = H or Cl) which were recovered unchanged, compounds **3** were readily hydrolyzed in dilute sodium hydroxide at 20° to the corresponding 2,2-dichloroacetanilides in good yield.

Contrary to a claim[3,4] that sulfuryl chloride cyclizes acetoacetanilide at 80° into 4-methyl-2(1H)-quinolone and, furthermore, chlorsulfonates the product to yield (ultimately) 4-methyl-6-sulfamyl-2(1H)-quinolone, the reaction in our hands gave instead 2,2,4′-trichloroacetoacetanilide (**3b**). Moreover, 4-methyl-2(1H)-quinolone and sulfuryl chloride at 80° formed 3,6-dichloro-4-methyl-2(1H)-quinolone (**2b**) and not the alleged[3] 6-chlorsulfonyl derivative; in chlororoform solution the product was 3-chloro-4-methyl-2(1H)-quinolone (**2a**) converted by sulfuryl chloride into **2b.**

The effect of concentrated sulfuric acid on anilides **3** is now considered. 2,2-Dichloroacetoacetanilide (**3a**) was warmed (*ca.* 95°) with the acid for 15 min and evolved hydrogen chloride; addition of water afforded 3-chloro-4-hydroxymethyl-2(1H)-quinolone (**4b**) in 40% yield. 2,4′-Dichloro-2-methylacetoacetanilide (**5**) and sulfuric acid likewise gave (47%) 6-chloro-4-hydroxymethyl-3-methyl-2(1H)-quinolone (**4c**) and established that only one Cl atom need be available in the 2 position for this type of reaction to occur. Under similar conditions 2,2-dichloro-2′,4′,6′-trimethylacetoacetanilide (**3d**) and also compound **3h** formed little if any hydrogen chloride and were recovered unchanged; this suggested that cyclization of anilides **3a** and **5** probably was a prerequisite to hydrogen chloride production in the above instances.

CHART I



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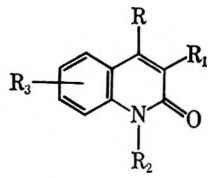
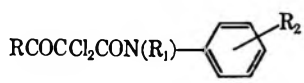
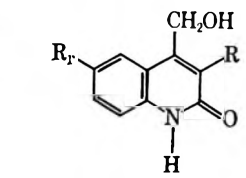


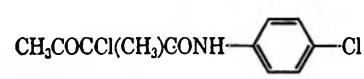
2a, R = CH_3; R_1 = Cl; R_2 = R_3 = H
b, R = CH_3; R_1 = Cl; R_2 = H; R_3 = 4′-Cl
c, R = CH_2Br; R_1 = Cl; R_2 = R_3 = H



3a, R = CH_3; R_1 = R_2 = H
b, R = CH_3; R_1 = H; R_2 = 4′-Cl
c, R = CH_3; R_1 = H; R_2 = 4′-Br
d, R = CH_3; R_1 = H; R_2 = 2′,4′,6′-$(CH_3)_3$
e, R = CH_2Br; R_1 = R_2 = H
f, R = C_6H_5; R_1 = R_2 = H
g, R = C_6H_5; R_1 = H; R_2 = 4′-Cl
h, R = C_6H_5; R_1 = H; R_2 = 2′,4′,6′-$(CH_3)_3$
i, R = C_6H_5; R_1 = H; R_2 = 4′-Cl-2′,5′-$(CH_3)_2$
j, R = C_6H_5; R_1 = C_2H_5; R_2 = H
k, R = C_6H_5; R_1 = C_2H_5; R_2 = 4′-Cl



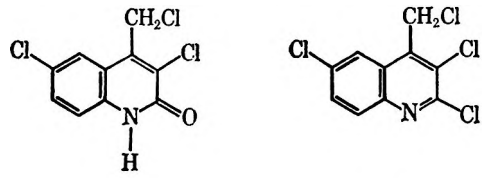
4a, R = R_1 = H
b, R = Cl; R_1 = H
c, R = CH_3; R_1 = Cl
d, R = R_1 = Cl



5

After reaction of 2,2,4′-trichloroacetoacetanilide (**3b**) with sulfuric acid, the mixture, when poured into water, furnished (22%) 4-chloromethyl-3,6-dichloro-2(1H)-quinolone (**6**) while it, when treated portionwise with water, furnished 3,6-dichloro-4-hydroxymethyl-2(1H)-quinolone (**4d**) in 77% yield, derived in part by hydrolysis of **6.** Compound **4d,** characterized also as its O-acetate and O-benzoate, gave on dehalogenation with Raney nickel and hydrogen the known[5] 4-hydroxymethyl-2(1H)-quinolone (**4a**), and with phosphorus oxychloride it formed the 4-chloromethyl derivative **6,** while, with a mixture of phosphorus oxychloride and pentachloride, the product was 4-chloromethyl-2,3,6-trichloroquinoline (**7**).

(1) "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, p 32.
(2) C. Bülow and E. King, *Ann.*, **439**, 211 (1924).
(3) L. Monti and S. Palmieri, *Gazz. Chim. Ital.*, **71**, 662 (1941); *Chem. Abstr.*, **37**, 128 (1943).
(4) Reference 1, p 150.
(5) T. Kametani, M. Hiiragi, and K. Kigasawa, *Yakugaku Zasshi*, **85**, 867 (1965); *Chem. Abstr.*, **64**, 5041 (1966).

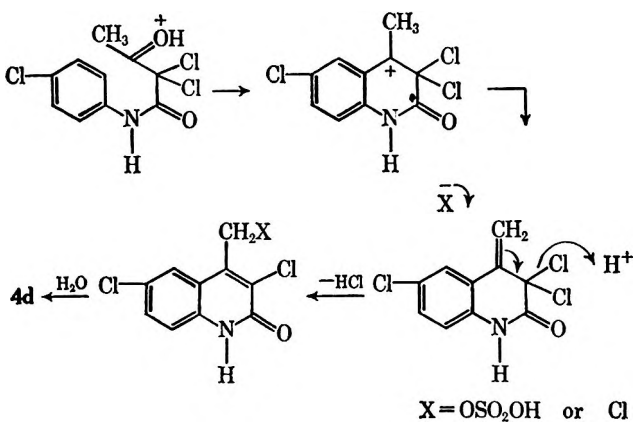


6 7

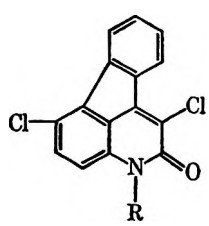
The aforementioned 4-hydroxymethyl-2(1H)-quinolone products **4** were identified by analysis and spectral data and their structures confirmed in each instance by comparison with authentic material. These reference compounds were prepared by acting on the appropriate acetoacetanilide in acetic acid with bromine, converting the resulting 4-bromo derivative **1** (R = CH_2Br) with sulfuric acid into the corresponding 4-bromomethyl-2(1H)-quinolone **2** (R = CH_2Br), and finally hydrolyzing the latter with dilute alkali.

A tentative mechanism for the anilide **3b** → quinolone **4d** conversion is outlined in Scheme I.

SCHEME I



The behavior of 2,2-dichlorobenzoylacetanilides **3** (R = C_6H_5) when allowed to react with concentrated sulfuric acid was in marked contrast to that of anilides **3** (R = CH_3). Thus, addition of the acid to 2,2,4′-trichlorobenzoylacetanilide (**3g**) resulted in a green solution which liberated hydrogen chloride (copiously) and chlorine (trace) and when poured into water afforded (60%) a yellow compound of molecular formula $C_{15}H_7Cl_2NO$. The identical product was obtained (43%) also from the 2,2-dichloroanilide **3f** and the analytical and spectral evidence available at present is consistent with structure **8a**. A similar reaction was undergone by the N-ethyl derivatives of the aforementioned two anilides, and the common product, $C_{17}H_{11}Cl_2NO$, is tentatively assigned structure **8b**. Study of this reaction and into the nature of the products is being continued.



8a, R = H
b, R = C_2H_5

Experimental Section[6]

Acetoacetanilides were prepared by rapid addition of boiling arylamine (0.1 mol) to boiling β-keto ester (0.33 mol) and refluxing the mixture for 4 min.[7] After cooling in ice, the solid material was filtered off, washed with ether, and recrystallized from aqueous alcohol. Acetoacetanilides **1** (R = CH_3, R_2 = H) obtained were (R_1, R_3 substituents, per cent yield, melting point, and analysis) H, 4′-Cl, 38%, 134–135° (lit.[8] mp 132–133°); H, 4′-Br, 38%, 137–139° (lit.[8] mp 137°); H, 2′,4′,6′-$(CH_3)_3$, 75%, 138–139° (*Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.78. Found: C, 71.06; H, 7.73); CH_3, 4′-Cl, 25%, 98–100° (*Anal.* Calcd for $C_{11}H_{12}ClNO_2$: N, 6.20. Found: N, 6.35).

Benzoylacetanilides.—Equimolar amounts of arylamine and ethyl benzoylacetate (20 g, 0.1 mol) were allowed to react at 140–145° for 1 hr.[9] Benzoylacetanilides **1** (R_1 = H) obtained were (R, R_2, R_3 substituents, per cent yield, melting point, and analysis) C_6H_5, H, 4′-Cl, 24%, 156° (lit.[10] mp 154–156°); C_6H_5, H, 2′,4′,6′-$(CH_3)_3$, 78%, 173–174° (*Anal.* Calcd for $C_{18}H_{19}NO_2$: N, 4.95. Found: N, 5.13); C_6H_5, C_2H_5, 4′-Cl, 32%, 109–110° (*Anal.* Calcd for $C_{17}H_{16}ClNO_2$: N, 4.65. Found: N, 4.60); o-$NO_2C_6H_4$, H, 4′-Cl (from ethyl o-nitrobenzoylacetate and 4-chloroaniline), 16%, 130–131° (*Anal.* Calcd for $C_{15}H_{11}ClN_2O_4$: C, 56.52; H, 3.45. Found: C, 56.72; H, 3.48); C_6H_5, H, 2′,5′-$(CH_3)_2$, 28%, 145–146° (*Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37. Found: C, 76.47; H, 6.29).

Bromination of Acetoacetanilides.[11]—A solution of bromine (9 g) in glacial acetic acid (45 ml) containing a crystal of iodine was added dropwise, over a period of 1 hr, to the anilide (0.05 mol) dissolved in glacial acetic acid (30 ml), with stirring at 20°. After a further 3 hr the mixture was poured into water, and the precipitated solid was filtered, washed with water, dried and recrystallized from benzene. 4-Bromoacetoacetanilides **1** (R = CH_2Br; R_2 = H) obtained were (R_1, R_3 substituents, per cent yield, melting point and analysis) H, H, 88%, 134–135° (lit.[11] mp 136–138°); H, 4′-Cl, 90%, 110–112° (*Anal.* Calcd for $C_{10}H_9BrClNO_2$: C, 41.31; H, 3.09. Found: C, 41.16; H, 3.13); CH_3, 4′-Cl, 81%, 109–110° (*Anal.* Calcd for $C_{11}H_{11}BrClNO_2$: C, 43.35; H, 3.62. Found: C, 43.22; H, 3.48). Similar bromination of 2,2-dichloroacetoacetanilide (**3a**) gave 4′-bromo-2,2-dichloroacetoacetanilide (**3c**), 70%, mp 71–72° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: C, 36.92; H, 2.45. Found: C, 36.90; H, 2.51) as evidenced by nmr, and alkaline hydrolysis to 4-bromoaniline. The required anilide **3e** was eventually prepared by the action of sulfuryl chloride on 4-bromoacetoacetanilide (see below).

Chlorination of Acetoacetanilides and Benzoylacetanilides with Sulfuryl Chloride. A. Introduction of One 2-Cl Atom.[2]—A solution of sulfuryl chloride (5.4 g, 0.04 mol) in dry ether (or chloroform, 5 ml) was added dropwise over 0.5 hr to the acetoacetanilide or benzoylacetanilide (0.04 mol) in dry ether (or chloroform, 25 ml) with stirring at 0°. After a further 1 hr at 20°, the solvent was removed (rotary evaporator), and the residue recrystallized from aqueous ethanol. The 2-chloro derivatives **1** (R_1 = Cl) were obtained (R, R_2, R_3 substituents, per cent yield, melting point, and analysis): CH_3, H, H, 63%, 137–139° (lit.[2] mp 137.5°); CH_3, H, 4′-Cl (chloroform), 65%, 136° (*Anal.* Calcd for $C_{10}H_8Cl_2NO_2$: N, 5.70. Found: N, 5.83); CH_2Br, H, H, 60%, 76–77° (*Anal.* Calcd for $C_{10}H_9BrClNO_2$: N, 4.82. Found: N, 4.80); CH_2Br, H, 4′-Cl, 60%, 97–98° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: N, 4.30. Found: N, 4.19); C_6H_5, H, 4′-Cl, 57%, 108–110° (*Anal.* Calcd for $C_{16}H_{11}Cl_2NO_2$: N, 4.54. Found: N, 4.61); C_6H_5, H, 4′-CH_3, 75%, 108–111° (*Anal.* Calcd for $C_{16}H_{14}ClNO_2$: N, 4.88. Found: N, 4.75); C_6H_5, C_2H_5, H, 61%, 156° (*Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.77; H, 5.31. Found: C, 67.86; H, 5.43). Also obtained was **5**, 56%, 59–61° (*Anal.* Calcd for $C_{11}H_{11}Cl_2NO_2$: N, 5.38. Found: N, 5.27).

(6) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 spectrophotometer, using 1 mg of substance per 300 mg of KBr or a 4% solution in chloroform. Nmr spectra were measured on a Varian A-60 model. Mass spectra were recorded on a MS-9 mass spectrometer. All yields reported relate to the recrystallized material unless otherwise stated.

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B. Introduction of Two 2-Cl Atoms. i. Dichloroacetoacetanilides.[2]—Sulfuryl chloride (21.7 g, 0.16 mol) was added dropwise over 0.5 hr to the appropriate anilide (0.053 mol) in dry ether (50 ml) with stirring at 0°. After a further 0.5 hr the solvent and excess reagent were removed (rotary evaporator) and the residue was recrystallized from aqueous ethanol. 2,2-Dichloroacetoacetanilides **3** (R_1 = H) were obtained (R, R_2 substituents, per cent yield, melting point, and analysis): CH_3, H, 69%, 42–43° (lit.[2] mp 46–47°) (*Anal.* Calcd for $C_{10}H_9Cl_2NO_2$: N, 5.70. Found: N, 5.80); CH_3, 4′-Cl, 56%, 62–63° (lit.[2] mp 64°) (*Anal.* Calcd for $C_{10}H_8Cl_3NO_2$: N, 4.98. Found: N, 4.94); CH_2Br, H, 71%, 56–57° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: C, 36.92; H, 2.45. Found: C, 37.02; H, 2.48); CH_3, 4′-Br, 55%, 71–72° (identical with the compound from **3a** and bromine); CH_3, 2′,4′,6′-$(CH_3)_3$, 74%, 97–98° (*Anal.* Calcd for $C_{13}H_{15}Cl_2NO_2$: C, 54.51; H, 5.21. Found: C, 54.33; H, 5.35).

ii. 2,2-Dichlorobenzoylacetanilides.—An excess of sulfuryl chloride (4.7 g, 0.035 mol) was added to the appropriate benzoylacetanilide (0.007 mol) at 20° and after 0.5 hr the mixture was poured into ice water, the product was filtered off, washed, and recrystallized from aqueous ethanol. Obtained in this way were the following **3** (R = C_6H_5) (R_1, R_2 substituents, per cent yield, melting point, and analysis): H, H, 77%, 136° (*Anal.* Calcd for $C_{15}H_{11}Cl_2NO_2$: Cl, 23.05; N, 4.54. Found: Cl, 22.48; N, 4.62); H, 4′-Cl (from 4′-chlorobenzoylacetanilide), 62%, 144–145° (*Anal.* Calcd for $C_{15}H_{10}Cl_3NO_2$: C, 52.55; H, 2.92; Cl, 31.04; N, 4.09. Found: C, 53.06; H, 2.97; Cl, 31.16; N, 3.90), this product resulted also (61% yield) from benzoylacetanilide and a 10 *M* amount of sulfuryl chloride refluxed for 15 min; C_2H_5, H, 64%, 98–99° (*Anal.* Calcd for $C_{17}H_{15}Cl_2NO_2$: C, 60.71; H, 4.46. Found: C, 60.72; H, 4.50); the same N-ethyl-2,2-dichloroanilide was obtained after refluxing N-ethylbenzoylacetanilide with a 8 *M* amount of sulfuryl chloride for 30 min; C_2H_5, 4′-Cl (from 4′-chloro-N-ethylbenzoylacetanilide), 75%, 97–98° (*Anal.* Calcd for $C_{17}H_{14}Cl_3NO_2$: C, 55.21; H, 3.79. Found: C, 55.00; H, 3.68); H, 4′-Cl-2′,5′-$(CH_3)_2$ (from 2′,5′-dimethylbenzoylacetanilide), 72%, 116–117° (*Anal.* Calcd for $C_{17}H_{14}Cl_3NO_2$: C, 55.24; H, 3.52. Found: C, 55.20; H, 3.71); H, 2′,4′,6′-$(CH_3)_3$, 72%, 156–158° (*Anal.* Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.71; H, 4.86. Found: C, 61.65; H, 5.06). The recrystallized anilides in i and ii gave no color with alcoholic ferric chloride.

Hydrolysis of 2,2-Dichloroacetoacetanilides to 2,2-Dichloroacetanilides.—Compound **3a** (1.0 g) was stirred with 10% sodium hydroxide (10 ml) at 20° for 10 min. Acidification with dilute acetic acid afforded insoluble material which after recrystallization from aqueous ethanol was identified as 2,2-dichloroacetanilide (0.5 g, 60%), mp 115–116° (lit.[12] mp 117°), by comparison (mixture melting point, infrared spectrum) with a sample prepared from aniline and dichloroacetic acid.[13] Similar treatment of **3b** and **3c** gave 2,2,4′-trichloroacetanilide (67%), mp 135° (lit.[14] mp 136–137°), and 4′-bromo-2,2-dichloroacetanilide (59%), mp 145–147° (lit.[12] mp 146–147°), respectively, identified by their infrared spectra.

Anilide **3c** (0.5 g) was refluxed with 10% sodium hydroxide (10 ml) for 0.5 hr. Ether extraction of the mixture provided, after evaporation of the solvent, crude 4-bromoaniline (0.2 g, 85%), mp 85–86°, identified by its infrared spectrum.

Conversion of Anilides Having One or Two 2-H Atoms into 2(1H)-Quinolones.—The appropriate acetoacetanilide or benzoylacetanilide (1 g) was treated with concentrated sulfuric acid (2 ml) and heated on the water bath (*ca.* 95°) for 1 hr after which the mixture was poured into ice–water (~20 ml) and the insoluble product recrystallized from aqueous ethanol. The 2(1H)-quinolones **2** prepared were (R, R_1, R_2, R_3 substituents, per cent yield, melting point, and analysis) CH_3, H, H, H, 85%, 216–218° (lit.[1] mp 217°); CH_3, Cl, H, H, 87%, 272–274° (lit.[2] mp 276°); CH_3, H, H, 6-Cl, 82%, 298–300° (lit.[11] mp 292–294°); CH_3, Cl, H, 6-Cl, 86%, 300–302° (*Anal.* Calcd for $C_{10}H_7Cl_2NO$: Cl, 31.10; N, 7.25. Found: Cl, 30.65; N, 7.25); CH_2Br, H, H, H, 86%, 258–260° (lit.[11] mp 262–265°); CH_2Br, Cl, H, H, 75%, 238–240° (*Anal.* Calcd for $C_{10}H_7BrClNO$: N, 5.15. Found: N, 5.01); CH_2Br, Cl, H, 6-Cl, 85%, 278–280° (*Anal.* Calcd for $C_{10}H_6BrCl_2NO$: N, 4.56. Found: N, 4.65); CH_2Br, CH_3, H, 6-Cl, 45%, 284–286° (*Anal.* Calcd for $C_{11}H_9BrClNO$: C, 46.05; H, 3.19. Found: C, 46.17; H, 3.09); C_6H_5, Cl, H, 6-Cl, 80%, 288–290° (*Anal.* Calcd for $C_{15}H_9Cl_2NO$: N, 4.81. Found: N, 4.90); C_6H_5, Cl, H, 6-CH_3, 95%, 284–288° (*Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.26; H, 4.08. Found: C, 71.39; H, 4.12); C_6H_5, Cl, C_2H_5, H, 81%, 158–160° (*Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 72.08; H, 4.95. Found: C, 72.14; H, 4.95); C_6H_5, H, C_2H_5, 6-Cl, 75%, 102–104° (*Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 72.08; H, 4.95. Found: C, 72.16; H, 4.88). After similar reaction, 2′,4′,6′-trimethylbenzoylacetanilide was recovered (50%) unchanged, as was 4′-chloro-*o*-nitrobenzoylacetanilide (50%), while 2′,4′,6′-trimethylacetoacetanilide afforded an alkali-soluble product containing S, showing no CO absorption in the infrared spectrum, and apparently derived from sulfuric acid and mesidine (*Anal.* Calcd for $C_9H_{13}NO_3S$: C, 50.2; H, 6.04; N, 6.51. Found: C, 49.88; H, 6.38; N, 6.64).

Attempted Cyclization of Acetoacetanilide with Sulfuryl Chloride.—The work of Monti and Palmieri[3] was repeated. Sulfuryl chloride (10 g, 0.07 mol) and acetoacetanilide (7 g, 0.04 mol) were heated together for 3 hr at 80°; on addition of the sulfuryl chloride, a vigorous evolution of hydrogen chloride occurred. The product was poured onto ice, treated with concentrated ammonia and the solution evaporated on a water bath. The residue was extracted with dilute ammonia and carbon dioxide passed through this solution. Under these conditions no material separated. Monti and Palmieri reported obtaining 4-methyl-6-sulfamyl-2(1H)-quinolone, mp 316–318°. However, a recognizable product was obtained, using a modified work-up procedure: after reaction of the sulfuryl chloride (10 g) and acetoacetanilide (7 g) for 3 hr at 80° as before, the mixture was poured into ice–water, whereupon an oil separated. This was extracted with ether, dried over sodium sulfate and the ether evaporated to give a yellow oil (5 g, 55%) which could not be induced to crystallize, and was identified as crude 2,2,4′-trichloroacetoacetanilide (**3b**) by its infrared spectrum.

Attempted Chlorsulfonation of 4-Methyl-2(1H)-quinolone.—Sulfuryl chloride (3 g, 0.022 mol) and 4-methyl-2(1H)-quinolone (1.9 g, 0.012 mol) were allowed to react for 3 hr at 80°;[3] addition of the sulfuryl chloride to the quinolone led to a ready evolution of hydrogen chloride. Treatment with water yielded crude 3,6-dichloro-4-methyl-2(1H)-quinolone (**2b**) which was obtained as colorless crystals (from aqueous dimethylformamide) (2 g, 77%), mp 300–301°, identified by comparison (mixture melting point, infrared spectrum) with a sample derived by cyclization of 2,4′-dichloroacetoacetanilide (see below). Monti and Palmieri[3] reported forming 6-chlorsulfonyl-4-methyl-2(1H)-quinolone.

4-Methyl-2(1H)-quinolone (1.9 g) was treated with a solution of sulfuryl chloride (3 g) in dry chloroform (50 ml) and refluxed for 20 min. Removal of the chloroform and excess reagent under reduced pressure afforded crude 3-chloro-4-methyl-2(1H)-quinolone (**2a**), colorless crystals from aqueous ethanol (1.5 g, 65%), mp 272–274° (lit.[2] mp 276°), identified by comparison with the quinolone from 2-chloroacetoacetanilide and concentrated sulfuric acid.

Compound **2a** (1.9 g) was allowed to react with sulfuryl chloride (3 g) at 80° for 3 hr; pouring into water gave the 3,6-dichloroquinolone **2b**, colorless crystals (1.8 g, 78%), mp 300–301°, from aqueous dimethylformamide.

Conversion of 2,2-Dichloroacetoacetanilides into 4-Hydroxymethyl-2(1H)-quinolones. 3-Chloro-4-hydroxymethyl-2(1H)-quinolone (4b).—Concentrated sulfuric acid (6 ml) was added to 2,2-dichloroacetoacetanilide (**3a**, 2 g) and allowed to remain at room temperature (*ca.* 20°) for 1 hr; hydrogen chloride was evolved after 20 min. Water (20 ml) was added slowly and the white solid which deposited (1.2 g, mp 40–94°) proved to be a mixture; repeated recrystallizations from aqueous ethanol failed to provide a pure compound. The crude product (0.7 g) was dissolved in pyridine (5 ml) and chromatographed on silica gel (50 g) using benzene–methanol (6:1 v/v) as eluent. Fifteen 20-ml fractions were collected, from which was recovered anilide **3a** [0.09 g, mp 41–43° (fractions 1–5)], an unidentified mixture [0.06 g, mp 220–235° (fractions 10–15)], and the main product (fractions 6–9), *viz.* 3-chloro-4-hydroxymethyl-2(1H)-quinolone (**4b**), colorless crystals from aqueous ethanol (0.40 g, 40%): mp 259–261°; ir 2.95 (OH), 3.35 (NH), and 6.02 μ (CO).

Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.41; H, 3.83. Found: C, 57.22; H, 3.92.

Reaction of anilide **3a** (1 g) with sulfuric acid (2 ml) at 95°, for 5, 15, and 60 min, led to quinolone **4b** in 10, 32 and 20% yields, respectively.

The product was identical (mixture melting point, infrared

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(14) N. G. Clark and A. F. Hams, *Biochem. J.*, **55**, 839 (1953).

spectrum) with **4b** derived by refluxing 4-bromomethyl-3-chloro-2(1H)-quinolone (**2c**, 0.5 g) with 10% sodium hydroxide (10 ml) for 1 hr and neutralizing the solution with dilute acetic acid; colorless crystals from aqueous ethanol (0.3 g, 75%): mp 259–261°. Reaction of 2,2-dichloro-2',4',6'-trimethylacetoacetanilide (**3d**, 2 g) with concentrated sulfuric acid (6 ml) at 95° for 1 hr, and pouring into ice–water (200 ml) led to the recovery (1.8 g, 90%) of unchanged anilide, identified by its melting point and infrared spectrum.

6-Chloro-4-hydroxymethyl-3-methyl-2(1H)-quinolone (4c).—To 2,4'-dichloro-2-methylacetoacetanilide (**5**, 2 g) was added concentrated sulfuric acid (6 ml) and the mixture heated at 95° for 0.5 hr, during which period hydrogen chloride was evolved. After cooling (to *ca.* 20°) water (20 ml) was added slowly and the precipitated solid recrystallized from aqueous pyridine: colorless crystals (0.8 g, 47%); mp 298–300°; ir 2.95 (OH), 3.33 (NH), and 6.05 μ (CO).

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.19; H, 4.48. Found: C, 59.01; H, 4.61.

The product was identical (infrared spectrum) with the 4-hydroxymethylquinolone derived (0.3 g, 77%, mp 298–300°) by hydrolysis of 4-bromomethyl-6-chloro-3-methyl-2(1H)-quinolone (0.5 g) with 10% sodium hydroxide (10 ml) as before.

4-Chloromethyl-3,6-dichloro-2(1H)-quinolone (6) and 3,6-Dichloro-4-hydroxymethyl-2(1H)-quinolone (4d).—Concentrated sulfuric acid (6 ml) was added to 2,2,4'-trichloroacetoacetanilide (**3b**, 3 g) and warmed (*ca.* 95°) for 15 min, whereupon hydrogen chloride was evolved. After cooling (to *ca.* 20°) the mixture was divided into two equal portions.

i.—One amount was poured slowly with stirring into ice–water (100 ml); the insoluble **6** was filtered off, washed, and obtained as colorless crystals (0.3 g, 22%; mp 258–260°) from aqueous ethanol, ir 3.50 (NH) and 6.00 μ (C=O).

Anal. Calcd for $C_{10}H_6Cl_3NO$: C, 46.00; H, 2.30; Cl, 40.20; mol wt, 261 (Cl = 35). Found: C, 45.89; H, 2.42; Cl, 39.22; mol wt (mass spectrometer), 261.

A 43% yield of compound **6** was obtained after reaction of anilide **3b** (1 g) with PPA (10 g) at 140° for 0.5 hr.

A mixture of **6** (0.5 g) and 60% (v/v) sulfuric acid (10 ml) was refluxed for 1 hr and poured into water; the acid-insoluble product (colorless crystals, 0.3 g, 65%, mp 310–313°, from aqueous ethanol) proved to be quinolone **4d** obtained in ii below.

ii.—Water (100 ml) was added slowly, without cooling, to the remaining portion of the reaction mixture and the insoluble material was filtered off, washed, and recrystallized from aqueous ethanol, colorless crystals (1.0 g, 77%), mp 313–315°, of 3,6-dichloro-4-hydroxymethyl-2(1H)-quinolone (**4d**), ir 3.00 (OH), 3.35 (NH), and 6.10 μ (CO) [*Anal.* Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.40; H, 2.88; Cl, 29.10; mol wt, 243 (Cl = 35). Found: C, 49.20; H, 2.87; Cl, 29.12; mol wt (mass spectrometer), 243].

Yields of **4d** after 5, 10, 60 and 120 min were 50, 65, 75 and 34%, respectively. The product was identical (infrared spectrum) with that obtained (0.3 g, 75%, mp 313–315°) by alkaline hydrolysis of 4-bromomethyl-3,6-dichloro-2(1H)-quinolone (0.5 g). The **O-acetate** was prepared by addition of acetyl chloride (6 ml) over 5 min to a solution of **4d** (1 g) in dry pyridine (5 ml) stirred at 0°. After a further 10 min, the mixture was heated at 95° for 2 min and poured into ice–water (20 ml): colorless crystals (from glacial acetic acid) (0.80 g, 70%); mp 263–264°; ir 3.38 (NH), 5.75 (ester CO), and 6.0 μ (amide CO).

Anal. Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.52; H, 3.12; Cl, 24.60; mol wt, 285 (Cl = 35). Found: C, 50.43; H, 2.97; Cl, 25.12; mol wt (mass spectrometer), 285.

The **O-benzoate** was obtained from benzoyl chloride (6 ml), quinolone **4d** (1 g) and 10% sodium hydroxide (40 ml) shaken vigorously for 15 min: colorless crystals (from glacial acetic acid) (0.85 g, 60%); mp 292–294°; ir 3.37 (NH), 5.81 (ester CO), and 6.05 μ (amide CO).

Anal. Calcd for $C_{17}H_{11}Cl_2NO_3$: C, 58.88; H, 3.17; Cl, 20.90. Found: C, 58.71; H, 3.20; Cl, 20.66.

A mixture of quinolone **4d** (0.5 g) and phosphorus oxychloride (5 ml) was refluxed for 1 hr and poured into ice–water (20 ml); the insoluble product was recrystallized from aqueous ethanol to give (0.4 g, 74%; mp 258–260°) 4-chloromethyl-3,6-dichloro-2(1H)-quinolone (**6**) identified by its infrared spectrum. With added phosphorus pentachloride (1.8 g) the reaction furnished, after pouring into ice–water, crude 4-chloromethyl-2,3,6-trichloroquinoline (**7**): colorless needles from aqueous ethanol (1.0 g, 87%); mp 123°, identified by its infrared and nmr spectra.

Anal. Calcd for $C_{10}H_6Cl_4N$: C, 42.75; H, 1.78; N, 4.98. Found: C, 42.90; H, 1.90; N, 4.82.

Dehalogenation of the 3,6-dichloroquinolone **4d** (1 g) was effected by stirring its solution in ethanol (250 ml) and 10% sodium hydroxide (10 ml) with Raney nickel (~1 g) and hydrogen (160 psi) at 20° for 8 hr. The filtered solution was evaporated to dryness and the residue extracted with absolute alcohol (20 ml). Removal of the solvent afforded 4-hydroxymethyl-2(1H)-quinolone (**4a**), colorless crystals from aqueous ethanol (0.5 g, 70%), mp 272–274° (lit.[5] mp 274–276°), identified by comparison (infrared spectrum) with the product of alkaline hydrolysis of 4-bromomethyl-2(1H)-quinolone.

Action of Sulfuric Acid on 2,2,4'-Trichlorobenzoylacetanilide (3g).—Concentrated sulfuric acid (6 ml) was added to the anilide (3 g) and the mixture heated on the water bath (*ca.* 95°) for 15 min. On addition of the acid, a light yellow color appeared, and after 1 min at 20° the solution was dark green; heating at 95° for about 5 min led to the evolution of hydrogen chloride and a trace of chlorine (detected by starch–potassium iodide paper). The brown solution was cooled and poured into ice–water (200 ml) to deposit a yellow solid which was recrystallized from aqueous pyridine to afford **8a** as yellow crystals (1.5 g, 60%): mp >350°; ir 3.60 (NH), and 6.10 μ (amide CO).

Anal. Calcd for $C_{15}H_7Cl_2NO$: C, 62.72; H, 2.42; N, 4.88; Cl, 24.80; mol wt, 287 (Cl = 35). Found: C, 62.77; H, 2.49; N, 4.96; Cl, 24.84; mol wt (mass spectrometer), 287.

The identical yellow product (as evidenced by analysis, infrared and mass spectra) was obtained (43% yield) from 2,2-dichlorobenzoylacetanilide (**3f**, 3 g) and concentrated sulfuric acid (6 ml) at 95° for 15 min.

Action of Sulfuric Acid on 2,2,4'-Trichloro-N-ethylbenzoylacetanilide (3k).—The anilide (2 g) and concentrated sulfuric acid (5 ml) were heated at 95° for 15 min; a green solution formed initially and hydrogen chloride and chlorine were subsequently evolved. After cooling and pouring into ice–water (100 ml), the insoluble yelow product (of possible structure **8b**) was recrystallized from aqueous pyridine: yellow crystals (1.4 g 82%), mp 198–201°; ir (NH absent) 6.10 μ (amide CO).

Anal. Calcd for $C_{17}H_{11}Cl_2NO$: C, 64.76; H, 3.49; mol wt, 315 (Cl = 35). Found: C, 64.93; H, 3.59; mol wt (mass spectrometer), 315.

The identical product (mixture melting point, infrared spectrum) was isolated (32% yield) after reaction of 2,2-dichloro-N-ethylbenzoylacetanilide (**3j**, 1 g) and concentrated sulfuric acid (3 ml) at 95° for 10 min.

2,2-Dichloro-2',4',6'-trimethylbenzoylacetanilide (**3h**, 1 g) and concentrated sulfuric acid (3 ml) were warmed (95°) for 1 hr; unlike the previous instances, the solution developed no green color and little, if any, hydrogen chloride was evolved. After pouring into water, unchanged anilide (0.5 g, 50%) identified by its melting point and infrared spectrum was recovered.

Registry No.—Acetoacetanitide **1** R = CH_3, R_2 = H, R_1 = H, R_3 = 2',4',6'-$(CH_3)_3$, 19359-16-1; **1** R = CH_3, R_2 = H, R_1 = CH_3, R_3 = 4'-Cl, 19359-17-2; benzoylacetanilide **1** R_1 = H, R = C_6H_5, R_2 = H, R_3 = 2',4',6'-$(CH_3)_3$, 19359-18-3; **1** R_1 = H, R = C_6H_5, R_2 = C_2H_5, R_3 = 4'-Cl, 19359-19-4; **1** R_1 = H, R = *o*-$NO_2C_6H_4$, R_2 = H, R_3 = 4'-Cl, 19359-20-7; **1** (R_1 = H), R = C_6H_5, R_2 = H, R_3 = 2',5'-$(CH_3)_2$, 19359-21-8; 4-bromoacetoacetanilide **1** (R = CH_2Br, R_2 = H), R_1 = H, R_3 = 4'-Cl, 19359-22-9; **1** (R = CH_2Br, R_2 = H), R_1 = CH_3, R_3 = 4'-Cl, 19359-23-0; 2-chloro derivative **1** (R_1 = Cl), R = CH_2Br, R_2 = H, R_3 = 4'-Cl, 19359-24-1; **1** (R_1 = Cl), R = C_6H_5, R_2 = H, R_3 = 4'-Cl, 19359-25-2; **1** (R_1 = Cl), R = C_6H_5, R_2 = H, R_3 = 4'-CH_3, 19359-26-3; **1** (R_1 = Cl), R = C_6H_5, R_2 = C_2H_5, R_3 = H, 19359-27-4; **1b**, 19359-28-5; **1c**, 19359-29-6; **2c**, 19359-30-9; 2(1H)-quinolone **2** (R, R_1, R_2, R_3), CH_3, Cl, H, 6-Cl, 19359-31-0; **2**, CH_2Br, Cl, H, 6-Cl, 19359-32-1; **2**

CH_2Br, CH_3, H, 6-Cl, 19359-33-2; **2**, C_6H_5, Cl, H, 6-Cl, 17259-82-4; **2**, C_6H_5, Cl, H, 6-CH_3, 19398-22-2; **2**, C_6H_5, Cl, C_2H_5H, 19359-35-4; **2**, C_6H_5, H, C_2H_5, 6-Cl, 19359-36-5; **3c**, 19359-37-6; **3d**, 19359-38-7; **3e**, 19375-64-5; **3f**, 19359-39-8; **3g**, 19359-40-1; **3h**, 19359-41-2; **3i**, 19359-42-3; **3j**, 19359-43-4; **3k**, 19359-44-5; **4b**, 19359-45-6; **4c**, 19359-46-7; **4d**, 19359-47-8; **4d** O-acetate, 19359-48-9; **4d** O-benzoate, 19359-49-0; **5**, 19359-50-3; **6**, 19359-51-4; **7**, 19359-52-5; **8a**, 19359-53-6; **8b**, 19359-54-7.

Synthesis and Cyclizations of Semicarbazidomethylenemalonates and Related Compounds

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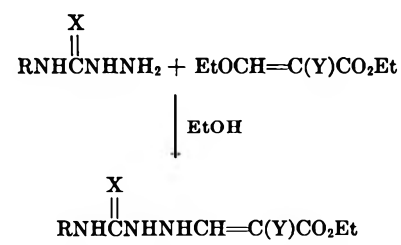
Reaction of semicarbazides and thiosemicarbazides with diethyl ethoxymethylenemalonate produced **1a–c** and **2a–c** in high yields. Use of ethyl 2-cyano-3-ethoxyacrylate led to **3a–c** and **4a–c**. Reaction of semicarbazides with ethoxymethylenemalononitrile (EMMN) produced **5a** and **b** and **6a** and **b**. Thiosemicarbazides and EMMN produced **7a** and **b**. Attempts to cyclize **1a** and **b** in hot ethanol were unsuccessful. Cyclization of **2a** and **2c** in hot ethanol gave 2-(ethylamino)- and 2-(anilino)-1,3,4-thiadiazole, respectively. Cyclization of **3a** gave **8a**, and **3b** gave **8b**, which readily lost the 1-phenylcarbamoyl group through solvolysis. Compound **4a** gave **9** upon cyclization, and **4c** gave ethyl 5-amino-4-pyrazolecarboxylate.

Hydrazinomethylenemalonates[1] and 3-hydrazino- and 3-(acylhydrazino)-2-cyanoacrylates[2,3] have been reported, and their cyclizations to pyrazole derivatives have been studied.[1–3] Hydrazines react with ethoxymethylenemalononitrile to produce pyrazoles *via* intermediate hydrazinomethylenemalononitriles which generally were not isolable.[4] Diethyl semicarbazidomethylenemalonate and diethyl thiosemicarbazidomethylenemalonate have been reported.[5] The reaction of semicarbazide with ethoxymethylenemalononitrile has been reported to give semicarbazidomethylenemalononitrile[6,7] under mild reaction conditions and 5-amino-4-cyano-1-pyrazolecarboxamide[8] under more vigorous reaction conditions.

We have studied the reactions of 4-substituted semicarbazides and 4-substituted 3-thiosemicarbazides with diethyl ethoxymethylenemalonate, ethyl 2-cyano-3-ethoxyacrylate, and ethoxymethylenemalononitrile. Reactions of semicarbazides and thiosemicarbazides with diethyl ethoxymethylenemalonate in ethanol at 20–25° gave semicarbazido- and thiosemicarbazidomethylenemalonates **1a–c** and **2a–c**, and use of ethyl 2-cyano-3-ethoxyacrylate in this condensation reaction gave **3a–c** and **4a–c** (Scheme I, Table I).

The reaction of semicarbazide with ethoxymethylenemalononitrile (EMMN) was reinvestigated; that semicarbazidomethylenemalononitrile[6,7] (**5a**) is obtained under mild reaction conditions was verified through

SCHEME I

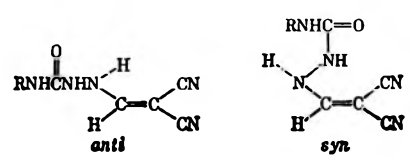


1a, X = O; R = CH_3; Y = CO_2Et
b, X = O; R = C_6H_5; Y = CO_2Et
c, X = O; R = 3,4-$Cl_2C_6H_3$; Y = CO_2Et
2a, X = S; R = Et; Y = CO_2Et
b, X = S; R = allyl; Y = CO_2Et
c, X = S; R = C_6H_5; Y = CO_2Et
3a, X = O; R = CH_3; Y = CN
b, X = O; R = C_6H_5; Y = CN
c, X = O; R = 3,4-$Cl_2C_6H_3$; Y = CN
4a, X = S; R = Et; Y = CN
b, X = S; R = allyl; Y = CN
c, X = S; R = C_6H_5; Y = CN

nmr analysis of the product.[9] Reaction of 4-methylsemicarbazide with ethoxymethylenemalononitrile (EMMN) in ethanol at 23° led to (4-methylsemicarbazido)methylenemalononitrile[9] (**5b**) in 52% yield

(1) L. Claisen and E. Haase, *Chem. Ber.*, **28**, 35 (1895).
(2) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956).
(3) P. Schmidt, K. Eichenberger, and J. Druey, *ibid.*, **41**, 1052 (1958).
(4) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
(5) A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).
(6) M. J. Kamlet, *J. Org. Chem.*, **24**, 714 (1959).
(7) C. Runti, L. Sindellari, and C. Nisi, *Ann. Chim.* (Rome), **49**, 1649 (1959).
(8) C. L. Dickinson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, **29**, 1915 (1964).

(9) The nmr spectra of **5a** and **5b** reveal hindered rotation about the vinyl carbon–nitrogen bond, with unequal populations of the *anti* and *syn* conformers; the vinyl proton and the adjacent NH proton each appear as two singlets of unequal intensity. Similarly, *anti–syn* isomerism has been observed with N-alkylaminomethylenemalononitriles (R. K. Howe, unpublished work),



and hindered rotation about the vinyl carbon–nitrogen bond of N,N-dimethylaminomethylenemalononitrile has been reported by A. Mannschreck and U. Koelle [*Tetrahedron Lett.*, 863 (1967)].

TABLE I

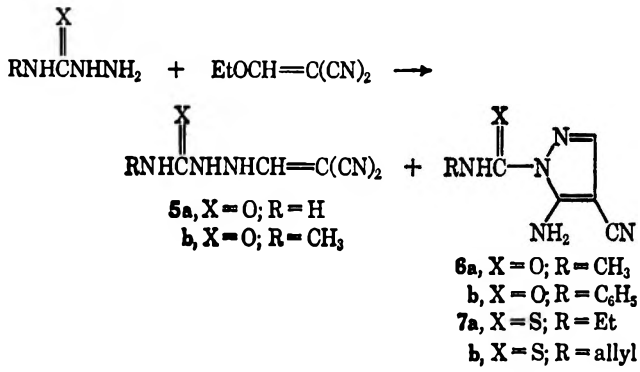
SEMICARBAZIDO- AND THIOSEMICARBAZIDOMETHYLENEMALONATES, AND SEMICARBAZIDO- AND THIOSEMICARBAZIDO-2-CYANOACRYLATES

Compd	Mp, °C	Yield, %	Formula	Calcd, %			Found, %			Ir spectra		
				C	H	N	C	H	N	NH	C=O	CN
1a	190–192	97[a]	$C_{10}H_{17}N_3O_5$	46.33	6.61	16.21	46.51	6.72	16.18	3.00, 3.10	5.89, 6.01	
1b	161–162	95	$C_{15}H_{19}N_3O_5$	56.07	5.96	13.08	56.11	5.79	13.01	3.00, 3.10	5.85 sh, 5.95, 6.10	
1c	178–180	96	$C_{15}H_{17}Cl_2N_3O_5$	46.17	4.39	10.77	45.88	4.44	10.64	3.05, 3.15	5.85, 5.95, 6.01	
2a	160–162	84	$C_{11}H_{19}N_3O_4S$	45.66	6.62	14.52	45.81	6.80	14.57	3.08, 3.24	5.87, 6.04	
2b	151–153	66	$C_{12}H_{19}N_3O_4S$	47.83	6.35	13.94	47.62	6.45	13.81	3.08, 3.22	5.84, 6.05	
2c	129–131	74[b]	$C_{15}H_{19}N_3O_4S$	53.40	5.68	12.45	53.47	5.73	12.56	3.10, 3.20	5.85, 6.03	
3a	180–181	85[a]	$C_9H_{12}N_4O_3$	45.28	5.70	26.40	45.47	5.55	26.57	3.02, 3.10	5.85 sh, 5.95, 6.01	4.51
3b	158–161	85	$C_{13}H_{14}N_4O_3$	56.93	5.15	20.43	56.73	5.12	20.25	3.07	5.85 sh, 5.97	4.51
3c	161–163	72	$C_{13}H_{12}Cl_2N_4O_3$	45.50	3.52	16.33	45.63	3.57	16.14	3.00, 3.08	5.85 sh, 5.91, 6.05	4.51
4a	141–142	90	$C_9H_{14}N_4O_2S$	44.61	5.82	23.12	44.59	5.99	23.01	3.02, 3.20	5.85 sh, 5.92	4.51
4b	139–141	68	$C_{10}H_{14}N_4O_2S$	47.23	5.55	22.03	47.10	5.68	21.68	3.20	5.85, 5.90 sh	4.51
4c	137–138	28	$C_{13}H_{14}N_4O_2S$	53.78	4.86	19.30	54.04	4.91	19.14	3.20	5.85	4.51

[a] Reaction in 50% aqueous ethanol. [b] Reaction in ethanol–THF, and solution cooled on ice to precipitate product.

and also to **6a** in 25% yield (Scheme II). The solubility differences of **5b** and **6a** allowed isolation of each in pure form. Conversion of **5b** to **6a** occurred in 75% yield in ethanol at reflux for 2 hr. The reaction of 4-phenylsemicarbazide with EMMN in ethanol at 23° led to **6b** in 32% yield. Attempts to obtain pure noncyclized product in this case were unsuccessful. The reactions of 4-ethyl- and 4-allyl-3-thiosemicarbazides with EMMN led to **7a** and **7b** in good yields. That the products are ring closed is indicated by the recovery of **7a** unchanged from ethanol at reflux for

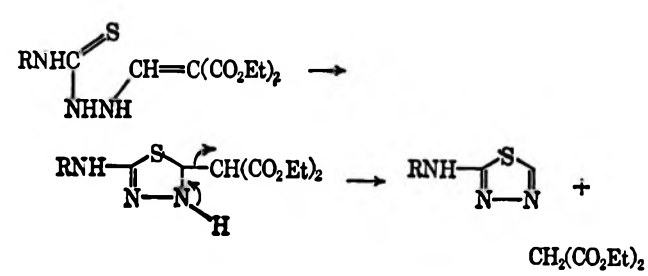
SCHEME II



4 hr and by the nmr spectrum of **7a** that shows one NH signal and one NH_2 singlet (in dimethyl sulfoxide-d_6). The intermediate thiosemicarbazidomethylenemalononitriles were not detected; cyclization of these derivatives apparently is extremely facile.

Attempted cyclization of **1a** in ethanol at reflux for 10 days led to 78% recovery of **1a**, while **1b** in ethanol at reflux for 4.6 days gave 1,6-diphenylbiurea, in 24% yield, through an undetermined pathway. Cyclization of **2a** and **2c** in hot ethanol was achieved; **2a** gave 2-ethylamino-1,3,4-thiadiazole (31% yield) and diethyl malonate (59%), and **2c** gave 2-anilino-1,3,4-thiadiazole (77%). This reaction (Scheme III) is quite similar to the preparation of 1,3,4-thiadiazoles from thiosemicarbazides and triethyl orthoformate reported by Whitehead and Traverso.[10]

SCHEME III

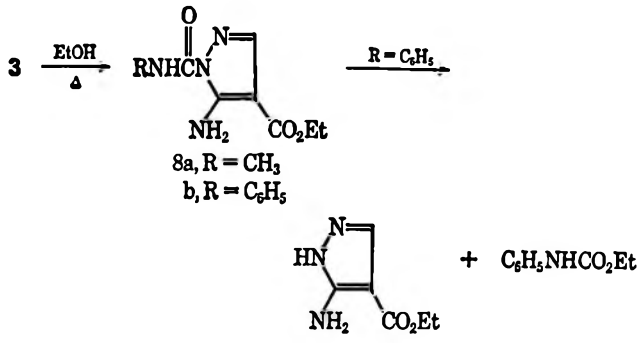


The major cyclization pathway taken by compounds **3** is the one leading to the 5-amino-1-carbamoyl-4-pyrazolecarboxylates (Scheme IV). In ethanol at reflux **3a** gave **8a** in 55% yield. Ethyl 5-amino-4-pyrazolecarboxylate was formed in 74% yield from **3b** in ethanol at reflux for 16 hr, *via* solvolysis of the

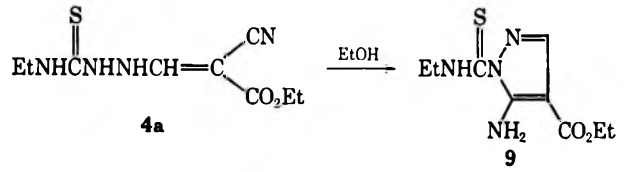
(10) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **77**, 5872 (1955).

intermediate **8b**. A shorter reaction time allowed isolation of **8b** in 15% yield.

SCHEME IV



Thiosemicarbazido-2-cyanoacrylates cyclize to 5-amino-4-pyrazolecarboxylates. Cyclization of **4a** in ethanol gave **9** in 59% yield. In hot ethanol **4c**



4a **9**

produced a mixture that contained ethyl 5-amino-4-pyrazolecarboxylate (19%) and 1,6-diphenyl-2,5-dithiobiurea (14%). The phenylthiocarbamoyl group is also readily lost from the ring nitrogen atom of pyrazoles in hot ethanol. The available data do not allow a choice to be made among the numerous possibilities for pathways leading to the biurea.

The present work illustrates that compounds of the type **1–5** are readily obtainable under mild reaction conditions and outlines the major cyclization pathways taken by these compounds. The previous literature and the present results show that uncatalyzed intramolecular cyclization into the ester group of 3-hydrazinoacrylates is difficult. Cyclization of diethyl phenylhydrazinomethylenemalonate to ethyl 1-phenyl-5-pyrazolon-4-carboxylate required a temperature of *ca.* 170°.[1] Thus compounds of type **1** do not readily cyclize to pyrazoles, and compounds of type **2** cyclize through an alternative pathway to thiadiazoles. In contrast, cyclization into the cyano group of 3-hydrazinoacrylonitriles is a relatively easy process.[2,3] Semicarbazido- and thiosemicarbazido-2-cyanoacrylates, and semicarbazido- and thiosemicarbazidomethylenemalononitriles readily cyclize into the cyano group in hot ethanol to 5-aminopyrazole derivatives. The methylenemalononitriles cyclize easier than the 2-cyanoacrylates, as expected from the relative electron withdrawing effects of a cyano substituent and a carbethoxy substituent α to the cyano group that undergoes nucleophilic attack in the cyclization reaction.

Experimental Section[11]

General Procedure for Semicarbazidomethylene Compounds.—A solution of the semicarbazide or thiosemicarbazide and 1.05 equiv of diethyl ethoxymethylenemalonate, ethyl 2-cyano-3-ethoxyacrylate, or ethoxymethylenemalononitrile in ethanol is held overnight at 20–25°. The resultant solid is collected and washed with ethanol.

4-(3,4-Dichlorophenyl)semicarbazide.—A solution of 215 g (1.15 mol) of 3,4-dichlorophenyl isocyanate in 2 l. of ether was added slowly to 298 g (8 equiv) of hydrazine in ether with stirring and cooling. The temperature was maintained below 20°. After the addition was completed, the ether layer was decanted from an oily layer. Dilution of the oily layer with water produced a solid, which, after vacuum drying, weighed 237.5 g. This material was recrystallized from ethanol, with filtration to remove the insoluble 1,6-bis(3,4-dichlorophenyl)-biurea, to give 108.6 g of solid, mp 175–177°. This solid was recrystallized from 700 ml of ethyl acetate (filtration) to give 77.3 g (30%) of solid: mp 173–175°; ir 3.00, 3.10 (NH), 5.90 μ (C=O). *Anal.* Calcd for $C_7H_7Cl_2N_3O$: C, 38.20; H, 3.20; N, 19.09. Found: C, 38.38; H, 3.28; N, 18.99.

Diethyl [(4-methylsemicarbazido)methylene]malonate (1a) (see Table I) had nmr τ 0.27 (broad d, 1, J = 11 Hz, NHCH=C), 1.32 (bs, 1, NH), 2.25 (d, 1, J = 11 Hz, NHCH=C), 3.51 (b, 1, CH_3NH), 5.87 (q, 2, J = 7 Hz, OCH_2CH_3), 5.92 (q, 2, J = 7 Hz, OCH_2CH_3), 7.40 (d, 3, J = 4.5 Hz, CH_3NH), 8.78 (t, 6, J = 7 Hz, OCH_2CH_3).

Diethyl [(4-phenylsemicarbazido)methylene]malonate (1b) (see Table I) had nmr τ −0.05 (broad d, 1, J = 11 Hz, NHCH=C), 0.92 (s, 1, NH), 1.13 (s, 1, NH), 2.05 (d, 1, J = 11 Hz, NHCH=C), 2.3–3.1 (m, 5, C_6H_5), 5.83 (m, 4, OCH_2CH_3), 8.77 (t, 6, J = 7 Hz, OCH_2CH_3).

Ethyl 2-cyano-3-(4-methylsemicarbazido)acrylate (3a) (see Table I) had nmr τ −0.04 (bs, 1, NH), 1.38 (b, 1, NH), 2.21 (s, 1, CH=C), 3.53 (bm, 1, CH_3NH), 5.86 (q, 2, J = 7 Hz, OCH_2CH_3), 7.39 (d, 3, J = 4.5 Hz, CH_3NH), 8.79 (t, 3, J = 7 Hz, OCH_2CH_3).

Ethyl 2-cyano-3-(4-phenylsemicarbazido)acrylate (3b) (see Table I) had nmr τ −0.10 (bs, 1, NH), 1.14 (b, 2, NH), 2.12 (s, 1, CH=C), 2.35–3.15 (m, 5, C_6H_5), 5.85 (q, 2, J = 7 Hz, OCH_2CH_3), 8.78 (t, 3, J = 7 Hz, OCH_2CH_3).

Ethyl 2-Cyano-3-(4-phenyl-3-thiosemicarbazido)acrylate (4c).—A solution of 50 g (0.299 mol) of 4-phenyl-3-thiosemicarbazide and 52.4 g (1.05 equiv) of ethyl 2-cyano-3-ethoxyacrylate in ethanol–tetrahydrofuran was allowed to stand overnight. The resultant solid, 10.6 g (23%), mp 178–179° (lit.[12] mp 173°), was collected and identified as 1,6-diphenyl-2,5-dithiobiurea from the ir and nmr spectra.

Anal. Calcd for $C_{14}H_{14}N_4S_2$: C, 55.60; H, 4.67; N, 18.53; S, 21.20. Found: C, 55.73; H, 4.76; N, 18.49; S, 20.94.

Concentration of the filtrate gave 31.5 g of solid, mp 131–148°. The solid was dissolved in 600 ml of tetrahydrofuran at 35°, the solution was cooled on ice, and water was added to the cloud point. The resultant solid was collected and washed well with ethanol to give 23.9 g (28%) of **4c**: mp 137–138°, resolidified at 138° and remelted at 144–146° (see Table I).

Semicarbazidomethylenemalononitrile (5a).—To a solution of 11.1 g (0.10 mol) of semicarbazide hydrochloride in 75 ml of water was added 8.2 g (0.10 mol) of sodium acetate. To the resultant solution was added 12.2 g of ethoxymethylenemalononitrile in 175 ml of ethanol. The clear solution slowly deposited solid. After 1.5 hr, the solid was collected and washed with 35 ml of water. There resulted 5.5 g of solid, mp 169°, with melting and rapid resolidification: ir 2.9, 3.08 (NH), 4.51 (CN), 5.96 (C=O), 6.12 μ (amide II); nmr τ −0.40 (s, 1, NH), 1.28, 1.40 (singlets, 0.3 H and 0.7 H, NHCH=C), 2.03, 2.38 (singlets, 0.3 H and 0.7 H, NHCH=C), 3.83 (bs, 2, NH_2).

Anal. Calcd for $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.60; H, 3.18; N, 46.18.

(4-Methylsemicarbazido)methylenemalononitrile (5b) and 5-Amino-4-cyano-N-methyl-1-pyrazolecarboxamide (6a).—A solution of 40 g (0.45 mol) of 4-methylsemicarbazide in 50% aqueous ethanol was added to 57.5 g (1.05 equiv) of ethoxymethylenemalononitrile in ethanol. The solution was allowed to stand overnight. The resultant solid, 3.7 g, mp 171–174°, was collected. The filtrate was concentrated under vacuum below 30° to give 38.8 g (52%) of **5b**: mp 148–150°; ir 3.00, 3.20 (NH), 4.51 (CN), 5.90 μ (C=O); nmr τ −0.53 (b, 1, NH), 1.17, 1.24 (singlets, 0.25 H and 0.75 H, NHCH), 1.93, 2.05 (singlets,

(11) Melting points were determined with a Mel-Temp apparatus in open capillary tubes and are corrected. Nmr spectra were determined on a Varian A-60 spectrometer with dimethyl sulfoxide-d_6 solvent and internal tetramethylsilane standard. Ir spectra were determined on the compounds in mineral oil mulls on a Beckman IR-5 spectrometer.

(12) S. L. Jannah and P. C. Guha, *J. Indian Inst. Sci.*, **16A**, 11 (1963); *Chem. Abstr.*, **27**, 3711 (1933).

0.25 H and 0.75 H, NHCH), 3.42 (m, 1, CH_3NH), 7.73 (d, 3, J = 4.5 Hz, CH_3NH).

Anal. Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.86; H, 4.36; N, 42.63.

The filtrate from **5b** after standing overnight gave 21.2 g of solid, mp 172–175°. This solid was combined with the 3.7 g of solid, mp 171–174°; 24.9 g of solid was dissolved in warm water, and the solution was cooled on ice to give 18.3 g (25%) of **6a**: mp 173–175°; ir 2.9–3.1 (NH), 4.51 (CN), 5.85 μ (C=O); nmr τ 1.72 (b, 1, CH_3NH), 2.16 (s, 1, CH=), 2.33 (b, 2, NH_2), 7.21 (d, 3, J = 5 Hz, CH_3NH).

Anal. Found: C, 43.43; H, 4.30; N, 42.15.

A 2-g sample of **5b** in ethanol was held 2 hr at reflux. Upon cooling the solution produced 1.5 g (75%) of **6a**, mp 175–177°, identified by ir and nmr spectra and by melting point.

5-Amino-4-cyano-N-phenyl-1-pyrazolecarboxamide (6b).—A solution of 25 g (0.165 mol) of 4-phenylsemicarbazide and 21.2 g (1.05 equiv) of ethoxymethylenemalononitrile in 450 ml of ethanol was allowed to stand overnight. The solution was concentrated. The solid residue was extracted with hot acetone, and the insoluble solid was removed by filtration. The filtrate was concentrated and cooled on ice to give 11.7 g (32%) of **6b**: mp 171–173°; ir 2.9–3.1 (NH), 4.51 (CN), 5.80 μ (C=O).

Anal. Calcd for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.32; H, 4.01; N, 30.89.

5-Amino-4-cyano-N-ethyl-1-pyrazolethiocarboxamide (7a).—A solution of 25 g (0.210 mol) of 4-ethyl-3-thiosemicarbazide and 26.8 g (1.05 equiv) of ethoxymethylenemalononitrile in ethanol was allowed to stand overnight. The resultant solid, mp 146–148°, weighed 33.4 g (81%): ir 3.06 (NH), 4.51 μ (CN); nmr τ −0.24 (bs, 1, NH), 1.30 (bs, 2, NH_2), 2.03 (s, 1, CH=), 6.33 (bq, 2, NCH_2CH_3), 8.79 (t, 3, NCH_2CH_3).

Anal. Calcd for $C_7H_9N_5S$: C, 43.06; H, 4.65; N, 35.87. Found: C, 43.18; H, 4.65; N, 35.92.

A sample of **7a** was recovered unchanged after 4 hr at reflux in ethanol.

N-Allyl-5-amino-4-cyano-1-pyrazolethiocarboxamide (7b).—A solution of 15 g (0.114 mol) of 4-allyl-3-thiosemicarbazide and 14.6 g (1.05 equiv) of ethoxymethylenemalononitrile in ethanol was allowed to stand overnight. The resultant solid, mp 135–137°, weighed 18.3 g (77.5%): ir 3.06 (NH), 4.51 μ (CN); nmr τ −0.23 (bt, 1, NH), 1.35 (bs, 2, NH_2), 2.10 (s, 1, CH=), 3.7–5.0 (m, 3, CH_2=CH–), 5.73 (bm, 2, CH_2=$CHCH_2$–).

Anal. Calcd for $C_8H_9N_5S$: C, 46.36; H, 4.38; N, 33.79. Found: C, 46.48; H, 4.31, N, 34.01.

Attempted Cyclization of 1a.—A solution of 5 g of **1a** in ethanol was held at reflux 10 days and then was cooled on ice. There was obtained 3.9 g of **1a**, mp 191–194°, the ir spectrum of which was identical with that of starting material.

Attempted Cyclization of 1b.—A solution of 5 g of **1b** in ethanol was held at reflux 110 hr. The odor of diethyl malonate was evident. The solid obtained, mp 241–243°, 0.5 g (24%), possessed an ir spectrum identical with that of authentic 1,6-diphenylbiurea (lit.[13] mp 242–243°).

2-Ethylamino-1,3,4-thiadiazole from 2a.—A solution of 15 g of **2a** in ethanol was held 28 hr at reflux. The solvent was removed under vacuum, and the residual oil was partially distilled to give 4.9 g (59%) of liquid distillate, bp 61–63° (2.5 mm), identified as diethyl malonate from the ir spectrum, and 5.0 g of pot residue. The residue was chromatographed on neutral, activity I alumina. With 2% ethanol in benzene 2.1 g (31%) of 2-ethylamino-1,3,4-thiadiazole, mp 70–71° (lit.[10] mp 70°), was eluted: ir 3.00 μ (NH), no C=O, strong 6.6-μ absorption; nmr τ 1.37 (s, 1, CH=), 2.28 (bs, 1, NH), 6.66 (m, 2, CH_2CH_3), 8.80 (t, 3, J = 7 Hz, CH_2CH_3).

(13) L. Horner and H. Fernekess, *Chem. Ber.*, **94**, 712 (1961).

2-Anilino-1,3,4-thiadiazole from 2c.—A solution of 5 g of **2c** in ethanol was held 24 hr at reflux. Concentration and cooling of the solution yielded 2-anilino-1,3,4-thiadiazole, 2.0 g (77%), mp 173–175° (lit.[10] mp 173°).

Ethyl 5-Amino-1-(methylcarbamoyl)-4-pyrazolecarboxylate (8a) from 3a.—A 15-g sample of **3a** in ethanol was held 18 hr at reflux and then was cooled on ice. The resultant solid, 5.6 g, mp 131–133°, was collected: ir 2.90, 2.99 (NH), 5.80 (C=O), 5.96 μ (ester C=O); nmr τ 1.98 (broad, 1 H, CH_3NH), 2.28 (s, 1, CH), 2.85 (broad, 2, NH_2), 5.77 (q, 2, J = 7 Hz, OCH_2CH_3), 7.19 (d, 3, J = 5 Hz, CH_3NH), 8.71 (t, 3, J = 7 Hz, OCH_2CH_3). The filtrate was held at reflux an additional 16 hr and was again cooled to produce another 2.6 g of solid, mp 131–133°. The total yield was 55%.

Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.58; H, 5.81; N, 26.14.

Ethyl 5-Amino-4-pyrazolecarboxylate from 3b.—A 15-g sample of **3b** in ethanol was held 16 hr at reflux and then was cooled on ice. The resultant solid, 0.3 g (4%), mp 245–247°, was identified from the ir spectrum as 1,6-diphenylbiurea. The filtrate was concentrated under vacuum, and the residue was crystallized from benzene to give 6.3 g (74%) of ethyl 5-amino-4-pyrazolecarboxylate, mp 100–102° (lit.[2] mp 102–103°), identified from the ir and nmr spectra: ir 2.90, 3.11 (NH), 6.00 μ (C=O); nmr τ −1.85 (b, 1, NH), 2.40 (s, 1, CH=), 4.22 (b, 2, NH_2), 5.82 (q, 2, J = 7 Hz, OCH_2CH_3), 8.76 (t, 3, J = 7 Hz, OCH_2CH_3).

Ethyl 5-Amino-1-(phenylcarbamoyl)-4-pyrazolecarboxylate (8b) from 3b.—A mixture of 12 g of **3b** and ethanol was held at reflux 6.5 hr, the resultant solution was cooled on ice, and 0.3 g of 1,6-diphenylbiurea, mp 238–241°, was collected. The filtrate was concentrated and cooled on ice to give 1.8 g (15%) of solid, mp 119–121°. This solid was crystallized from ethyl acetate to give 0.9 g of solid: mp 125–127°; ir 2.90, 3.02 (NH), 5.81 (C=O), 5.98 μ (ester C=O); nmr τ −0.20 (s, 1, NH), 2.05–2.95 (m, 8, C_6H_5, CH=, NH_2), 5.71 (q, 2, J = 7 Hz, OCH_2CH_3), 8.70 (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.74; H, 5.23; N, 20.29.

Ethyl 5-Amino-1-(ethylthiocarbamoyl)-4-pyrazolecarboxylate (9) from 4a.—A mixture of 10 g of **4a** and ethanol was held 1 hr at reflux. The solution was concentrated and cooled on ice to produce 5.9 g (59%) of **9**: mp 88–89°; ir 2.98, 3.07 (NH), 5.95 μ (C=O); nmr τ −0.12 (b, 1, NH), 1.82 (b, 2, NH_2), 2.21 (s, 1, CH=), 5.75 (q, 2, J = 7 Hz, OCH_2CH_3), 6.33 (q, 2, J = 7 Hz, NCH_2CH_3), 8.76 (m, 6, OCH_2CH_3, NCH_2CH_3).

Anal. Calcd for $C_{19}H_{14}N_4O_2S$: C, 44.61; H, 5.82; N, 23.12. Found: C, 44.78; H, 5.86; N, 23.16.

Cyclization of 4c.—A mixture of 5 g of **4c** in ethanol was held 11 hr at reflux and then was filtered hot to remove 0.4 g (14%) of 1,6-diphenyl-2,5-dithiobiurea (ir identification). The filtrate was concentrated under vacuum, and the residue was crystallized from benzene to give 0.6 g of unidentified solid. From the filtrate was obtained 0.5 g (19%) of impure 5-amino-4-pyrazolecarboxylate (ir identification).

Registry No.—**1a**, 19359-71-8; **1b**, 19359-72-9; **1c**, 19359-73-0; **2a**, 19359-74-1; **2b**, 19359-75-2; **2c**, 19359-76-3; **3a**, 19375-48-5; **3b**, 19375-49-6; **3c**, 19375-50-9; **4a**, 19375-51-0; **4b**, 19375-52-1; **4c**, 19375-53-2; **5a**, 19375-54-3; **5b**, 19375-55-4; **6a**, 19375-56-5; **6b**, 19375-57-6; **7a**, 19375-58-7; **7b**, 19375-59-8; **8a**, 19375-60-1; **8b**, 19375-61-2; **9**, 19375-62-3; 4-(3,4-dichlorophenyl)semicarbazide, 19375-63-4.

A New Synthesis of Unsaturated Acids. V. Application to Cycloalkene-1-carboxylic and β,γ-Unsaturated Acids[1]

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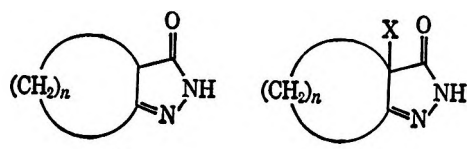
The method of converting 4-halo-4-substituted 2-pyrazolin-5-ones into α,β-unsaturated acids by treatment with aqueous alkali has been extended to the 3,4-polymethylene derivatives (II, X = Cl or Br; n = 4–6) although the reaction was unsuccessful in the case of the trimethylene derivative (II, X = Cl or Br; n = 3). It has also been possible to extend the reaction to the synthesis of β,γ-unsaturated acids. Treatment of 3-(bromomethyl)-4,4-dimethyl-2-pyrazolin-5-one (X) with sodium hydroxide gave 2,2-dimethyl-3-butenoic acid. The precursor (X) was obtained by treatment of ethyl γ-bromo-α,α-dimethylacetoacetate with hydrazine or NBS bromination of 1-acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (XIII).

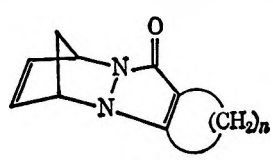
Previous studies[2,3] have demonstrated the generality of the conversion of 4,4-dihalo- and 4-substituted 4-halo-2-pyrazolin-5-ones to α,β-unsaturated acids upon treatment with aqueous alkali. In the present paper we describe extensions of this reaction to two special cases, cycloalkene-1-carboxylic acids for which previously described synthetic methods[4–7] are not completely satisfactory, and β,γ-unsaturated acids. In view of the



I II

earlier demonstration[2b,3] that it is the labile isomer which predominates in the case of acyclic α,β-olefinic acids, it seemed possible that its application in the cyclic series might allow eventual development of a synthetic route to the unique, unknown *trans* isomers of the higher ring acids.[8] A series of 3,4-polymethylene-4-halo-2-pyrazolin-5-ones (II, X = Cl or Br, n = 3–6) has been prepared and studied. The precursor β-keto esters were obtained from the corresponding cycloalkanones by methods cited in Table I. Halogenation of the pyrazolones was carried out by treatment with chlorine in methylene chloride, bromine in acetic acid, or, most conveniently, by the use of N-bromosuccinimide in carbon tetrachloride. Both the 4-chloro- and 4-bromo-3,4-trimethylene-2-pyrazolones (II, X = Cl or Br, n = 3) were too unstable to be purified for elemental analysis. In the cases of the chloro and bromo derivatives of the 3,4-tetra-, -penta-, and -hexamethylene-2-pyrazolin-5-ones (II, X = Cl or Br, n = 4–6) alkaline degradation gave the corresponding cycloalkene-1-carboxylic acids in moderate-to-fair yields, consistently better in the bromo series (30–70% in comparison with yields of 19–50% for the analogous chloro derivatives). In the case of the hexamethylene derivative (II, X = Cl or Br, n = 6) only the known[9] *cis* acid was obtained. Thus the driving force[2b,3] favoring the labile isomer of a geometric pair of α,β-olefinic acids is not sufficient to overcome the natural reluctance of a 1-substituted cyclooctene to support the strained *trans* structure.[9,10] Whether the present method will be applicable to the synthesis of the larger ring *trans*-cycloalkene-1-carboxylic acids remains to be determined.

As in the previous work[3] it has been possible in two cases (II, X = Cl or Br, n = 5,6) to demonstrate the labile intermediacy in these reactions of fused diazacyclopentadienones by trapping reactions with cyclopentadiene.[11] Curiously the 3,4-trimethylene derivative (II, X = Cl or Br, n = 3) gave no cyclopentene-1-carboxylic acid. In this case treatment with aqueous alkali gave only a charcoal-like cindery material which could not be identified. In an effort to determine whether this effect was general for other pyrazolones bridged by three methylene units, attempts were made to obtain pyrazolones from 2-carbethoxy-1-indanone,[12] 1-carbethoxy-2-indanone[13] and 3-carbethoxycamphor[14] but in no case could the appropriate compounds be made by reaction of the β-keto esters with hydrazine. In addition trapping experiments with II (X = Cl or Br, n = 3) in the presence of triethylamine and cyclopentadiene at −80° gave the same cindery material obtained at higher temperatures in the presence of aqueous alkali. However, in one case a trace of a crystalline white substance was isolated which on the basis of spectral data is believed to be the adduct (III, n = 3) derived from the appropriate diazacyclo-



III

pentadienone and cyclopentadiene. In the cases of the

(1) Abstracted from a portion of the Ph.D. thesis of E. G. S. Rundberg, Jr., 1967.

(2) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **80**, 599 (1958); (b) *ibid.*, **80**, 601 (1958); (c) *ibid.*, **80**, 5796 (1958).

(3) L. A. Carpino, P. H. Terry, and S. D. Thatte, *J. Org. Chem.*, **31**, 2867 (1966).

(4) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950).

(5) E. A. Braude, W. F. Forbes, and E. A. Evans, *ibid.*, 2202 (1953).

(6) A. C. Cope, M. Burg, and S. W. Fenton, *J. Amer. Chem. Soc.*, **74**, 173 (1954).

(7) O. H. Wheeler and I. Lerner, *ibid.*, **78**, 63 (1956).

(8) The patent literature contains an unconfirmed report of the isolation of a pair of cycloundecene-1-carboxylic acids; see Pierre Lafont and Y. Bonnett, German Patent 1,145,169 (March 14, 1963); *Chem. Abstr.*, **59**, 7392*h* (1963).

(9) E. A. Braude, W. F. Forbes, B. F. Gofton, R. P. Houghton, and E. S. Waight, *J. Chem. Soc.*, 4711 (1957).

(10) *Cf.* A. C. Cope, E. Ciganek, C. F. Howell, and E. E. Schweizer, *J. Amer. Chem. Soc.*, **82**, 4663 (1960).

(11) Since our earlier studies B. T. Gillis and R. Weinkham [*J. Org. Chem.*, **32**, 3321 (1967)] have generated and trapped similar intermediates by the oxidation of pyrazolones with lead tetraacetate in the presence of cyclopentadiene.

(12) W. H. Perkin and A. F. Titley, *J. Chem. Soc.*, **121**, 1562 (1922).

(13) A. F. Titley, *ibid.*, 2571 (1928).

(14) T. F. Dankova, L. G. Evdokimova, I. I. Stepanov, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **18**, 1724 (1948); *Chem. Abstr.*, **43**, 2606 (1946).

TABLE I

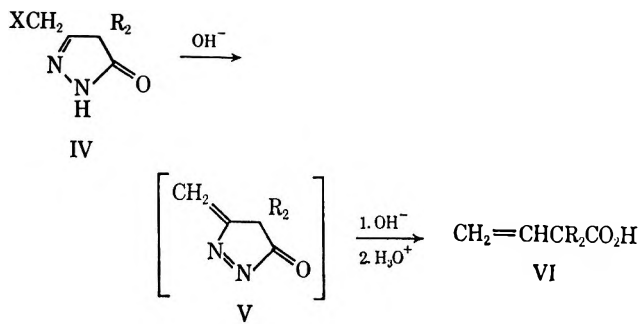
3,4-POLYMETHYLENE-2-PYRAZOLIN-5-ONES (II)[a-d]

X	n	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	Br (Cl)	Found, % C	H	N	Br (Cl)
Cl[e]	3	79	117–118 dec	$C_6H_7ClN_2O$								
Br[e]	3	53	102–103 dec	$C_6H_7BrN_2O$								
Cl	4	58	112.5–113	$C_7H_9ClNO_2$	48.71	5.25	16.23	(20.54)	48.59	5.25	16.02	(20.41)
H	5	96	211–212 dec	$C_8H_{12}N_2O$	63.14	7.94	18.46		63.28	8.03	18.42	
Cl	5	40	54–55.5	$C_8H_{11}ClN_2O$	51.48	5.94	15.00	(18.99)	51.36	6.02	14.80	(18.79)
Br	5	61	80–80.5	$C_8H_{11}BrN_2O$	41.58	4.80	12.12	34.58	41.70	4.81	11.98	34.44
H	6	88	230–232 dec	$C_9H_{14}N_2O$	65.03	8.48	16.86		65.03	8.36	16.93	
Cl	6	69	73–75	$C_9H_{13}ClN_2O$	53.88	6.53	13.96	(17.67)	53.97	6.73	13.83	(17.53)
Br	6	79	85.5–86.3	$C_9H_{13}BrN_2O$	44.10	5.34	11.43	32.60	44.23	5.51	11.37	32.53

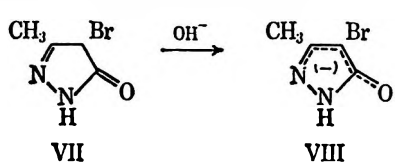
[a] The 4-unsubstituted 3,4-polymethylene-2-pyrazolin-5-ones were obtained by modifications of standard techniques; see W. Dieckmann, *Ann.*, **317**, 60 (1901). [b] Chlorination was carried out using molecular chlorine in methylene chloride; bromination by means of molecular bromine in acetic acid or N-bromosuccinimide in carbon tetrachloride. The yields given in the table are those obtained by the latter method. An example is given in the Experimental Section. [c] The precursor 2-carbethoxycycloalkanones were obtained by three general methods: (1) the Stork enamine technique [*n* = 4; G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963)]; (2) carbethoxylation by diethyl carbonate–sodium hydride [*n* = 4, 5, 6; S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, 19, 1625 (1963)]; and (3) carbethoxylation by triethyl phosphonoformate-sodium hydride [*n* = 4; I. Shahak, *Israel J. Chem.*, **3** (No. 4a), 45 (1966); *Tetrahedron Lett.*, 2201 (1966)]. [d] The halopyrazolones were recrystallized from benzene–ligroin. [e] This compound was too unstable to be purified for elemental analysis. Spectral data (infrared and nmr) confirmed the structure.

penta- and hexamethylene pyrazolones no difficulty was experienced in obtaining the corresponding adducts (III, $n = 5$ or 6).

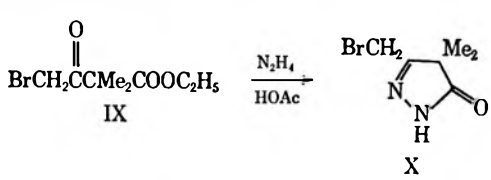
The second extension of the halopyrazolone reaction examined in the present work involved its possible use in the synthesis of acids having unsaturation at the β,γ position. By assuming a mechanism analogous to that which has been demonstrated to be likely in the case of 4-substituted 4-halopyrazolones it would be expected that a 3-(halomethyl) derivative such as IV would yield the corresponding β,γ-olefinic acid VI



through the intermediacy of the methylene diazacyclopentenone V. As a model a 4,4-disubstituted pyrazolone was chosen in order to avoid possible complication due to the formation of a stable anion from a 4-substituted pyrazolone. Thus, in contrast to the cases of 3,4-dimethyl-4-bromo- and 3-methyl 4,4-dibromo-2-pyrazolin-5-ones, 3-methyl-4-bromo-2-pyrazolin-5-one[15] (VII) does not undergo the alkaline degradation reaction presumably because of the stability of anion VIII, from which loss of bromide ion is precluded.



An appropriate substrate, 3-(bromomethyl)-4,4-dimethyl-2-pyrazolin-5-one (IV, X = Br; R = CH_3), was obtained by two procedures, one of which promises to be of general utility. The first approach involved the carefully controlled reaction of ethyl γ-bromo-α,α-dimethylacetoacetate (IX) with hydrazine in ethanol in the presence of acetic acid.[16] Since the method was

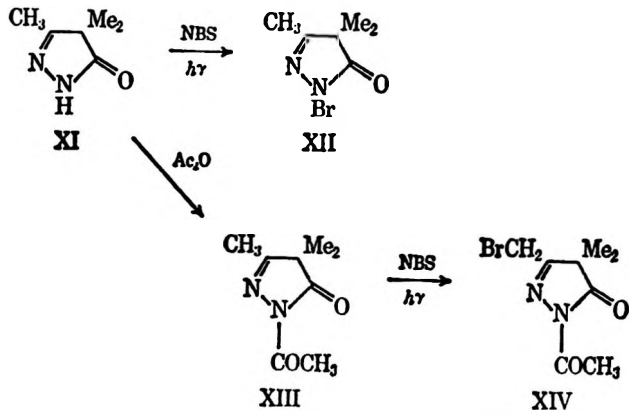


tedious and the yield poor, other approaches were sought. Although direct NBS bromination of 3,4,4-trimethyl-2-pyrazolin-5-one (XI) gave the N-bromo derivative (XII)[17] as expected, use of the N-acetyl derivative (XIII) allowed bromination at the 3-methyl group. Unexpectedly the 3-bromomethylpyrazolone (X) was obtained directly, the first-formed N-acetyl derivative XIV being presumably hydrolyzed during the reaction or the subsequent work-up. Treatment

(15) E. Muckermann, *Ber.*, **42**, 3449 (1909).

(16) This method was first applied by Paul H. Terry (Ph.D. Thesis, University of Massachusetts, 1963).

(17) R. Hüttel, E. Wagner, and B. Sickenberger, *Ann.*, **607** 109 (1957).



of X with aqueous sodium hydroxide at 0° was accompanied by vigorous gas evolution and gave 2,2-dimethyl-3-butenoic acid in 37% yield. No direct evidence has yet been obtained relative to the postulated occurrence of V as a labile intermediate in this reaction.

Experimental Section[18]

4-Bromo-3,4-tetramethylene-2-pyrazolin-5-one (II, X = Br, n = 4).—A suspension of 1.38 g of 3,4-tetramethylene-2-pyrazolin-5-one[19] and 1.78 g of N-bromosuccinimide in 80 ml of CCl_4 was stirred for 2 hr while irradiating with a 275-W sun lamp (Westinghouse). The reaction mixture was cooled, filtered and the filtrate evaporated from a water bath with the aid of a water aspirator to give an orange solid. The solid was treated successively with eight 50-ml portions of hot ligroin (bp 60–70°), the ligroin evaporated and the resulting solid recrystallized from benzene–ligroin (bp 60–70°) (1:9) to give 1.43 g (66.9%) of the pyrazolone as pale yellow platelets: mp 126.5–128°; ir ($CHCl_3$) 3475, 1725, 1610 cm^{-1}; nmr ($CDCl_3$) δ 1.10–2.85 (complex multiplet, 8 H), 9.95 (broad singlet, 1 H). Related compounds were made similarly. Chlorination was carried out as previously described.[2] In most cases bromination could be carried out with free bromine in acetic acid but the products were less easily purified than those obtained by the NBS procedure given here. The results are collected in Table I.

Anal. Calcd for $C_7H_9BrN_2O$: C, 38.73; H, 4.18; Br, 36.81; N, 12.90. Found: C, 38.86; H, 4.33; Br, 36.65; N, 12.75.

7,8-Pentamethylene-1,4-methano-1,4-dihydropyrazolo[1,2-a]-pyridazin-6-one (III, n = 5).—To a stirred, ice-cold solution of 2.31 g of 4-bromo-3,4-pentamethylene-2-pyrazolin-5-one and 3.3 g of freshly cracked cyclopentadiene in 100 ml of anhydrous ether there was added 1.21 g of triethylamine. After 2 hr in the ice bath, the mixture was filtered and the filtrate evaporated to give a solid which was dissolved in the minimum amount of ether and the solution cooled in a Dry Ice–acetone bath. Rapid filtration gave 1.04 g (48%) of the adduct as pale yellow flakes: mp 117.5–118.3° dec; ir ($CHCl_3$) 1645, 1605, 2990, 2930, 2860 cm^{-1}; nmr ($CDCl_3$) δ 1.0–2.73 (complex multiplet, 12 H), 4.73 (broad singlet, 1 H), 5.08 (broad singlet, 1 H), 5.80–5.95 (multiplet, 1 H), 6.00–6.20 (multiplet, 1 H).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.40; H, 7.59; N, 13.11.

7,8-Pentamethylene-1,4-methano-1,2,3,4-tetrahydropyrazolo-[1,2-a]pyridazin-6-one.—Hydrogenation of the above adduct in THF over 10% Pd–C on a Parr apparatus at 46 psi gave the dihydro derivative: mp 116–117° (methylene chloride–petroleum ether, bp 30–59°); ir ($CHCl_3$) 1615, 2980, 2940, 2870 cm^{-1}; nmr ($CDCl_3$) δ 1.0–2.85 (complex multiplet, 16 H), 4.48 (broad singlet, 1 H), 4.77 (broad singlet, 1 H). The same compound, identified by infrared spectral comparison, was obtained by reaction of 2-carbethoxycycloheptanone,[20,21] with 2,3-diazabicyclo[2.2.1]heptane hydrochloride.[3,22]

Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.36; H, 8.25; N, 13.01.

7,8-Hexamethylene-1,4-methano-1,4-dihydropyrazolo[1,2-a]-pyridazin-6-one (III, n = 6) was obtained as described for the corresponding pentamethylene analog, mp 98–98.5°.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.93; H, 8.03; N, 12.06.

***cis*-Cyclooctene-1-carboxylic Acid.**—Treatment of 4-bromo-3,4-hexamethylene-2-pyrazolin-5-one (II, X = Br; n = 6) with ice-cold aqueous NaOH as described earlier[2] gave *cis*-cyclooctene-1-carboxylic acid in 65.7% yield, mp 100.5–102° (lit.[6] mp 101.8–102.6°). From the corresponding chloro derivative the yield was 46.7%. The related cyclohexene- and cycloheptene-1-carboxylic acids were obtained similarly in 29.8 and 70% yields from the bromopyrazolones and 19 and 50% yields from the chloropyrazolones, respectively.

1-Acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (XIII).—A solution of 12.6 g of 3,4,4-trimethyl-2-pyrazolin-5-one[23] in 50 ml of acetic anhydride was refluxed for 6 hr, the mixture cooled, excess anhydride removed by evaporation from a water bath with the aid of a water aspirator and the residue recrystallized from ligroin (bp 60–70°) to give 14.6 g (86.9%) of the 1-acetyl derivative[24] as yellow needles: mp 112–113°; ir ($CHCl_3$) 1785, 1755, 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (singlet, 6 H), 2.15 (singlet, 3 H), 2.57 (singlet, 3 H).

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 57.29; H, 7.33; N, 16.46.

3-Bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (X). A.—From 1-Acetyl-3,4,4-trimethyl-2-pyrazolin-5-one.—A stirred solution of 8.40 g of the 1-acetylpyrazolone and 9.79 g of N-bromosuccinimide in 200 ml of CCl_4 was irradiated with a 275-W sun lamp (General Electric) for 10.5 hr. The mixture was cooled, succinimide removed by filtration and the residue obtained on evaporation of the filtrate by means of a current of air was recrystallized from benzene–ligroin (bp 60–70°) to give 4.67 g (53%) of the pyrazolone as pale yellow needles, mp 135.5–137°.

B.[16] From Ethyl γ-Bromo-α,α-dimethylacetoacetate.—To a stirred solution of 47.4 g of the β-keto ester[25] and 12.5 g of acetic acid in 180 ml of 60% aqueous ethanol there was added dropwise over 30 min a solution of 10 g of hydrazine hydrate (100%) in 60 ml of ethanol. The solution was stored in a refrigerator at 5° for 17 days, treated with 175 ml of water and extracted with 800 ml of ether in a liquid–liquid extractor for 3 days. Recrystallization of the residue obtained after evaporation of the ether extracts gave 16.4 g (40%) of the bromomethylpyrazolone, mp 135–136.5°, identified by comparison with a sample prepared as described in A: ir ($CHCl_3$) 3400, 1735 cm^{-1}; nmr ($CDCl_3$) δ 1.40 (singlet, 6 H), 4.21 (singlet, 2 H) and 10.06 (broad singlet, 1 H).

Anal. Calcd for $C_6H_9BrN_2O$: C, 35.14; H, 4.92; Br, 38.97; N, 13.66. Found: C, 35.33; H, 4.58; Br, 38.96; N, 13.57.

2,2-Dimethyl-3-butenoic Acid.—To an ice cold, stirred solution of 50 ml of 2 *N* NaOH there was added 4.1 g of 3-bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (X). The reaction mixture was stirred for 1 hr at ice bath temperatures and for 2 hr at room temperature. Acidification by means of concentrated HCl (Congo red), saturation with NaCl and extraction with eight 25-ml portions of ether gave 0.84 g (36.8%) of the acid after distillation, bp 184–187° (lit.[26] bp 185°). The *dibromo derivative* had mp 90–91.5° (lit.[27] mp 89–91°).

Registry No.—II, X = Cl, n = 3, 19462-57-8; II, X = Br, n = 3, 19462-58-9; II, X = Cl, n = 4, 19462-59-0; II, X = Br, n = 4, 19462-60-3; II, X = H, n = 5, 19462-61-4; II, X = Cl, n = 5, 19462-62-5; II, X = Br, n = 5, 19462-63-6; II, X = H, n = 6, 19462-64-7; II, X = Cl, n = 6,

(18) Elemental analyses are by A. Bernhardt, Mülheim (Ruhr), Germany. All melting and boiling points are uncorrected. Infrared spectra were recorded on Beckman IR-5 and IR-10 spectrophotometers. Nmr data were obtained on a Varian A-60 instrument in deuteriochloroform using TMS as internal standard.

(19) W. Dieckmann, *Ann.*, **317**, 60 (1901).

(20) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

(21) C. E. Sullivan, M. S. Thesis, Florida State University, 1962.

(22) O. Diels, J. H. Blom, and W. Koll, *Ann.*, **443**, 242 (1925).

(23) P. E. Verkade and J. Dhont, *Rec. Trav. Chim. Pays-Bas*, **64**, 165 (1945).

(24) A compound presumed to have structure XIII was first described by von Rothenberg [*J. Prakt. Chem.*, [2] **50**, 227 (1894)] but his formulation has now been shown to be incorrect. von Rothenberg claimed to have obtained XIII from the precursor XI which he described as having mp 268°. Subsequently Verkade and Dhont[23] showed that authentic XI had mp 108.5–109.5°.

(25) M. Conrad and R. Gast, *Ber.* **31**, 2726 (1898).

(26) A. Courtot, *Bull. Soc. Chim. Fr.*, [3] **35**, 111 (1906).

(27) H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, **76**, 5403 (1954).

19462-65-8; II, X = Br, n = 6, 19462-66-9; III, n = 5, 19462-67-0; 7,8′-pentamethylene-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-a]pyridozin-6-one, 19462-68-1; III, n = 6, 19462-69-2; X, 19462-70-5; XIII, 19462-71-6.

Acknowledgment.—This work was generously supported by grants from the U. S. Army Research Office (Durham). We are also indebted to P. H. Terry, D. J. Voaden, and G. Soldati for preliminary studies on the synthesis of some of the intermediates.

The Lithium Aluminum Hydride Reduction Products from Heterocycles Containing an Isoindolone Nucleus

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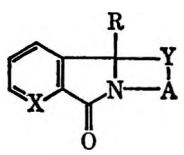
Received September 28, 1968

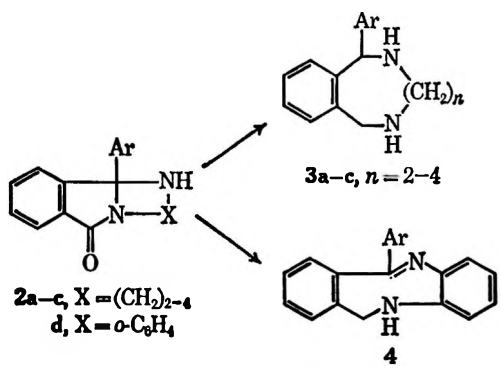
The lithium aluminum hydride reduction of a number of fused isoindolones (**1**) has been carried out in refluxing diethyl ether or tetrahydrofuran. Product composition was dependent on the type of heteroatom Y and the size of the fused ring A. All compounds where Y = O (**5a–c**, **8**, **11**) gave isoindolines as the major product while those with Y = NR (**13b** and **c**, **26**) gave isoindoles. When Y = NH the products were either medium-sized heterocycles (**14** and **23**) or isoindoles (**15c** and **d**, **19**, **22a–c**). A mechanism is proposed to account for the variation in product composition.

Recent studies have demonstrated that the reaction of 2-alkanoyl or 2-aroylbenzoic acids with amino alcohols,[1a,b] diamines,[1b–g] mercaptoamines,[1b,h] anthranilic acid,[1i] anthranilamides,[1i] and salicylamides[1i] is a convenient method for preparing heterocycles containing an isoindolone nucleus. The types of ring systems that have been obtained by this procedure are exemplified by **1**.



1, A = $(CH_2)_{2-4}$, o-C_6H_4, o-COC_6H_4; R = alkyl, aryl; X = CH or N; Y = NH, NR, O, S

The lithium aluminum hydride ($LiAlH_4$) reduction of some ring systems of type **1** has recently been reported. Compounds **2a–c** are reported[1c,e,f,2] to give the medium-sized heterocycles **3a–c** while **2d**[3] is reported to give dibenzo[b,f][1,4]diazocines[1c] **4**.



2a–c, X = $(CH_2)_{2-4}$
d, X = o-C_6H_4

3a–c, n = 2–4

4

In this work we present our findings on the products obtained when various **1** are treated with excess lithium aluminum hydride in refluxing diethyl ether or tetrahydrofuran.

Reduction of oxazolo[2,3-a]isoindol-5(9bH)-one **5a** with excess $LiAlH_4$ in refluxing diethyl ether gave the known[3] **6a**. Treatment of oxazino[2,3-a]isoindol-6-one **5b** and oxazepino[2,3-a]isoindol-6-one **5c** in a similar manner gave hydroxyalkyl isoindolines **6b** and **6c**. In addition phthalimidine **7** was isolated from the reduction of **5c**. As with **6a** the three benzylic protons in **6b** and **6c** produced an $H_AH_BCNCH_C$ nmr pattern that exhibited long-range spin–spin interactions[4] between H_C and H_AH_B.

Reduction of isoindolo[1,2-b][1,3]benzoxazine-10,12-dione **8a** in refluxing tetrahydrofuran gave, after chromatography on silica gel, two products. The minor product was the known 3-methylphthalimidine **9a** and the major product has been assigned structure **10** based on nmr data. Reduction of the 9a-phenyl analog (**8b**) of **8a** gave as the only isolable product the known 3-phenylphthalimidine **9b**.

When **11** was reduced with LAH in refluxing tetrahydrofuran there were obtained after chromatography on silica gel two novel compounds in approximately equal quantities. The more polar substance was a blue oil that decomposed before identification could be completed. The nmr spectrum of the less polar compound gave the long-range coupled $CH_CNCH_AH_B$ system and other nmr data in agreement with isoindoline structure **12** (Chart I).

Treatment of imidazo[2,1-a]isoindol-5-one **13a** with $LiAlH_4$ in diethyl ether gave the previously reported[1e,2,5] 2,5-benzodiazocine **14a**. When the 1-methyl-9b-phenyl and 1-ethyl-9b-phenyl analogs (**13b–c**) of **13a** were reduced under similar conditions none of the eight-membered analogs of **14a** were obtained. Instead, the unstable 1-phenyl-2-N-alkylaminoethylisoindoles **15a**

(1) (a) T. S. Sulkowski, U. S. Patent 3,336,306 (Aug 15, 1967); (b) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 165 (1969); (c) American Home Products Corp., Netherlands Patent Appl. 6,403,794 (1964); *Chem. Abstr.*, **63**, 9972 (1965); (d) J. R. Geigy, A.-G., Belgian Patent 659,530 (Aug 10, 1965); *Chem. Abstr.*, **64**, 664 (1966); (e) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebolt, *J. Org. Chem.*, **32**, 2180 (1967); (f) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967); (g) W. J. Houlihan, U. S. Patents 3,329,684 (July 4, 1967) and 3,334,113 (Aug 1, 1967); (h) J. R. Geigy, A.-G. Belgian Patent 659,528 (Aug 10, 1965); *Chem. Abstr.*, **64**, 3545 (1966); (i) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 2402 (1968).

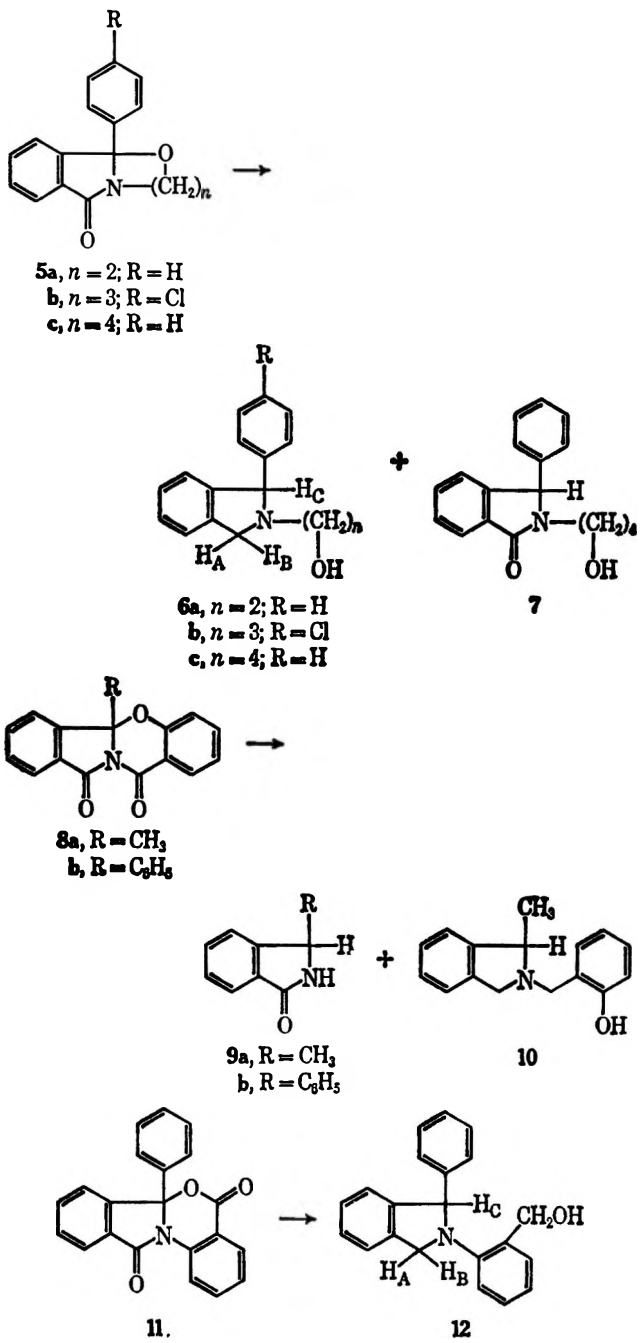
(2) Sandoz, Ltd., Netherlands Patent Appl. 6,614,399 (April 19, 1967); *Chem. Abstr.*, **68**, 3861 (1968).

(3) These compounds are incorrectly reported as 11-aryldibenzo[b,f][1,4]-diazocin-6(5H)-ones in ref 1c. Evidence for structure **2d** is given in ref 1b.

(4) Long-range proton spin–spin interactions in the isoindoline system have been reported.[1b,e,f] A recent communication indicates the J values for this type of interaction is influenced by the group attached to the isoindoline nitrogen atom; J. T. Gerig, *Tetrahedron Lett.*, 4625 (1967).

(5) An independent synthesis of this compound has been given by D. H. Kim, A. A. Santilli, T. S. Sulkowski, and S. J. Childress, *J. Org. Chem.*, **32**, 3720 (1967).

CHART I

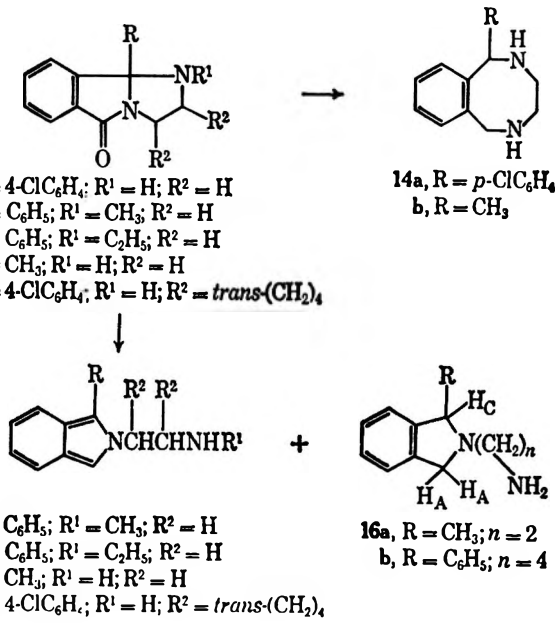


and **15b** were formed. Both of the compounds gave ultraviolet[6] and nmr data in agreement with an isoindole system.

Reduction of 9b-methyl analog **13d** gave an oil that afforded two products after distillation. The high-boiling component was identified as isoindole **15c.** The empirical formula of the low-boiling compound, $C_{11}H_{16}N_2$, agrees with either the eight-membered ring **14b** or isoindoline **16a.** The nmr showed a CH_3 doublet, a long-range coupled isoindoline $CH_AH_BNH_C$ system with further splitting of the H_C component by the methyl group, and other signals in agreement with the isoindoline structure **16a.** Further evidence for the isoindoline structure was obtained when **16a** gave a monoacetyl derivative on treatment with acetic anhydride in pyridine. *trans*-2,3-Tetramethylene analog **13e** gave isoindole **15d** when reduced with $LiAlH_4$ in diethyl ether (Scheme I).

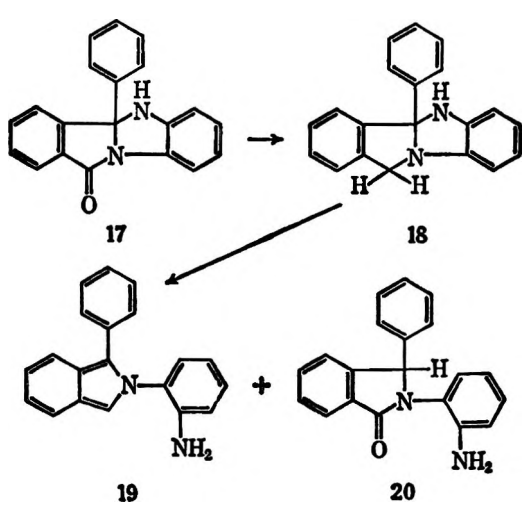
(6) D. F. Verber and W. Lwowski, *J. Amer. Chem. Soc.*, **86**, 4152 (1964); R. I. Fryer, J. V. Early, and L. H. Sternbach, *ibid.*, **88**, 3173 (1966).

SCHEME I



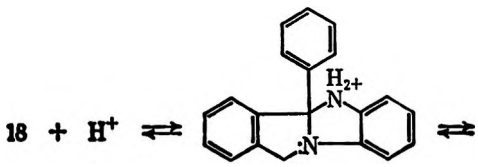
Reduction of isoindolo[2,1-*a*]benzimidazol-11-one **17** furnished an oil that gave an nmr spectrum with a 2 H AB system (J = 16 cps), one D_2O exchangeable H, and 13 aromatic protons. When the oil was dissolved in ethanol or $CHCl_3$ there was obtained a crystalline material. The nmr spectrum of this compound did not contain the AB system originally found in the oil but instead gave an nmr and uv spectrum in agreement with 1-phenyl-2-(*o*-aminophenyl)isoindole (**19**) (Scheme II).

SCHEME II

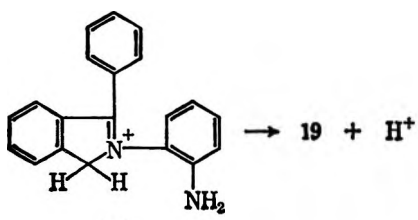


Apparently the oil, which we consider to be **18,** underwent a facile acid-catalyzed isomerization to the more stable isoindole system possibly *via* intermediates **18a** and **18b.** In a separate experiment where the crude oil was chromatographed on silica gel there was obtained **19** and 6% phthalimidine **20.** Our findings in the

reduction of **17** are inconsistent with those reported[1c] earlier since we did not obtain any compound corresponding to structure **4.**

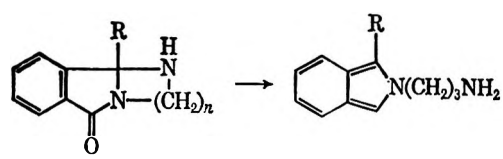


18a



18b

When pyrimido[2,1-*a*]isoindol-6(2H)-one **21a** was reduced with $LiAlH_4$ in diethyl ether there was obtained a compound that gave nmr and uv data in agreement with isoindole structure **22a.** This finding is also in disagreement with the report[1c] that compounds of **2b** are reduced to the nine-membered derivatives **3b.**

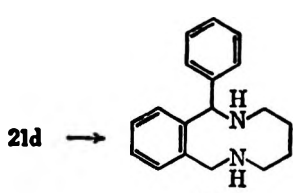


21a, R = 4-ClC_6H_4; $n = 3$
b, R = CH_3; $n = 3$
c, R = H; $n = 3$
d, R = C_6H_5; $n = 4$

22a, R = 4-ClC_6H_4
b, R = CH_3
c, R = H

Reduction of the 10b-methyl and 10b-hydrogen analogs **21b** and **c** also gave isoindole systems **22b** and **22c,** respectively.

From the reduction of [1,3]diazepino[2,1-*a*]isoindol-7-one **21d** in diethyl ether there was obtained a compound that analyzed as **23** or **16b.** The nmr of this compound gave a 2 H AB system, a 1 H singlet, eight methylene, eight aromatic, and two D_2O exchangeable protons. The singlet AB arrangement[7] of the three benzylic protons is in agreement with structure **23** rather than **16b**[8] where the long-range coupled CH_AH_B-NCH_C would be expected. Additional evidence for the ten-membered ring structure was obtained when a

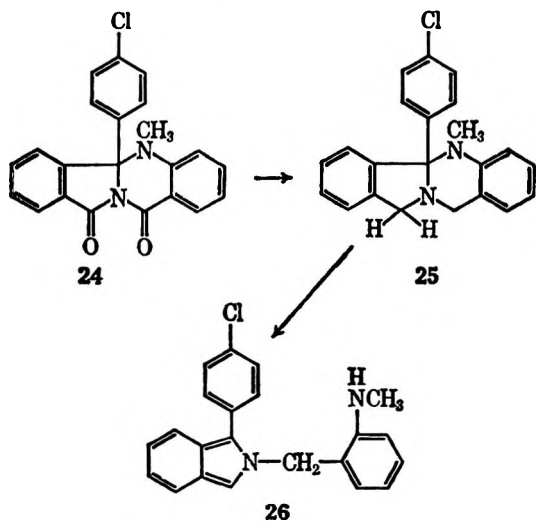


23

diacetyl derivative was obtained from **23** and acetic anhydride.

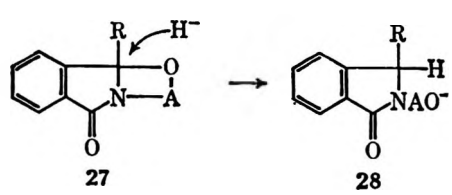
The reduction of isoindole[1,2-*b*]quinazoline-10,12-dione **24** in refluxing tetrahydrofuran afforded an oil that gave an nmr spectrum in agreement with structure **25.** When **25** was dissolved in methylene chloride–methanol or chromatographed on silica gel it formed an isomeric solid that gave an nmr and uv spectrum indicating isoindole structure **26.** The transformation **25** → **26** is similar to that of **18** → **19** and most likely proceeds by the same pathway (Scheme III).

SCHEME III



24 **25** **26**

From the findings given above the reduction of fused isoindole **1** with excess $LiAlH_4$ in refluxing ether or tetrahydrofuran can give either an isoindoline, isoindole, or medium-sized ring. The reduction product depends on the heteroatom Y and for derivatives of **1** where Y is a NH or NR group the size and presence of substituents on the fused ring and the type of R group present on the bridgehead carbon will determine product composition. In all cases where Y is O (**5a–c, 8a,** and **11**) the major reduction product is an isoindoline (**6a–c, 10,** and **12**). The reduction pathway probably proceeds by a hydride attack on the C–O bond of **27** to form phthalimidine **28** which then undergoes amide carbonyl reduction to form



27 **28**

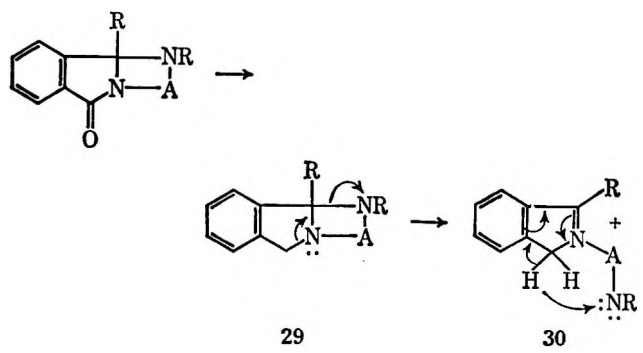
an isoindoline. Evidence for this pathway is supported by the isolation of the phthalimidine products **7** and **9a** and **b** from the reduction of **5c** and **8a** and **b** and the literature reports[1b,f,9] that $LiAlH_4$ reduction of 2-substituted phthalimidines gives isoindolines and not isoindoles. For the fused isoindolones where Y is NH or NR the reduction pathway is more complex. The compounds that form isoindoles (**13a–e, 17, 21a–d, 24**)

(7) A similar pattern is found in the eight-membered compound **17a**; *cf.* ref 1e.

(8) This compound was incorrectly reported by W. J. H. to give **16b**; Sandoz S. A., French Patent 1,513,593 (Feb 2, 1968).

(9) (a) C. F. Huebner, U. S. Patent 3,031,458 (1962); *Chem. Abstr.*, **59**, 9989 (1963); (b) A. Pernot and A. Willemart, *Bull. Soc. Chim. Fr.*, 324 (1953).

are probably first reduced[10] at the amide carbonyl[11] to form fused isoindolines **29.** These compounds isomerize, possibly *via* intermediate **30,** in the reducing media or more likely during work-up to give the isoindoles. Support for this pathway is found in the reduction of **17** and **24** to **18** and **25** (analogs of **29**) and isomerization of these to **19** and **26.**

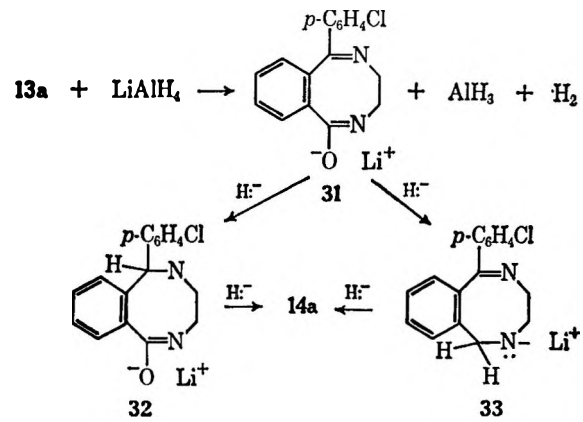


29 **30**

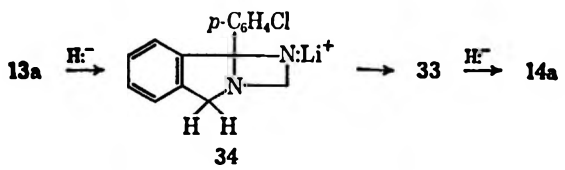
The formation of eight- and ten-membered ring compounds **14a** and **23** from **13a** and **21d** can be formulated in several ways. One mechanism[12] (Scheme IV) involves reaction of **13a** with $LiAlH_4$ to the isomerized[13] eight-membered ring anion **31.** Reduction of C=N or C=O to **32** or **33** followed by reduction of the remaining group leads to **14a.** A second pathway (Scheme V) requires reduction of the C=O group to the fused isoindoline anion **34** which undergoes isomerization to the eight-membered anion **33** and then reduction to **14a.** The third possibility (Scheme VI) involves the formation of the AlH_3 complex **35.** Hydride transfer to the bridgehead carbon atom accompanied by C–NCO bond cleavage leads to the eight-membered amide anion **33.** This anion can then be reduced at the amide carbonyl to form **14a.**

The three pathways given in Scheme IV–VI require that an NH group must be present for isomerization to occur and therefore agree with the observation that NCH_3 and NC_2H_5 analogs (**13b** and **c**) of **13a** do not give eight-membered ring compounds. That the isomerization is not dependent only on the presence of an NH group is clearly demonstrated by the reduction of **13d** and **e** to isoindoles **15c** and **d** rather than the eight-membered ring system. Schemes IV and V are very similar in that both require the reduction of a C=N bond (**31** or **33**) and C=O bond to form **14a** while Scheme VI requires the reduction of an iminal bond (**35**) and a C=O bond (**32**). Recent findings[14] in our laboratories have shown that the C=N bond in 1-(*p*-chlorophenyl)-6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine (**36**) is not reduced by $LiAlH_4$ under conditions that resulted in the formation of **14a** from **13a.** This result suggests that Schemes IV or V are not operative in forming **14a.** The formation[12] of **14a** probably occurs by the pathway given in Scheme VI.

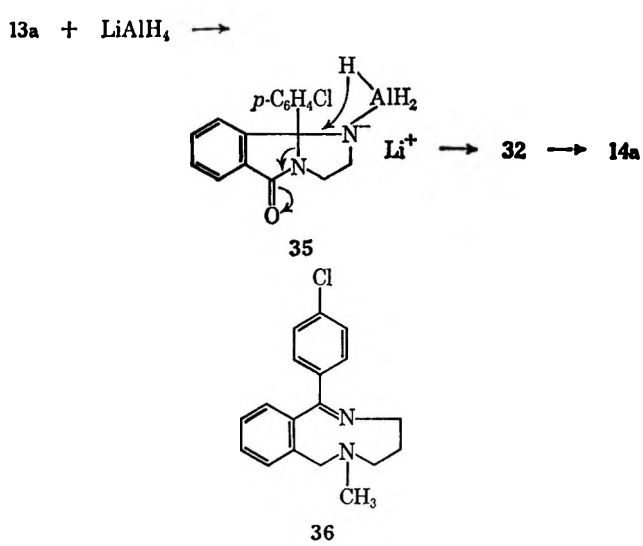
SCHEME IV



SCHEME V



SCHEME VI



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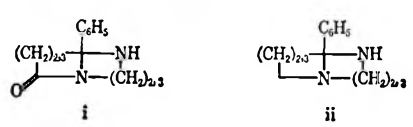
Experimental Section[15]

Synthesis of Fused Isoindolones.—Compounds **5a–c, 8a, b, 11, 13a, 17,** and **21b–d** have been reported in earlier literature.[1b,e,i]

(10) It is reported in ref 1b that the closely related fused lactams i are reduced by $LiAlH_4$ at the amide carbonyl to give the stable fused aminals ii.



i ii

(11) For a discussion on the mechanism of amide carbonyl reduction, see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y., 1956, p 546.

(12) For simplicity in formulation all mechanisms in Schemes IV–VI are given with **13a.** The same pathways are postulated for **21d.**

(13) A similar isomerization has been suggested by Sulkowski, *et al.*, in ref 1e to explain the formation of **14e.**

(14) W. J. Houlihan and R. E. Manning, First International Congress of Heterocyclic Chemistry, The University of New Mexico, Alburquerque, N. M., June 1967, Paper No. 37; *J. Org. Chem.*, in press.

(15) Melting points were determined on a Thomas–Hoover capillary melting apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates Model A-60 spectrometer and are expressed either in cycles per second (cps) or δ values (ppm) relative to a Me_4Si internal standard. Infrared spectra were determined in an appropriate solvent or as potassium bromide pellets using a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 15. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG.

TABLE I

PHYSICAL DATA FOR FUSED ISOINDOLONES

No.	Yield, %	Mp, °C	C=O, μ	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % O	Found, % C	Found, % H	Found, % N	Found, % O
5b[a]	82	140–142[b]	5.85	$C_{17}H_{14}ClNO_2$	68.1	4.7	4.7	10.7	68.1	4.9	4.6	10.6
13b	67	120–120[b]	5.90	$C_{17}H_{16}N_2O$	77.3	6.1	10.5	6.1	77.1	6.0	10.7	6.2
13c[c]	58	113–115[d]	5.89	$C_{18}H_{18}N_2O$	77.7	6.5	10.1	5.8	78.0	6.8	10.1	5.8
13d[e]	65	108–110[f]	5.84	$C_{11}H_{12}N_2O$	70.2	6.4	14.9		70.2	6.7	14.6	
13e	55	212–213[d]	5.86	$C_{20}H_{19}ClN_2O$	70.8	5.6	8.2	4.7	70.6	5.5	8.1	4.7
21a[j]	81	160–162	5.85	$C_{17}H_{15}ClN_2O$	68.3	5.1	9.4	5.4	68.7	5.5	9.3	5.5
24	51	209–210	5.68 5.97	$C_{22}H_{15}ClN_2O_2$	70.5	4.0	7.5	8.5	70.8	4.3	7.4	8.8

[a] Nmr ($CDCl_3$) δ 1.58 (2 H, m, $-CCH_2C-$), 3.08 (1 H, d-m, J = 13 cps, CH_ANCO), 3.92 (2 H, *m*, CH_2O), 4.50 (1 H, d-m, J = 13 cps, CH_BNCO), 7.43–786 (8 H, m, C_6H_4Cl and C_6H_4). [b] From CH_3OH–H_2O. [c] Nmr ($CDCl_3$) δ 0.99 (3 H, t, J = 7.0 cps, CH_3), 2.08 (2 H, m, CH_2NEt), 3.15 (3 H, m, $MeCH_2N$ and CH_ANCO), 3.85 (1 H, d-m, J = 13 cps, CH_BNCO), 7.08–792 (9 H), m, C_6H_5 and C_6H_4). [d] From ethanol–water. [e] Nmr ($CDCl_3$) δ 1.61 (3 H, s, CH_3), 2.00 (1 H, D_2O exchangeable, NH), 3.57 (4 H, m, NCH_2CH_2N), 7.32–7.61 (4 H, m, C_6H_4). [f] From diethyl ether. [g] Nmr ($CDCl_3$) δ 1.52 (2 H, m, $-CCH_2C-$), 1.92 (1 H, D_2O exchangeable, NH), 2.98.

Novel compounds have been prepared by published[1b,i] procedure and are listed in Table I.

General Procedure for Lithium Aluminum Hydride Reductions.—To a flask equipped with a Soxhlet extraction apparatus and maintained under a nitrogen blanket there was added anhydrous diethyl ether or tetrahydrofuran and lithium aluminum hydride and to the Soxhlet thimble there was added the isoindolone to be reduced. The mixture was stirred and refluxed and then cooled in an ice bath and treated with 2 *N* sodium hydroxide (2 ml/g of $LiAlH_4$), water (3 ml/g of $LiAlH_4$), and anhydrous sodium sulfate. The salts were filtered off and washed with diethyl ether or tetrahydrofuran. The filtrate was concentrated *in vacuo* and the resultant residue treated as indicated under the examples given below.

Reduction of 9b-Phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5-(9bH)-one (5a).—From 5.0 g (0.02 mol) of **5a**, 1.9 g (0.05 mol) of lithium aluminum hydride, and 100 ml of anhydrous diethyl ether (26 hr reflux) there was obtained 4.2 g of an oil. Distillation of this in a kugelrohr (180°, 0.5 mm) gave 3.9 g (81%) of 1-phenyl-2-(2-hydroxethyl)isoindoline[1b] (**6a**) as a viscous oil: ir ($CHCl_3$) 2.92 μ (OH); nmr ($CDCl_3$) δ 2.85 (2 H, m, CH_2N), 3.12 (1 H, D_2O exchangeable, OH), 3.58 (2 H, m, CH_2O), 3.78 (H_A), 4.52 (H_B), 4.79 (H_C, J_{AB} = 12 cps, J_{AC} = 3 cps, J_{BC} = 2 cps, $ArCH_AH_BNCH_CAr$).

Comparison of the infrared and nmr spectrum of **6a** prepared by $LiAlH_4$ reduction of 2-(2-hydroxyethyl)-3-phenylphthalimidine[1b] showed them to be identical.

Reduction of 10b-*p*-Chlorophenyl-3,4,6,10b-tetrahydro-2H-[1,3]oxazino[2,3-*a*]isoindol-6-one (5b).—From 25.0 g (0.083 mol) of **5b**, 7.9 g (0.20 mol) of lithium aluminum hydride, and 1000 ml of anhydrous diethyl ether (48 hr reflux) there was obtained 23.5 g of a semisolid substance that crystallized from methylene chloride–pentane (1:3) to give 22.2 g (91%) of 1-*p*-chlorophenyl-2-(3-hydroxypropyl)isoindoline (**6b**): mp 95–97°; R_f 0.45 ($CHCl_3$–CH_3OH, 98:2); ir (KBr) 2.95 and 2.98 μ (OH); nmr ($CDCl_3$) δ 1.68 (2 H, m, $-CCH_2C$), 2.82 (2 H, m, NCH_2C), 3.60 (1 H, D_2O exchangeable, OH), 3.61 (2 H, m, CH_2O), 3.68 (H_A), 4.53 (H_B), 4.58 (H_C, J_{AB} = 12 cps, J_{AC} = 3 cps, J_{BC} = 2 cps, $ArCH_AH_BNCH_CAr'$), 6.22–7.23 (8 H, m, C_6H_4Cl and C_6H_4); nmr ($CDCl_3$–CF_3COOH) δ 1.78 (2 H, m, $-CCH_2C$) 2.92 (2 H, m, CH_2N), 3.63 (2 H, m, CH_2O), 3.88 (H_A), 4.64 (H_B), 4.91 (H_C, J_{AB} = 13 cps, J_{AC} = 2 cps, J_{BC} = 2 cps, $ArCH_AH_BNCH_CAr'$) 6.81–7.32 (8 H, m, C_6H_4Cl and C_6H_4).

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.0; H, 6.3; Cl, 12.4; N, 4.9; O, 5.6. Found: C, 71.1; H, 6.5; Cl, 12.4; N, 5.0; O, 5.6.

A solution of 693 mg of **6b**, 2.7 ml of dry pyridine and 2.2 ml of acetic anhydride was refluxed for 3 hr and processed in the usual manner to give 500 mg of the acetate of **6b** as an oil: R_f 0.60 ($CHCl_3$–CH_3OH, 98:2); ir (CH_2Cl_2) 5.81 μ (C=O); nmr ($CDCl_3$) δ 1.90 (3 H, s, CH_3), 1.92 (2 H, m, CH_2), 2.68 (2 H, t, J = 6.0 cps, CH_2N), 4.05 (2 H, t, J = 6.0 cps, CH_2O), 3.73 (H_A), 4.47 (H_B), 4.75 (H_C, J_{AB} = 12 cps, J_{AC} = 2.0 cps, J_{BC} = 2.0 cps, $ArCH_BH_PNCH_CAr'$), and 6.80–7.40 (8 H, m, aromatic protons).

Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.1; H, 6.1; O, 9.8. Found: C, 69.3; H, 6.0; O, 9.7.

Reduction of 11b-Phenyl-2,3,4,5,7,11b-hexahydro[1,3]oxazepino[2,3-*a*]isoindol-7-one (5c).—From 6.9 g (0.025 mol) of **5c**, 2.4 g (0.063 mol) of lithium aluminum hydride, and 500 ml of anhydrous diethyl ether (72 hr reflux) there was obtained 6.5 g of an oil; tlc on silica gel ($CHCl_3$–CH_3OH 95:5) gave R_f 0.42 and 0.48. Chromatography on silica gel (60 g) gave fraction 1 [3.6 g, (eluent, C_6H_6–$CHCl_3$ 80:20), R_f 0.42] and fraction 2 [2.4 g (eluent, $CHCl_3$), R_f 0.48]. Crystallization of fraction 1 from isopropyl alcohol–water gave 1-phenyl-2-(4-hydroxybutyl)isoindoline (**6c**): mp 72–74°; ir (CH_2Cl_2) 2.78 and 3.15 μ (OH); nmr ($CDCl_3$) δ 1.58 (4 H, m, $-CCH_2CH_2C-$), 2.70 (2 H, m, NCH_2), 3.48 (2 H, t, J = 6.0 cps, CH_2O), 3.95 (1 H, OH), 3.72 (H_A), 4.49 (H_B), 4.73 (H_C, J_{AB} = 12 cps, J_{AC} = 2.0 cps, $ArCH_AH_BNCH_CAr'$), 6.82–7.52 (9 H, m, aromatic H).

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.9; H, 7.9; N, 5.2; O, 6.0. Found: C, 80.6; H, 8.1; N, 5.2; O, 5.9.

Fraction 2 was distilled in a kugelrohr (180°, 0.2 mm) to give 1.9 g of 2-(4-hydroxybutyl)-3-phenylphthalimidine (**7**): ir (CH_2Cl_2) 2.77 and 2.94 (OH), 5.91 μ (C=O); nmr ($CDCl_3$) δ 1.62 (4 H, m, $C-CH_2CH_2-C$), 2.98 (1 H, m), 3.68 (3 H, m), 3.73 (1 H, D_2O exchangeable, OH), 5.79 (1 H, s, CH), 7.28 (8 H, m, C_6H_3 and C_6H_5), 7.88 (1 H, m, =CHCO).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 76.8; H, 7.1; N, 4.9.

Reduction of 5a-Methyl-11,12-dihydro-5aH-isoindolo[1,2-*b*]-[1,3]benzoxazine-10,12-dione (8a).—From 12.0 g (0.045 mol) of **8a**, 8.6 g (0.23 mol) of lithium aluminum hydride, and 500 ml of anhydrous tetrahydrofuran (18 hr reflux) there was obtained 12.8 g of an orange oil ($CHCl_3$–CH_3OH 98:2), R_f 0.25 and 0.80. Chromatography of a 6.0-g sample of the oil on a silica gel column ($CHCl_3$ eluent) gave fraction 1 (4.7 g, R_f 0.80), fraction 2 (1.2 g, R_f 0.25), and fraction 3 (0.2 g, R_f 0.90 and 0.3). Fraction 3 was not studied. Fraction 2 was crystallized from methylene chloride–diethyl ether–pentane to give 0.158 g of 3-methylphthalimidine (**9a**): mp 112–114° (lit.[16] mp 110–111°); nmr ($CDCl_3$) δ 1.52 (3 H, d, J = 6.5 cps, CH_3), 4.74 (1 H, q, J = 6.5 cps, CH), 8.60 (1 H, D_2O exchangeable CONH), and 7.27–8.00 (4 H, m C_6H_4). Fraction 1 was crystallized from methylene chloride–pentane to give 4.2 g of 1-methyl-2-(*o*-hydroxybenzyl)isoindoline (**10**): mp 105–108°; ir (KBr) 2.95 μ (OH); uv maxima 266 mμ (ε 2740) and 272 (3670); nmr ($CDCl_3$) δ 1.52 (3 H, d, J = 6.5 cps, CH_3), 3.63 (H_A), 4.41 (H_P, J = 12 cps, NCH_AH_BArOH), 3.98 (H_C), 4.18 (H_A), 4.32 (H_C, J_{AB} = 13 cps, J_{AC} = 1.5 cps, J_{C-CH_3} = 7 cps, $CH_CNCH_AH_B$), 6.68–7.36 (8 H, m, $C_6H_4C_6H_4$), 8.55 (1 H, D_2O exchangeable, OH).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.3; H, 7.1; N, 5.9; O, 6.7. Found: C, 80.5; H, 7.4; N, 5.9; O, 6.8.

Reduction of 5a-Phenyl-11,12-dihydro-5aH-isoindolo[1,2-*b*]-

(16) A. Rosenthal, R. F. Astbury, and A. Hubscher, *J. Org. Chem.*, **23**, 1037 (1958).

[1,3]benzoxazine-10,12-dione (8b).—From 3.0 g (0.0092 mol) of 8b, 1.1 g (0.029 mol) of lithium aluminum hydride, and 250 ml of anhydrous tetrahydrofuran (24 hr reflux) there was obtained 2.7 g of a blue oil. Crystallization from ethanol gave 0.95 g of 3-phenylphthalimidine (9b): mp 225–227° (lit.[17] mp 220°); ir (KBr) 2.95 (NH), 5.91 μ (C=O); nmr (C_2D_6SO) δ 5.73 (1 H, s, ArCHAr'), 7.20–7.90 (9 H, m, C_6H_4 and C_6H_5), 9.05 (1 H, D_2O exchangeable, CONH).

Concentration of the filtrate from 9b gave a blue oil that rapidly darkened to an intractable tar.

Reduction of 6a-Phenyl-6a,11-dihydro-5H-isoindolo[2,1-a]-[3,1]benzoxazine-5,11-dione (11).—From 13.0 g (0.04 mol) of 11, 7.6 g (0.20 mol) of lithium aluminum hydride, and 750 ml of anhydrous tetrahydrofuran (56 hr reflux) there was obtained 12.2 g of a dark brown oil, R_f 0.20 and 0.40 ($CHCl_3$–CH_3OH 95:5). Chromatography on silica gel (240 g) gave fraction 1 [6.1 g (eluent C_6H_6–$CHCl_3$ 1:1), R_f 0.40], fraction 2 [0.8 g (eluent $CHCl_3$), R_f 0.40 and 0.20], and fraction 3 [6.0 g (eluent, $CHCl_3$–CH_3OH 98:2)].

Fraction 1 was crystallized from diethyl ether–pentane to give 1-phenyl-2-(*o*-hydroxymethylphenyl)isoindoline (12): mp 83–86°; ir (CH_2Cl_2) 2.78 and 2.93 μ (OH); uv maxima 258 mμ (ε 6690), 263 sh (6020), and 272 sh (4460); nmr ($CDCl_3$) δ 3.75 (1 H, D_2O exchangeable, OH), 4.33 (H_A) and 4.78 (H_B, J = 13.0 cps, CH_AH_BO), 4.38 (H_A), 4.95 (H_B), 5.89 (H_C, J_{AB} = 13.0 cps, J_{AC} = 1.5 cps; $ArCH_AH_BNCH_CAr'$), 6.83–7.45 (13 H, m, aromatic H).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.7; H, 6.4; O, 5.3. Found: C, 83.4; H, 6.6; O, 5.6.

Fraction 2 was not studied. Fraction 3 could not be identified because it rapidly decomposed to a dark brown tar.

Reduction of 1-Methyl-9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one (13b).—From 6.0 g (0.023 mol) of 13b, 2.2 g (0.058 mol) of lithium aluminum hydride, and 500 ml of anhydrous diethyl ether (30 hr reflux) there was obtained 5.7 g of a pale yellow oil. Distillation in a kugelrohr (180°, 0.5 mm) gave 5.1 g (89%) of 1-phenyl-2-methylaminoethylisoindole (15a): $n^{20}D$ 1.6629; ir (CH_2Cl_2) 2.76 and 3.02 (NH_2), 6.25 and 7.50 μ; uv maxima 222 mμ (ε 30,000), 272 (5200), 283 (5200), 320 infl (5200) and 345 (7600); nmr ($CDCl_3$) δ 0.88 (1 H, D_2O exchangeable, NH), 2.17 (3 H, s, NCH_3), 2.74 (2 H, t, J = 6.0 cps, CH_2N), 4.24 (2 H, t, J = 6.0 cps, N^2CH_2), 7.15 (1 H, s, CCHN), and 6.91–7.65 (9 H, m, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.6; H, 7.3; N, 11.2. Found: C, 81.0; H, 7.5; N, 11.6.

Reduction of 1-Ethyl-9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one (13c).—From 5.0 g (0.018 mol) of 13c, 1.7 g (0.045 mol) of lithium aluminum hydride, and 500 ml of anhydrous diethyl ether (16 hr reflux) there was obtained 5.1 g of an oil, R_f 0.23 and trace at 0.56 ($CHCl_3$–CH_3OH 95:5). Distillation through a Vigreux column gave 3.6 g (75%) of 1-phenyl-2-(2-ethylaminoethyl)isoindole (15b): bp 185–190° (0.5 mm); $n^{20}D$ 1.6610; uv maxima 274 mμ (ε 5300), 285 (5000), 345 (8000); nmr (CCl_4) δ 0.91 (3 H, t, J = 7.0 cps, CH_3), 1.26 (1 H, D_2O exchangeable, NH), 2.40 (2 H, q, J = 7.0 cps, NCH_2Me), 2.75 (2 H, t, J = 6.0 cps, CH_2N), 4.16 (2 H, t, J = 6.0 cps, CH_2N=), 7.32 (1 H, s, C=CHN), 7.25 (9 H, m, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.8; H, 7.6; N, 10.6. Found: C, 81.6; H, 7.5; N, 10.7.

Reduction of 9b-Methyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one (13d).—From 8.0 g (0.046 mol) of 13d, 4.3 g (0.116 mol) of lithium aluminum hydride and 500 ml of anhydrous diethyl ether (56 hr reflux) there was obtained 7.8 g of a liquid, R_f 0.26 and 0.55 ($CHCl_3$–CH_3OH 80:20). Distillation (nitrogen atmosphere) gave fraction 1 [3.8 g, bp 92° (0.50 mm), $n^{20}D$ 1.5572, R_f 0.26], fraction 2 [0.4 g, bp 92–123°, $n^{20}D$ 1.5813, R_f 0.26 and 0.55], and fraction 3 [3.5 g, bp 123° (0.50 mm), $n^{20}D$ 1.6257, R_f 0.55].

Fraction 1 was identified as 1-methyl-2-aminoethylisoindoline (16a): nmr ($CDCl_3$) δ 1.43 (3 H, d, J = 6.0, CH_3), 1.45 (2 H, D_2O exchangeable, NH_2), 2.82 (4 H, m, NCH_2CH_2N), 3.54 (H_A), 3.83 (H_B), 4.31 (H_C, J_{AB} = 13.0 cps, J_{AC} = 2.0 cps, J_{BC} = 2.0 cps, $ArCH_HH_PNCH_C$).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 75.4; H, 8.6; N, 16.0. Found: C, 75.2; H, 8.4; N, 16.1.

Fraction 2 was not studied. Fraction 3 was identified as 1-methyl-2-aminoethylisoindole (15c): ir (CH_2Cl_2) 2.73 and 2.95 μ (NH_2); uv maxima 227 mμ (ε 22,500), 269 (2250), 280 (2010), 341 (2200), 404 (450), 428 (600), and 443 (750); nmr ($CDCl_3$) δ 1.23 (2 H, D_2O exchangeable, NH_2), 2.48 (3 H, s, CH_3), 2.96 (2 H, t, J = 6.0 cps, CH_2N, 4.07 (2 H, t, J = 6.0 cps, CH_2N), 6.97 (1 H, s, NCH=), 6.83 (2 H), and 7.44 (2 H, A_2B_2 multiplet, C_4H_4).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1. Found: C, 75.7; H, 8.1.

A solution of 0.90 g of 16a, 1.0 ml of acetic anhydride, and 5 ml of pyridine was allowed to stir for 15 hr under a nitrogen atmosphere. The dark colored solution was concentrated *in vacuo*, dissolved in chloroform and washed with cold sodium bicarbonate solution. The solvent was removed *in vacuo* and the residue distilled in a kugelrohr (150°, 0.5 mm) to give 0.70 g of 1-methyl-2-(acetamidoethyl)isoindoline: nmr ($CDCl_3$) δ 1.41 (3 H, d, J = 6.0 cps, CH_3), 1.97 (3 H, s, CH_3CO), 2.40–4.00 (5 H, m, CH_2CH_2 and CH_AN), 3.58 (H_B), 4.28 (H_C, J_{AB} = 13.0 cps, J_{AC} = 2.0 cps, $ArCH_AH_BNCH_C$), 6.32 (1 H, D_2O exchangeable, NH), and 7.28 (4 H, m, C_6H_4).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 79.2; H, 8.6; O, 8.1. Found: C, 79.0; H, 8.4; O, 8.0.

Reduction of *trans*-4-*p*-Chlorophenyl-4a,5,6,7,8,9-hexahydroisoindolo[2,1-a]-11H-benzimidazol-11-one (13e).—From 8.5 g (0.025 mol) of 13e, 1.9 g (0.05 mol) of lithium aluminum hydride and 200 ml of anhydrous diethyl ether (18 hr reflux) there was obtained 6.7 g of a blue oil that gave 2.9 g of 1-*p*-chlorophenyl-2-(*trans*-2-aminocyclohexyl)isoindole (15d): mp 119–120° (pentane–diethyl ether); ir (CH_2Cl_2) 2.73, 2.78, 2.96 (NH_2), 6.65, 7.42, 8.16, 9.10 μ; uv maxima 224 mμ (ε 40,850), 275 (4900), 286 (5034), 348 (12,465); nmr ($CDCl_3$) δ 0.92 (2 H, D_2O exchangeable, NH_2), 1.62 [8 H, m, $(CH_2)_4$], 3.04 (1 H, m, CHN), 3.88 (1 H, m, CHN^2), 6.91 (2 H, m, C_4HC_7H), 7.27 (1 H, s, =CHN), 7.42 (6 H, broad s, C_6H_4 and C_6HC_6H).

Anal. Calcd for $C_{20}H_{21}ClN_2$: C, 73.6; H, 6.5; Cl, 10.9; N, 8.6. Found: C, 74.0; H, 6.8; Cl, 10.8; N, 8.8.

Reduction of 4a-Phenyl-4a,5-dihydro-11H-isoindolo[2,1-a]-benzimidazol-11-one (17).—From 15.0 g (0.05 mol) of 17, 4.8 g (0.13 mol) of lithium aluminum hydride, and 500 ml of anhydrous diethyl ether (18 hr reflux) there was obtained 14.5 g of 4a-phenyl-4a,5-dihydro-11H-isoindolo[2,1-a]benzimidazole (18) as a pale yellow oil: R_f 0.95 ($CHCl_3$–CH_3OH 98:2); nmr ($CDCl_3$) δ 4.30 (H_A) 4.61 (H_B, J = 16 cps, CH_AH_B), 4.35 (NHD_2O exchangeable), 6.50–7.70 (13 H, m, aromatic H). Chromatography of 18 (14.1 g) on silica gel (200 g) gave 13.4 g of solid A ($CHCl_3$ eluent; R_f 0.90, $CHCl_3$–CH_3OH 98:2) and 0.9 of solid B ($CHCl_3$–CH_3 98:2 eluent; R_f 0.05, $CHCl_3$–CH_3OH, 98:2). Recrystallization of A from methanol–methylene chloride gave 11.3 g of 1-phenyl-2-(*o*-aminophenyl)isoindole (19): mp 142–145°; ir (KBr) 2.88 and 2.96 (NH_2), 6.18 and 7.20 μ; uv maxima 215 mμ (ε 33,560), 284 (7350), 304 (7350), 320 infl (6445), and 350 (6445); nmr ($CDCl_3$) δ 3.42 (2 H, D_2O exchangeable, NH_2), 7.00 (1 H, s, C=CHN–) and 6.50–7.70 (13 H, m, aromatic H).

Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.6; H, 5.6; N, 9.8. Found: C, 84.4; H, 5.9; N, 9.8.

The solid B was crystallized from methanol to give 0.6 g of 2-(*o*-aminophenyl)-3-phenylphthalinidine (20): mp 190–192°; ir (KBr) 2.92 and 2.98 (NH_2), 6.00 (C=O), 6.18 and 7.20 μ; nmr ($CDCl_3$) δ 3.88 (2 H, D_2O exchangeable, NH_2), 6.02 (1 H, s, CHN), 6.78 (4 H, q, NC_6H_4N), 7.07–7.59 (8 H, m, C_6H_5 and C_6H_4), 8.92 (1 H, m, HC=CCO).

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 80.0; H, 5.3; O, 5.3. Found: C, 80.2; H, 5.1; O, 5.4.

Reduction of 10b-*p*-Chlorophenyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindol-6(2H)-one (21a).—From 15.0 g (0.05 mol) of 21a, 5.0 g (0.13 mol) of lithium aluminum hydride, and 500 ml of anhydrous diethyl ether (48 hr reflux) there was obtained 14.4 g (92%) of 1-*p*-chlorophenyl-3-aminopropylisoindole (22a) as a yellow oil: ir (CH_2Cl_2) 2.75 and 2.98 μ (NH_2); uv maxima 222 mμ (ε 29,910), 274 (3870), 280 (3870), and 349 (9150); nmr ($CDCl_3$) δ 1.02 (2 H, D_2O exchangeable, NH_2), 1.74 (2 H, m, CCH_2C), 2.46 (2 H, t, J = 7.0 cps, CH_2N–), 4.23 (2 H, t, NCH_2), 7.16 (1 H, s, =CHN), 7.39 and 7.51 (4 H, A_2B_2 pattern, HC=CHCH=CH). On exposure to air or light 27a very rapidly darkened.

(17) G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **83**, 308 (1953); *Chem. Abstr.*, **47**, 12294 (1953).

A solution of 7.2 g of **22a** in 250 ml of anhydrous diethyl ether was cooled in an ice bath and then treated with a stream of dry hydrogen chloride gas. The resultant solid was filtered off and recrystallized from 95% ethyl alcohol. There was obtained 4.4 of **22a**·HCl, mp 260–262°.

Anal. Calcd for $C_{17}H_{18}N_2Cl_2$: C, 63.6; H, 5.6; Cl, 22.1; N, 8.7. Found: C, 63.8; H, 5.8; Cl, 21.9; N, 8.9.

Reduction of 10b-Methyl-1,3,4,10b-tetrahydropyrimido[2,1-*a*]-isoindol-6(2H)-one (21b).—From 15.0 g (0.074 mol) of **26b**, 7.1 g (0.19 mol) of lithium aluminum hydride, and 600 ml of anhydrous diethyl ether (48 hr reflux) there was obtained 14.7 g of oil. Distillation (nitrogen) gave 11.4 g (82%) of 1-methyl-2-(3-aminopropyl)isoindole (**22b**): bp 138° (0.5 mm); $n^{20}D$ 1.6130; uv maxima 227 mμ (ε 43,640), 269 (2005), 280 (1585), 342 (3940); nmr ($CDCl_3$) δ 1.15 (2 H, D_2O exchangeable, NH_2), 1.78 (2 H, quintet, J = 7 cps, $>CCH_2C<$), 2.50 (3 H, s, CH_3), 2.47 (2 H, t, J = 7 cps, $CH_2N<$), 3.91 (2 H, t, J = 7 cps, $CH_2NC=$), 7.01 (1 H, s, CH=N), 6.87 (2 H), and 7.48 (2 H, A_2B_2, $(CHCH)_2$).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.6; H, 8.6; N, 14.9. Found: C, 76.3; H, 8.4; N, 14.7.

Reduction of 1,3,4,10b-Tetrahydropyrimido[2,1-*a*]isoindol-6(2H)-one (21c).—From 6.0 g (0.032 mol) of **21c**, 3.0 g (0.08 mol) of lithium aluminum hydride, and 500 ml of diethyl ether (65 hr reflux) there was obtained 5.1 g of water-white liquid. Distillation in a kugelrohr (100°, 0.5 mm) gave 4.8 g (86%) of 2-(3-aminopropyl)isoindole (**22c**): $n^{20}D$ 1.6160; R_f 0.2 ($CHCl_3$–CH_3OH 95:5); ir (CH_2Cl_2) 2.74, 2.96, and 3.05 (NH_2), 6.80, 7.34, 7.53, and 8.82 μ; uv maxima 224 mμ (ε 31,500), 266 (1590), 270 (1520), 277 (1740), 289 (1380), 327 (4200), and 340 infl (3225); nmr ($CDCl_3$) δ 1.05 (2 H, D_2O exchangeable, NH_2), 1.58 (2 H, quintet, J = 6.0 cps, CH_2), 2.31 (2 H, t, J = 6.0 cps, CH_2N), 3.83 (2 H, t, J = 6.0 cps, $CH_2NC=$), 6.85 (2 H, s, HCN=CH), 6.88, and 7.43 (4 H, A_2B_2 pattern, HC=CH=CH=CH).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.9; H, 8.5; N, 16.4.

Reduction of 11b-Phenyl-1,2,3,4,5,11b-hexahydro-7H[1,3]-diazepino[2,1-*a*]isoindol-7-one (21d).—From 8.0 g (0.029 mol) of **21d**, 5.0 g (0.13 mol) of lithium aluminum hydride, and 25 ml of diethyl ether (17 hr reflux) there was obtained 8.2 g of oil. Crystallization from diethyl ether–heptane gave 3.1 g of solid, mp 116–160°, that was not studied. Concentration of the mother liquor gave 2.6 g of 1-phenyl-1,2,3,4,5,6,7,8-octahydro-2,7-benzodiazecine (**23**): mp 110–115°; analytical sample mp 112–114° (diethyl ether–pentane (lit.[1c] mp 114–116°); nmr ($CDCl_3$) δ 1.72 (4 H, m, $-CCH_2CH_2C-$), 2.35 (1 H, m, NCH), 2.82 (2 H, m, NCH_2), 2.60 (2 H, D_2O exchangeable, NH), 3.52 (1 H, m, NCH), 3.72 (H_A), 4.00 (H_B, J = 13.0 cps, $ArCH_AH_BN$), 5.17 (1 H, s, ArCHAr'), 6.50–7.53 (9 H, m, C_6H_5 and C_6H_4).

A solution of 0.3 g of **23**, 5.0 ml of pyridine, and 1.5 ml of acetic anhydride was refluxed (8 hr). The solvent was removed *in vacuo* and the residue crystallized from isopropyl alcohol to give 0.215 g of 2,7-diacetyl-substituted **23**: mp 174–176°; ir (KBr) 5.95 μ (CON); nmr ($CDCl_3$) δ 1.62 (4 H, m, $>CCH_2CH_2C<$), 2.08 (3 H, s, CH_3CO), 2.13 (1 H, m, NCH), 2.18 (3,H,s, CH_3CO), 3.10 (2 H, m, CH_2N), 4.32 (1 H, m, CHN), 4.28 (H_A), 5.68 (H_B, J = 14 cps, $ArCH_AH_BN$), 6.38 (1 H, s, ArCHAr'), 6.70–7.68 (9 H, m, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 7.5; N, 8.0; O, 9.1. Found: C, 75.1; H, 7.8; N, 8.3; O, 9.2.

Reduction of 5-Methyl-5a-*p*-chlorophenyl-5,5a,10,12-tetrahydroisoindolo[1,2-*b*]quinazoline-10,12-dione (24).—From 10.0 g (0.028 mol) of **24**, 5.2 g (0.14 mol) of lithium aluminum hydride, and 500 ml of anhydrous tetrahydrofuran (50 hr reflux) there was obtained 8.9 g of 5-methyl-5a-*p*-chlorophenyl-5,5a,10,12-tetrahydroisoindolo[1,2-*b*]quinazoline (**25**) as a yellow oil: R_f 0.92 ($CHCl_3$–CH_3OH 98:2); nmr ($CDCl_3$) δ 2.67 (3 H, s, NCH_3), 3.62 (H_A) and 4.07 (2 H, J = 17.0 cps, CH_AH_BN), 4.02 (2 H, s, CH_2N), and 6.40–7.35 (12 H, m, aromatic protons). Crystallization of 32 (8.5 g) from methanol–methylene chloride gave 6.8 g of 1-*p*-chlorophenyl-2-(*o*-methylaminobenzyl)isoindole (**26**): mp 206–208°; R_f 0.85 ($CHCl_3$–CH_3OH 98:2); ir (CH_2Cl_2) 2.72 and 2.91 (NH), 6.22, 6.30, 6.58, 6.67, 8.66, 9.14 and 9.90 μ; uv maxima 245 mμ sh (ε 19,500), 276 (6500), 287 (6500), 351 (6750), and 367 sh (1167); nmr ($CDCl_3$) δ 2.68 (3 H, s, NCH_3), 3.12 (1 H, broad, D_2O exchangeable, NH), 5.21 (2 H, s, NCH_2), 7.12 (1 H, s, C=CHN), and 6.51–7.67 (12 H, m, aromatic protons).

Anal. Calcd for $C_{22}H_{19}ClN_2$: C, 76.2; H, 5.5; Cl, 10.3; N, 8.0. Found: C, 76.4; H, 5.8; Cl, 10.0; N, 8.3.

Registry No.—Lithium aluminum hydride, 1302-30-3; **5b**, 17494-24-5; **6a**, 18409-76-2; **6b**, 19543-17-0; **6b** acetate, 19543-18-1; **6c**, 19543-19-2; **7**, 19543-20-5; **10**, 19543-21-6; **12**, 19543-22-7; **13b**, 5983-38-0; **13c**, 5983-39-1; **13d**, 5983-34-6; **13e**, 19553-20-9; **15a**, 19543-26-1; **15b**, 19104-44-0; **15c**, 19543-27-2; **15d**, 19581-60-3; **16a**, 19543-29-4; **19**, 19543-30-7; **20**, 19543-31-8; **21a**, 5965-49-8; **22a**, 19543-33-0; **22a** HCl, 19104-42-8; **22b**, 19543-35-2; **22c**, 19543-36-3; **23** (2,7-diacetyl), 19543-37-4; **24**, 19543-38-5; **25**, 19543-39-6; **26**, 19543-40-9; 1-methyl-2-(acetamidoethyl)isoindoline, 19543-28-3.

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Catalytic Effect of 4-Pyridone on the Free-Radical Oxidations of Secondary Alcohols with *t*-Butyl Peroxide[1]

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The rate of oxidation of secondary alcohols with *t*-butyl peroxide is enhanced by the presence of small amounts of 4-pyridone. The catalytic action of 4-pyridone arises from its ability to participate in the free-radical chain oxidation of the alcohol by the peroxide serving as a hydrogen atom carrier. Hydrogen atom transfer from an α-hydroxyalkyl radical to 4-pyridone yielding a 4-hydroxymonohydropyridyl radical apparently is a faster reaction than hydrogen atom transfer to the peroxide. The 4-hydroxymonohydropyridyl radical, however, reacts rapidly with the peroxide yielding *t*-butyl alcohol, a *t*-butoxy radical and 4-hydroxypyridine which on tautomerization regenerates the 4-pyridone. Reaction of the *t*-butoxy radical with the secondary alcohol yields the chain-carrying α-hydroxyalkyl radical. Similar catalytic action is not displayed by 2-pyridone or 3-hydroxypyridine.

The oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, by *t*-butyl peroxide (I) occurs by a free-radical chain reaction as evidenced by induced decomposition of the peroxide resulting from a hydrogen atom transfer to the peroxide from an α-hydroxyalkyl radical derived from the alcohol.[2] The observations of hydrogen atom transfer from alcohol-derived radicals to ketones[3] and the facile hydrogen atom transfer reaction from certain monohydropyridyl radicals to *t*-butyl peroxide[4] suggested that 4-pyridone (II) might be a catalyst for the *t*-butyl peroxide oxidations of secondary alcohols.

The decomposition of I in inert solvents, that is, solvents that do not induce the decomposition of the peroxide, is a unimolecular reaction as shown in reaction 1. Recent work has shown that the unimolecular

$$\underset{\text{I}}{(CH_3)_3COOC(CH_3)_3} \xrightarrow{k_1} 2(CH_3)_3CO\cdot \qquad (1)$$

decomposition of I is influenced to some extent by the medium[5] but these solvents effects differ both in magnitude and kind from the induced decompositions observed in secondary alcohols. In the latter, the decomposition of I occurs by two modes—one being the unimolecular decomposition shown in reaction 1 and the other a reduction of the peroxide by the α-hydroxyalkyl radical (reaction 3), a radical resulting from interaction of the secondary alcohol with a *t*-butoxy radical (reaction 2). Reactions 2 and 3

$$(CH_3)_3CO\cdot + R_2CHOH \xrightarrow{k_2} (CH_3)_3COH + R_2\dot{C}OH \qquad (2)$$

$$R_2\dot{C}OH + (CH_3)_3COOC(CH_3)_3 \xrightarrow{k_3} R_2C{=}O + (CH_3)_3COH + (CH_3)_3CO\cdot \qquad (3)$$

comprise a free-radical chain sequence that accounts for the oxidation of the alcohol by the peroxide and the over-all rate of decomposition of the peroxide can be expressed by reaction 4. If the interactions of the

$$\frac{-d[Per]}{dt} = k_1[Per] + k_3[R_2\dot{C}OH][Per] \qquad (4)$$

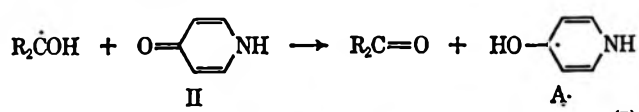
alcohol-derived radicals with the peroxide account for an appreciable amount of the decomposition of the peroxide, the observed rate of reaction of the peroxide will be appreciably faster than that of the unimolecular reaction. The precise rate law for the decomposition of the peroxide depends on the termination step of the chain sequence. In the case of decomposition of *t*-butyl peroxide in acyclic secondary alcohols where the concentrations of the alcohol and peroxide are of the same order of magnitude, the cross-termination reaction 5 most likely occurs. The derived rate law for the decomposition of the peroxide based on a steady-state

$$(CH_3)_3CO\cdot + R_2\dot{C}OH \xrightarrow{k_5} (CH_3)_3COH + R_2C{=}O \qquad (5)$$

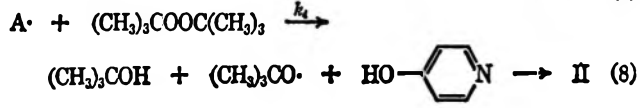
approximation of all radicals if termination by reaction 5 is operative is shown in equation 6. However, the reactions are not psuedo first order in peroxide when 4-pyridone is present, presumably because other termination processes occur. We have chosen, therefore, for comparison purposes, to report all rates in terms of the half-lives of the peroxide.

$$\text{rate} = \frac{-d[Per]}{dt} = \left[\frac{3}{4}k_1 \pm \frac{k}{2}\left(\frac{1}{4} + 2\frac{k_2k_3}{k_1k_5}[\text{alcohol}]\right)^{1/2}\right][Per] \qquad (6)$$

Table I shows the half-lives of *t*-butyl peroxide at 125° in several alcohols containing varying amounts of added reagents. The rate of decomposition of the peroxide is considerably faster in secondary alcohols from which an α-hydroxyalkyl radical can be formed than in *t*-butyl alcohol which, having no α hydrogens, cannot participate in the chain sequence 2 and 3. The presence of 4-pyridone in small amounts (1–10 mol % of the amount of *t*-butyl peroxide originally present) markedly enhances the rate of decomposition of the peroxide in all of the secondary alcohols but has no effect on the decomposition rate in *t*-butyl alcohol. An explanation for the rate enhancement is that the α-hydroxyalkyl radical transfers its hydrogen atom to 4-pyridone (reaction 7) yielding the 4-hydroxymonohydropyridyl radical (A·) which reduces the



II A· (7)



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(1) This work was supported by a grant from the National Institutes of Health (AM-08517-02).

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TABLE I

HALF-LIVES OF *t*-BUTYL PEROXIDE AT 125° IN SECONDARY ALCOHOLS

Alcohol[a]	Initial ratio of alcohol to peroxide	Added reagent (mole %)[b]	Half-life, min
t-Butyl alcohol	5.00	None	468
	4.94	4-Pyridone (9.86)	468
2-Butanol	4.92	None	266
	4.95	None	274
	4.68	4-Pyridone (0.93)	190
	5.21	4-Pyridone (5.27)	124
	4.95	4-Pyridone (9.88)	105
	5.02	2-Pyridone (5.14)	338
	4.69	2-Pyridone (9.66)	~375
	4.91	3-Hydroxypyridine (9.90)	275
	4.94	3-Hydroxypyridine (9.95)	268
2-Octanol	5.01	None	280
	4.90	4-Pyridone (1.19)	236
	6.89	4-Pyridone (5.44)	150
	4.85	4-Pyridone (9.79)	140
	4.95	2-Pyridone (9.99)	~350
Cyclopentanol	19.35	None	256
	5.01	None	248
	4.99	4-Pyridone (10.50)	160
Cyclohexanol	19.89	None	370
	4.90	None	425
	5.01	4-Pyridone (10.13)	240
Cycloheptanol	20.38	None	148
	5.11	None	150
	4.58	4-Pyridone (9.08)	59
Cyclooctanol	19.56	None	120
	5.00	None	120
	4.62	4-Pyridone (8.82)	44

[a] The respective registry numbers are 75-65-0, 78-92-2, 123-96-6, 96-41-3, 108-93-0, 502-41-0, and 696-71-9. [b] Based on amount of peroxide initially present.

peroxide by another hydrogen atom transfer reaction (reaction 8). In order for the 4-pyridone to exercise a positive catalytic effect, it is necessary that not only must reaction 7 compete favorably with reaction 3, but reaction 8, the hydrogen atom transfer from A· to the peroxide, must also be very rapid. The formation of 4-hydroxypyridine with its aromatic ring resulting from transfer of the nitrogen-bonded hydrogen of A· may well provide the driving force for this reaction. Tautomerization of 4-hydroxypyridine to 4-pyridone would regenerate the catalyst.

Table II shows that the rate enhancement by 4-pyridone is truly catalytic in that the reagent, present in 1 mol % relative to the peroxide, is not consumed

TABLE II

CONCENTRATION MEASUREMENTS OF 4-PYRIDONE IN THE REACTION OF *t*-BUTYL PEROXIDE AND 2-BUTANOL AT 125°

Time, min	% reaction of peroxide — Without catalyst[a]	With catalyst[b]	4-Pyridone remaining[c]
0	0	0	16.0
40	11	19	15.7
80	20	30	14.9
100	28	36	14.9
140		43	13.7
160	33	50	14.4
220	42		

[a] Initial molar ratio of alcohol/peroxide 4.92:1. [b] Initial molar ratio of alcohol/peroxide/4-pyridone 5:1:0.01. [c] Millimoles per liter.

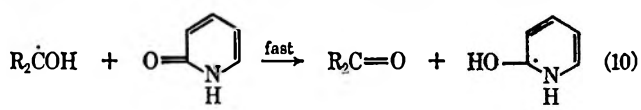
although the rate of reaction of the peroxide is faster than that of a reaction without the catalyst.

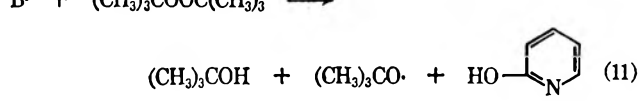
The observed rate of decomposition of the peroxide in the 4-pyridone catalyzed reactions would be given by eq 9. The effectiveness of the catalyst in enhancing

$$\frac{-d[Per]}{dt} = k_1[Per] + k_3[R_2\dot{C}OH][Per] + k_4[R_2\dot{C}OH][4\text{-pyridone}] \quad (9)$$

the reaction rate would therefore depend on both the reactivity of 4-pyridone toward reaction with the alcohol radical and on the concentration of 4-pyridone in the reaction mixture. Our data show that the catalytic effect does vary amongst the secondary alcohols studied and that the catalytic effect is concentration dependent.

3-Hydroxypyridine, as would be expected on the basis of structural requirements, displays no significant catalytic effect on the reaction. 2-Pyridone (III) might, however, be expected to behave similarly to 4-pyridone. We found that 2-pyridone impedes the reaction rate rather than enhances it (see Table I). One explanation for this behavior may be that hydrogen atom transfer to the carbonyl function of 2-pyridone (reaction 10) is fast but the resulting 2-hydroxymonohydropyridyl radical (B·) reacts slowly with the peroxide (reaction 11) and thus acts as a retarder. It





is not immediately obvious why reaction 11 should be slow since the driving force responsible for the rapid transfer of a hydrogen atom from B· to the peroxide, namely, formation of the aromatic ring, should be operative in this reaction as well. The lack of reactivity of B· cannot be attributed solely to the steric interaction caused by the 2-hydroxy group, a steric effect not present in the case of the 4-hydroxymonohydropyridyl radical A·. The 2,6-dimethyl-3,5-dicarboethoxymonohydropyridyl radical, which would be expected to experience even more steric hindrance than B· in reactions with *t*-butyl peroxide, transfers its hydrogen atom readily to the peroxide.[4] One plausible explanation is that the 2-hydroxymonohydropyridyl radical B· is more effectively solvated by the hydroxylic alcohol because of its greater polarity than is the 4-hydroxymonohydropyridyl radical A·. The energy of desolvation of the tightly solvated radical would then have to become part of the activation energy requirement for the hydrogen atom transfer to the peroxide.

Examination of the data in Table I shows that the half-lives of the peroxide in these secondary alcohols vary to a significant extent even in the absence of 4-pyridone. If it is assumed that the rate of the unimolecular decomposition is approximately the same for each alcohol, namely, about that of *t*-butyl alcohol, the differences in the rate serve as a measure of the ability of the alcohol to participate in the chain sequence 2 and 3. The half-lives of the peroxide in the acyclic

alcohols are almost identical. The varying extent of induced decomposition of the peroxide in the cycloalkanols, however, indicates that conformational aspects of the alcohol possibly play a significant role in these reactions. The apparent order of reactivity of the cycloalkanols toward participation in the chain sequence 2 and 3, namely, $C_6 < C_5 < C_7 < C_8$, parallels the reactivity of cyclic compounds in reactions that convert a carbon from the tetrahedral sp^3 configuration to the planar sp^2 configuration.[6] The hydrogen atom abstraction reaction 2, therefore, appears to play a significant role in these reactions. Conformation strain is introduced into the cyclohexane ring in this reaction and the ability of cyclohexanol to participate in the chain sequence 2 and 3 is significantly less than that of the acyclic alcohols. On the other hand, relief of conformation strain is experienced in hydrogen abstractions from cycloheptane and cyclooctane ring systems and the extent of induced decomposition of the peroxide is greater than in the open chain alcohols. Although some relief of conformational strain would be expected in the hydrogen abstraction from cyclopentanol, its ability to participate in the chain reaction, although greater than that of cyclohexanol, is about the same as 2-butanol and 2-octanol.

It should not be inferred, however, that the hydrogen atom abstraction reaction is the limiting factor in the oxidation of secondary alcohols by the chain sequence 2 and 3. The observation that 4-pyridone has a catalytic effect in each alcohol is significant since the interaction of 4-pyridone in the chain sequence does not involve any change in the configuration of the α carbon of the alcohol and hence should not have any effect on the conformational aspects of the reaction. If the limiting reaction of the chain sequence were the hydrogen abstraction, a process that does not involve 4-pyridone, no catalytic effect would be observed. The best explanation for the observation that both the conformational aspects and the catalysis are observed in these reactions is that the chain prograting reactions 2 and 3 proceed at about comparable rates. Any factor that would increase or decrease the rate of either reaction would effect the over-all rate of the induced decomposition of the peroxide since the rate of each reaction in the chain sequence would be increased or decreased in order to maintain steady-state concentrations (or nearly so depending on the kinetic chain length) of the chain-carrying radicals. That cross-termination (reaction 5) occurs in the reactions of many secondary alcohols as evidenced by the observation that the reactions are psuedo first order in peroxide supports the suggestion that neither reaction 2 nor 3 is rate limiting and the chain-carrying radicals have comparable concentrations. The deviation from the psuedo-first-order reactions in the presence of 4-pyridone may be caused by an imbalance in the steady-state concentrations of the chain-carrying radicals causing termination to occur, in part, by coupling of *t*-butoxy radicals. The steady-state concentration of the α-hydroxyalkyl radicals is likely decreased relative to the *t*-butoxy radicals because of the rapid reaction of the former with 4-pyridone.

Experimental Section[7]

Materials.—The following alcohols were obtained from the indicated commercial sources and redistilled before using: 2-Octanol (Eastman Organic), 2-butanol (J. T. Baker), *t*-butyl alcohol (Fisher), cyclopentanol (Matheson Coleman and Bell) and cyclohexanol (Fisher). Cycloheptanol [bp 54.5–55° (1.5 mm)] and cyclooctanol [bp 66° (1.5 mm)] were prepared by $NaBH_4$ reduction of cycloheptanone (Aldrich) and cyclooctanone (Aldrich), respectively. 4-Pyridone (Aldrich) was purified by the method described previously which consisted of recrystallizing it from chloroform as the dihydrate. The dihydrate is then dehydrated by heating under vacuum at 90°, mp 147–148° (lit.[8] mp 147.5–150°). 3-Pyridone (Aldrich) was recrystallized from benzene and melted at 125–127° (lit.[9] mp 126°). 2-Pyridone (Aldrich) was recrystallized from benzene and melted at 105–107° (lit.[10] mp 106–107°). Commercial *t*-butyl peroxide (Wallace and Tierman, Inc.) gave a single peak on gas chromatographic analysis and was used without further purification. Gas chromatographic analyses were performed on an F & M Model 5750 gas chromatograph using an 8 ft × 1/8 in. column packed with 2% diethylene glycol succinate and 8% SF-96 on Chromosorb W. The chromatograms were traced on a Mosely recorder equipped with a Disc integrator. Spectrophotometric analysis were made on a Beckman DU-2 spectrometer.

Determination of Decomposition Rate of *t*-Butyl Peroxide.—Solutions consisting of the reagents in the amounts shown in Table I were in each case divided into eitht Pyrex tubes, sealed and placed in a constant-temperature bath set at 125°. Tubes were removed at various time intervals and immediately cooled to 0°. A portion of the contents of each tube was accurately weighed out along with a known amount of an internal standard for chromatographic analysis. Benzene was used as the internal standard for the higher boiling alcohols and chlorobenzene for the lower boiling alcohols. The peak areas of the peroxide and the internal standard were used to determine the amount of peroxide remaining in the sample.

Determination of Catalyst Consumption.—In a reaction of 2-butanol with approximately 1 mol % 4-pyridone relative to *t*-butyl peroxide, the amounts of both peroxide and 4-pyridone in each sample were determined. The peroxide was determined by the method described above. The 4-pyridone was determined spectrophotometrically making use of its absorption maximum at 257 mμ (ϵ 1.48 × 10^4). The data found are given in Table II.

Registry No.—I, 110-05-4; II, 108-96-3.

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Aromatic Substitution. XXI. Kinetics of Nucleophilic Substitution of Some Bromopyridines and -picolines with Thiophenoxide Ion. Nature of Activation by ortho-Methyl Groups[1]

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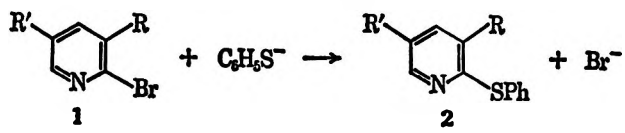
The rates and activation parameters were determined for the reaction of potassium thiophenoxide in methanol with 2-bromo-, 2-bromo-3-methyl-, 2-bromo-5-methyl-, 2,3-dibromo-, and 2,5-dibromopyridine. An *o*-methyl group accelerated the reaction, probably due to the combined effects of London forces and ion–dipole interactions. At 110°, $k_{o-CH_3}/k_{p-CH_3} = 5.0$, while $k_{o-Br}/k_{p-Br} = 2.5$. These results were compared with those obtained with methoxide ion in methanol. Substitutions with thiophenoxide ion in dimethyl sulfoxide were also studied. The increase in rate on going to this solvent was not as great as expected and is discussed. Thiophenol itself reacted faster in methanol than did the thiophenoxide ion due to a fast acid–base preequilibrium in which the bromopyridine was protonated and allowed to react as such with the thiophenoxide ion formed.

Quantitative studies[3] on orientation and reactivity in nucleophilic aromatic substitution of a hydride ion equivalent in the pyridine series by phenyllithium have brought to light the remarkable observation that a 3-methyl or a 3-ethyl group *activates* the 2 position of the pyridine nucleus toward this nucleophilic attack, the methyl substituent activating it more than ethyl. On the other hand, position 6 was normally deactivated, as expected from the electron-donating effect of the alkyl group. The relative rates were determined by the competitive technique and the total rate ratios and partial rate factors were: ${}^{Me}_{H}K = 1.30$, ${}^{Me}F_2 = 2.4$, ${}^{Me}F_6 = 0.13$ and ${}^{Et}_{H}K = 0.79$, ${}^{Et}F_2 = 1.4$, ${}^{Et}F_6 = 0.16$. In the Tschitschibabin reaction with sodamide, however, a 3-methyl group does not activate C-2 toward substitution although attack still takes place predominantly at the 2 rather than at the 6 position.[4] An ion–dipole attractive interaction of the 3-methyl group and the approaching amide ion might account for this observation.[5] Two possibilities were entertained to account for the results obtained in the phenyllithium reactions. (a) London dispersion forces acting between the 3-alkyl substitutent and the attacking nucleophile[6] could lower the energy of activation for attack at C-2 but not at C-6. The increase in the attractive force on going from the methyl to the more polarizable ethyl group would be counterbalanced by the increasing steric hindrance. (b) An alternative explanation invoked the existence of an electron-deficient type of bond between the 3-alkyl group and the organolithium compound which would facilitate attack at C-2. The ease of formation of such an electron-deficient bond would be expected to decrease as branching of the methyl substituent increased.[7] This type of bonding could be looked upon perhaps as a stronger version of an ion–dipole attraction.

In order to decide between the alternatives it was hoped to carry out kinetic studies on model systems and to get the required information from an analysis of the thermodynamic parameters. To this end, the reaction of 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine with methoxide ion was studied under a variety of conditions.[8] The rates were in the order 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methyl, and were dependent upon E_a. This order of reactivity parallels that found in the Tschitschibabin but not in the phenyllithium reaction. The lesser deactivation of the *ortho* then the *para* position by a 3-methyl group was attributed[8] to an ion–dipole attraction[9] between the methyl group and the attacking methoxide ion approaching the *ortho* position, this attraction overcompensating the greater inductive effect of the methyl substituent at the *ortho* than at the *para* position, and any steric hindrance by the 3 substituent to approach.[10] Release of steric compression between the bromine and methyl groups and the solvation shell around the lone pair of electrons on nitrogen in the ground state of 2-bromo-3-methylpyridine on going to the transition state, but not of 2-bromo-5-methylpyridine, may also play a minor role.

In a continuation of efforts to find a system amenable to kinetic study which would reporduce the order of reactivities observed with phenyllithium, attention was turned to the reaction of 2-bromopyridine derivatives (**1**) with thiophenoxide ion, since the latter is much more polarizable than methoxide ion, which could lead to greater London attractive forces between the *o*-methyl group and the attacking nucleophile.[6] Preliminary studies of relative reactivities were carried out using the competitive technique in which equimolar mixtures of 2-bromo- and 2-bromo-3-methylpyridine, 2-bromo- and 2-bromo-5-methylpyridine, and 2-bromo-3-methyl- and 2-bromo-5-methylpyridine were allowed to react with a small amount of potassium thiophenoxide in methanol. The products were analyzed by gas chromatography and the total rate ratios and partial rate factors calculated. Authentic samples



1 **2**

of the 2-thiophenoxypyridines (**2**) were prepared for comparison with the reaction products. When an

(1) Aromatic Substitution. XXI. Previous part in this series: R. A. Abramovitch and O. A. Koleoso, *J. Chem. Soc., B*, 1292 (1968).

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TABLE I

KINETIC DATA FOR THE REACTION OF 2-BROMOPYRIDINE DERIVATIVES WITH THIOPHENOXIDE ION IN METHANOL

Pyridine	10^5k_2[a], l. mol^{-1} sec^{-1} (temp, °C)	E_a, kcal/mol	$\Delta S^{\ddagger}$,[b] eu
2-Br	2.14 (110), 6.85 (123), 19.3 (136.8)	26.0	−13.5
2-Br-3-Me	3.0 (110), 3.64 (111), 7.35 (121), 14.3 (129.2), 27.4 (133.8)	24.0	−18.5
2-Br-5-Me	0.255 (101.5), 0.61 (110), 1.34 (120), 4.29 (133.5)	27.0	−13.5
2,3-Br_2	48.4 (99.5), 107 (110), 151 (114.5), 222 (120.5), 426 (130)	21.2	−19.0
2,5-Br_2	43.4 (110), 105.5 (121.2), 217.8 (131.2)	23.5	−14.0

[a] [PhS^-] = [bromopyridine] = 0.3075 N ≡ 0.0046125 mol of reactants. [b] Experimental errors are ±0.2 kcal in E_a and ± 1eu in $\Delta S^{\ddagger}$.

excess of potassium methoxide in methanol over thiophenol was used a substantial amount of the 2-methoxypyridines was formed in addition to **2**, and an analysis of the recovered starting materials indicated that, under these conditions, the rate of consumption of bromopyridines was in the order 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methyl. This is due to the greater reactivity of 2-bromopyridine with methoxide ion compared with the methyl derivatives.[8] If, however, equimolar amounts of potassium methoxide and thiophenol were used in the preparation of thiophenoxide no competition from methoxide ion (which would be present in small amounts due to the equilibrium $C_6H_5S^- + MeOH \rightleftharpoons C_6H_5SH + MeO^-$) was observed and no methoxypyridines could be detected by gas chromatography. Under these conditions the sought-for order of reactivities was finally encountered: 2-bromo-3-methyl- > 2-bromo- > 2-bromo-5-methylpyridine; ${}^{o\text{-}Me}_{H}K = 2.46$ and ${}^{p\text{-}Me}_{H}K = 0.63$; *ortho*:*para* ratio (at 80°) = 3.85.

Kinetic measurements were now carried out with the bromopyridines and thiophenoxide ion in methanol. The results are summarized in Table I.

The results clearly indicate the activation of the 2-bromopyridine by an *o*-methyl group and the expected deactivation by a *p*-methyl group. The *ortho* effect arises from a decrease in the energy of activation (ΔE_a = 2 kcal/mol) of the substitution process. This could be due either (i) to London dispersion attractive forces,[6] or (ii) to an ion–dipole attraction,[9,11] either of which should be large enough to overcome the electronic deactivation by the *o*-Me group (≥1 kcal/mol) and the steric hindrance to approach by the nucleophile. An examination of the *o*-Me:*p*-Me and *o*-Br:*p*-Br reaction rate ratios of benzyl chlorides with MeO^-, $C_6H_5S^-$, and I^- and calculations of the magnitude of London forces operating in the transition state led to the suggestion[12] that the differences in rate ratios could be assigned to these forces. This was questioned by Sisti and his coworkers who pointed out[11] that comparison of the *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br rate ratios, with the same reagents, showed trends contrary to those expected from London interactions alone (*i.e.*, charged nucleophiles gave higher *ortho*:*para* ratios with the less polarizable methyl group than with the more polarizable bromo group). Also, in the reaction of substituted phenacyl chlorides with various nucleophiles, it was shown[9] that the highly polarizable iodide ion gave $k_{o\text{-}CH_3}/k_{p\text{-}CH_3} = 1.06$ and $k_{o\text{-}Br}/k_{p\text{-}Br} = 0.23$, *i.e.*, a higher *ortho*:*para* ratio with the less polariable substituent, while this trend was reversed when the nucleophile was a neutral species, *i.e.*, pyridine: $k_{o\text{-}CH_3}/k_{p\text{-}CH_3} = 0.79$ and $k_{o\text{-}Br}/k_{p\text{-}Br} = 1.17$. It was proposed that such results were more in accord with favorable Coulombic interactions of the ion–dipole type between the *ortho* substituents and the nucleophile since the dipoles of the $\overleftarrow{C\text{–}CH_3}$ and $\overrightarrow{C\text{–}Br}$ groups are in opposite directions. Ho, Miller, and Wong[13] reported that the reactivity of thiomethoxide ion with *p*-halogenonitro- and 1-halogeno-2,4-dinitrobenzene in methanol showed a high value of the ratio F/I similar to that found for a nucleophile of low polarizability such as methoxide ion, and felt that there was no support for the suggestion that polarizability effect enhanced reactivity in such reactions. On the other hand, Di Nunno and Todesco[14] found that the rates of the reactions of *p*-halogenonitrobenzene and 2-halogenobenzothiazoles with thiomethoxide and methoxide ions fitted well a linear relationship between the logarithm of the ratio of the reaction rates of a pair of nucleophiles (one polarizable and the other poorly so) and the polarizability of the leaving group,[15] thus confirming the relevance of polarizability factors in determining nucleophilic reactivity.

In order to decide between the two alternative explanations for the *ortho*:*para* ratio observed here, the kinetics of the reactions of 2,3- and 2,5-dibromopyridine with thiophenoxide ion in methanol were studied. The choice of bromine as the substituent was guided by the fact that it is much more polarizable than methyl and has the opposite polarity, but is similar in size to Me.[6] It would then be expected that if only London dispersion forces were at work that a larger *ortho*:*para* ratio would have been observed with the β-bromo substituent than with the β-methyl. If, on the other hand, only ion–dipole interactions were involved then an *ortho*:*para* ratio <1 would have been predicted for attack by PhS^-. For the sake of comparison, the rates and Arrhenius parameters for the reactions of the same compounds with MeO^- in MeOH are given in Table II.

TABLE II

RATE CONSTANTS AND ARRHENIUS PARAMETERS FOR REACTIONS OF 2-BROMOPYRIDINE DERIVATIVES WITH POTASSIUM METHOXIDE IN MeOH

Pyridine	10^5k_2, l. mol^{-1} sec^{-1} (at 110°)	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
2-Br[c]	9.44	26.6_3	−10.5
2-Br-3-Me[c]	2.39	27.8_7	−10.0
2-Br-5-Me[c]	1.54	28.9_3	−7.8
2,3-Br_2[a]	155	23.83	−11.4
2,5-Br_2[b]	152	24.75	−9.5

[a] 10^5k_2 at temperatures in parentheses: 63.5 (99.5°), 221 (114.5°), 359 (120.5°), 705 (130°); log A = 10.78. [b] 10^5k_2 at temperatures in parentheses: 29.5 (91.5°), 395.3 (121.5°); log A = 11.35. [c] See ref 8.

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TABLE III

RATE RATIOS FOR REACTIONS OF 3-R- OR 5-R-2-BROMOPYRIDINES WITH POTASSIUM METHOXIDE AND POTASSIUM THIOPHENOXIDE IN MeOH AT 110°

R	k_{o-R}/k_{p-R}	$(k_{PhS^-}:k_{MeO^-})_R/(k_{PhS^-}:k_{MeO^-})_H$	$(k_{PhS^-}:k_{MeO^-})_{o-R}/(k_{PhS^-}:k_{MeO^-})_{p-R}$
CH_3	5.0 (PhS^-), 1.6 (MeO^-)	5.5 (*o*-Me), 1.7 (*p*-Me)	3.2
Br	2.5 (PhS^-), 1.0 (MeO^-)	3.1 (*o*-Br), 1.3 (*p*-Br)	2.4

The *ortho*:*para* ratios can be looked at in a number of ways. The rate ratios k_{o-R}/k_{p-R} can be compared directly for a given nucleophile and are very instructive. They do not, however, take into account differences in nucleophilicities when the behaviors of different reagents are compared. Two approaches have been used to cancel out nucleophilicity differences between reagents PhS^- and MeO^-. Reinheimer and Bunnett[6] used an expression such as eq 1 for this purpose, except

$$\frac{(k_{o-R}/k_H)_{PhS^-}}{(k_{o-R}/k_H)_{MeO^-}} \equiv \frac{(k_{PhS^-}/k_{MeO^-})_{o-R}}{(k_{PhS^-}/k_{MeO^-})_H} \quad (1)$$

that hydroxide ion (and not methoxide ion) was chosen as the basis for comparison because of its low polarizability and small size. On the other hand, it was felt by Sisti and Lowell[11] that eq 2 was a better way of adjusting the rate ratio to cancel out the nucleophilicity differences. All three of these ratios are given in Table III.

$$\frac{(k_{o-R}/k_{p-R})_{PhS^-}}{(k_{o-R}/k_{p-R})_{MeO^-}} \equiv \frac{(k_{PhS^-}/k_{MeO^-})_{o-R}}{(k_{PhS^-}/k_{MeO^-})_{p-R}} \quad (2)$$

A different way of looking at this "*ortho* effect" to take into account the difference in nucleophilicities of the two reagents is to consider the differences in Arrhenius parameters in these reactions as a function of the nature and position of the substituent. These data are given in Table IV from which it may be seen that

TABLE IV

DIFFERENCES IN ARRHENIUS PARAMETERS

	Substituent in 2-bromopyridine				
	H	3-CH_3	5-CH_3	3-Br	5-Br
ΔE_a ($\equiv E_{MeO^-} - E_{PhS^-}$)	0.6	3.9	1.9	2.6	1.3
$\Delta\Delta S^{\ddagger}_{(MeO^- - PhS^-)}$	3.0	8.5	5.7	7.6	4.5

ΔE_a for a 3-methyl substituent is larger than that for a 5-methyl substituent ($\Delta\Delta E_a = 2.6$). If the polarizability of sulfur is not taken into account the thiophenoxide ion is undoubtedly larger than methoxide and an unfavorable steric effect should have led to a trend in ΔE_a in the opposite direction. On the other hand, ΔE_a for 3-Br is not that much larger than ΔE_a for 5-Br ($\Delta\Delta E_a = 1.3$), and had only polarizability factors been involved this difference should have been greater than that for the β-methyl group.

Irrespective of which rate ratios are considered (Table III), the data are not consistent with either the involvements of pure London dispersion forces or of pure ion–dipole interactions to account for the observed "*ortho* effect," since the *ortho*:*para* ratio for a β-bromo substituent was not less than unity, but neither was it larger than the *ortho*:*para* ratio for a β-methyl group. It would seem reasonable to suggest a combination of these two factors to account for the observed results. Since these would act in opposition in the case of the 3-bromo derivative it appears that the polarizability factor is somewhat more important than the Coulombic interaction in this case. Such a situation may also well obtain in the substitutions of 3-picoline by phenyllithium and by sodium amide. In the former case, a combination of attractive interactions could explain the net activation of C-2; in the Tshitschibabin reaction, on the other hand, an ion–dipole attractive interaction would account for the observed high *ortho*:*para* ratio (10:1), but alone would not be strong enough to lead to an activation of C-2 by the 3-methyl group. Whether or not the activation of C-2 by a 3-methyl group in the reaction of 2-bromopyridine with theophenoxide ion is indeed due in large measure to polarizability effects or whether a heavy-nucleophile effect[13] is important is now under investigation using phenoxide and thiomethoxide ions with the above substrates.

The kinetics of the reactions with thiophenoxide ion were studied briefly under two other sets of conditions. As expected, the reaction of 2-bromopyridine with potassium thiophenoxide in dimethyl sulfoxide was faster than that in methanol. While the same reaction with MeO^- proceeded 3×10^3 faster in DMSO than in MeOH,[8] that with PhS^- was only 100 times faster in the nonprotic solvent, this being due to a lower energy of activation (by 3.7 kcal/mol) in DMSO than in MeOH. The entropy of activation was about the same in both solvents for the PhS^- reaction. This contrast with $\Delta\Delta S^{\ddagger}_{(MeOH-DMSO)} = 7.6$ eu and $\Delta E_{(MeOH-DMSO)} = 8.7$ kcal/mol when MeO^- was used as the nucleophile.[8] This suggests that thiophenoxide, but not methoxide, ions are appreciably solvated in DMSO solution, perhaps due to the high polarizability of the thiophenoxide ion compared with methoxide, or perhaps to an equilibrium which would lower the reactivity of

$$(CH_3)_2SO + PhS^- \rightleftharpoons (CH_3)_2\overset{O^-}{\overset{|}{S}}SPh \quad (3)$$

the nucleophile and the entropy of the ground state. There do not appear to be any data in the literature to support the latter suggestion.

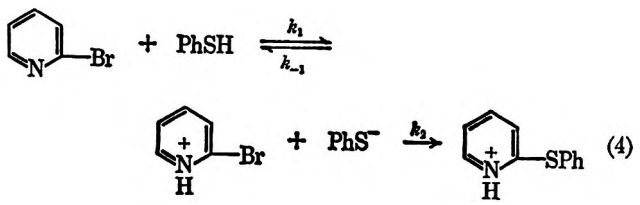
In early runs aimed at discouraging the intrusion of methoxide ions into the reactions, an excess of thiophenol over potassium methoxide was used so that both thiophenoxide ion and thiophenol were present in solution. The rate plots so obtained were unsatisfactory. Thus, at any one temperature and under identical conditions, the order of reactivity found was 3-CH_3 > H > 5-CH_3; but when an Arrhenius plot of the results at three temperatures was essayed a straight line could not be obtained. At the lower temperatures there was an initial rapid reaction, the extent of which appeared to depend on the time allowed for thermal equilibrium to be reached and on the amount of free thiophenol present. This suggested that the "free" thiophenol (always present in lesser quantities than the 2-bromopyridine) first protonated the pyridine nucleus, and that the initial fast reaction was due to an SNAr2 reaction of that fraction of the 2-bromopyridine present as the pyridinium ion with thiophenoxide ion (eq 4).[16]

(16) Presented by R. A. Abramovitch at the Gordon Conference on the Chemistry of Heterocyclic Compounds, New Hampton, N. H., July 4–8, 1966.

TABLE V

MISCELLANEOUS RUNS WITH 2-BROMOPYRIDINE

Nucleophile	Solvent	10^5k_2, l. mol^{-1} sec^{-1}	E_a, kcal/mol	$\Delta S^\ddagger$, eu
PhS^-	DMSO	5.89 (67.5°), 230 (110°)	22.3	−13.0
PhSH	MeOH	47.6 (110°), 150.1 (132°)	16.2	−10.8



(4)

In order to check this possibility the reaction of 2-bromopyridine with an equivalent amount of thiophenol in methanol (no methoxide added) was carried out at two temperatures (Table V). The product was shown to be 2-thiophenoxypyridine; no 2-methoxypyridine was detected by glc. Good second-order kinetics were observed. The activation parameters are uncertain to the extent that they were calculated from measurements at two temperatures only. The results are entirely consistent with a substitution proceeding *via* a pyridinium salt;[16] such salts are known to undergo nucleophilic substitution much faster than do the free bases.[17] The reaction with thiophenol itself proceeds 22.2 times faster at 110° than does that with thiophenoxy anion.

Similar observations have been reported in more extensive studies by Illuminati, Linda, and Marino,[18] who found the noncatalyzed reaction of a chloroquinoline with *p*-toluenethiol in methanol solution is faster than the reaction involving either the aryl sulfide or the chloroquinoline ion with the non-ionized form of the other reactant. In the present case, we believe the fast reaction taking place is that between the pyridinium *salt* and the thiophenoxide *ion* produced in eq 4. The reaction of the free base with thiophenoxide is known to be much slower and that between the pyridinium salt and unionized thiophenol is expected to be slow.[18] Assuming the preequilibrium in eq 4 is fast compared with the substitution process, a steady-state treatment will lead to eq 5 and, if $k_{-1} \gg k_2$ and $K = k_1/k_{-1}$,

$$\text{rate} = \frac{k_1k_2}{k_{-1} + k_2}[\text{PhSH}][\text{PyBr}] \qquad (5)$$

this reduces to eq 6 in accord with the observed second-order kinetics. The same result was obtained by Illuminati[18] in the chloroquinoline series.

$$\text{rate} = k_2K[\text{PhSH}][\text{PyBr}] \qquad (6)$$

Experimental Section

Materials.—Thiophenol (Eastman) was fractionally distilled, the cut bp 166–168° (740 mm) being used. The purification of dimethyl sulfoxide, methanol, 2-bromo-, 2-bromo-3-methyl- and 2-bromo-5-methylpyridine was as previously reported,[8] as was the preparation of solutions of potassium methoxide in methanol. 2,5-Dibromopyridine (Aldrich) was recrystallized from ethanol and had mp 94° (lit.[19] mp 94°).

Solutions of potassium thiophenoxide in methanol were prepared by adding an equivalent amount of potassium methoxide in methanol to a weighed amount of thiophenol.

Solutions of potassium thiophenoxide in dimethyl sulfoxide were prepared by dissolving solid potassium thiophenoxide in pure dimethyl sulfoxide and storing the solutions under nitrogen. These could be standardized either by direct titration with hydrochloric acid or by the addition of excess hydrochloric acid and back-titration with baryta (bromocresol green–methyl red indicator). Potassium thiophenoxide itself was prepared by the addition of slightly less than the equivalent amount of potassium methoxide solution to a solution of thiophenol in methanol. The solution was evaporated to near dryness, thiophenol (1–2 ml) was then added, and the solution taken completely to dryness to give the white salt.

2,3-Dibromopyridine.—A mixture of 3-bromo-2-pyridone[20] (4.0 g) and phosphorus oxybromide (20 g) was heated to near reflux for 2.5 hr. The mixture was then poured into ice–water, neutralized with potassium carbonate and extracted with ether. The solid residue after the evaporation of the ether was recrystallized from aqueous alcohol to give 2,3-dibromopyridine (4.0 g, 65%): mp 59° [lit.[19] mp 58–59°]; nmr (CCl_4) τ 1.75 (H-6, quartet $J_{5,6} = 4.5$ cps, $J_{4,6} = 1.5$ cps), 2.16 (H-4, quartet, $J_{4,5} = 8$ cps), 2.87 (H-3, quartet).

Reaction Products.—These were obtained by a preparative reaction of the appropriate 2-bromopyridine with potassium thiophenoxide in methanol under a dry nitrogen atmosphere under the conditions of the kinetic runs. 2-Thiophenoxypyridine had bp 121–122° (1 mm) [lit.[21] bp 160–162° (8 mm)]. The picrate (from water) had mp 142–143°.

3-Methyl-2-thiophenoxypyridine had bp 142–144° (2 mm) (72.7% yield).

Anal. Calcd for $C_{12}H_{11}NS$: C, 70.70; H, 5.47. Found: C, 70.21; H, 5.47.

The picrate (from benzene) had mp 158–159°.

Anal. Calcd for $C_{12}H_{11}NS$, $C_6H_3N_3O_7$: C, 50.20; H, 3.25. Found: C, 50.48; H, 3.45.

5-Methyl-2-thiophenoxypyridine had bp 148–150° (2 mm) (78.5% yield).

Anal. Calcd for $C_{12}H_{11}NS$: C, 70.70; H, 5.47. Found: C, 70.34; H, 5.51.

The picrate (from benzene) had mp 174–175°.

3-Bromo-2-thiophenoxypyridine was purified by gas chromatography on a 6 ft × 0.25 in. 20% SE 30 on Chromosorb column. It gave a picrate, mp 129–130° (from methanol).

Anal. Calcd for $C_{11}H_8BrNS$, $C_6H_3N_3O_7$: C, 41.23; H, 2.24. Found: C, 41.28; H, 2.30.

The nmr spectrum ($CDCl_3$) of free base showed τ 1.99 (1 H quartet, H-5), 1.20–1.60 (5 H multiplet), 1.16 (1 H doublet, H-4), 0.64 (1 H doublet, H-6).

5-Bromo-2-thiophenoxypyridine was similarly purified by glpc and the picrate, mp 111° (from methanol), was analyzed.

Anal. Calcd for $C_{11}H_8BrNS$, $C_6H_3N_3O_7$: C, 41.23; H, 2.24. Found: C, 41.35; H, 2.10.

The nmr spectrum ($CDCl_3$) of free base showed τ 3.28 (1 H doublet, H-3), 2.40–2.70 (6 H multiplet, H-4 and C_6H_5), 1.59 (1 H singlet, H-6).

Competitive Reactions.—The procedure used is illustrated by means of a typical run using 2-bromo- and 2-bromo-3-methylpyridine. A solution of 2-bromopyridine (0.3119 g), 2-bromo-3-methylpyridine (0.3285 g), and thiophenol (0.0530 g) in methanol was treated with 0.13 *N* potassium methoxide in methanol solution (1 ml) and heated in a sealed tube under dry oxygen-free nitrogen in a thermostat at 80° for 24 hr. The reaction mixture was analyzed by glpc using a 2.5 ft × 0.25 in. column packed with precipitated asphalt on Chromosorb W (15% w/w) operated at 163° and a helium inlet pressure of 40 psi. Standard calibration curves were plotted between concentration of authentic products and peak areas. The total rate ratios were calculated using the Ingold–Shaw equation (eq 7),[22]

$$_xvK = \log\left[1 - \frac{Z_0}{Y_0}R/(1 + R)\right] \Big/ \log\left[1 - \frac{Z_0}{X_0}1/(1 + R)\right] \qquad (7)$$

(17) M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).

(18) G. Illuminati, P. Linda, and G. Marino, *J. Amer. Chem. Soc.*, **89**, 3521 (1967).

(19) H. J. den Hertog, *Rec. Trav. Chim. Pays-Bas*, **64**, 85 (1945).

(20) M. Cava and B. Weinstein, *J. Org. Chem.*, **23**, 1616 (1958).

(21) E. Vantare, G. von Zenat, F. L. White, L. J. S. Brooker, G. H. Keyes, R. H. Sprague, and R. H. Van Dyke, *J. Amer. Chem. Soc.*, **73**, 5329 (1951).

(22) C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).

where X_0 = initial concentration of 2-bromopyridine, Y_0 = initial concentration of the substituted 2-bromopyridine, Z_0 = initial concentration of the nucleophilic reagent, and R = ratio of the isomers formed. Similar runs were carried out using mixtures of 2-bromo- and 2-bromo-5-methylpyridine and a ternary mixture of 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine.

Kinetic Procedures. A. Potassium Thiophenoxide in Methanol.—The runs were carried out in sealed tubes under nitrogen using 15-ml portions of solution containing equimolar (≡0.00461 mol) proportions of potassium thiophenoxide and the 2-bromopyridine. Aliquots were quenched in halide-free nitric acid and the solution was allowed to stand for 24 hr in air so that the unreacted thiophenol which was liberated was oxidized and did not interfere with the titration. Liberated bromide ion was titrated against silver nitrate. To check this procedure an aliquot was also quenched with hydrochloric acid and back-titrated with baryta to determine the amount of thiophenoxide consumed; data indicating that halide liberated is equivalent to thiophenoxide consumed [time in hours, titer for bromide determination *vs.* 0.0202 *N* $AgNO_3$ (a = 12.1 ml), titer for thiophenoxide determination after addition of aliquot of HCl *vs.* 0.0312 *N* $Ba(OH)_2$ (a = 18.72 ml)]: 0, 0.02, 11.00; 7.6, 0.78, 11.55; 24, 2.03, 12.25; 48, 3.42, 13.24; 73, 4.38, 13.95; 100, 5.40, 14.52; k_2 (from Br^- determination) = 4.853×10^{-5} l. mol^{-1} sec^{-1}; k_2 (from acid-base titration) = 4.942×10^{-5} l. mol^{-1} sec^{-1}.

B. Thiophenol in Methanol.—Equimolar amounts of the 2-bromopyridine and thiophenol in methanol were sealed in glass tubes under nitrogen. The rates were initially followed by pouring the reaction mixture into halide-free nitric acid, extraction with two portions of chloroform and then the addition of a few drops of hydrogen peroxide. After a few hours the solution was extracted with ether, the ether layer washed with water and the aqueous extracts combined and analyzed for bromide ion. This did not lead to consistent titration values, and the method was abandoned in favor of that of Bevan and Hirst.[23] The contents of the sample tube were added to 25 ml of 1 *N* hydrochloric acid, to which solid potassium iodide was added followed by a known volume of standard potassium iodate. The excess iodine was titrated against sodium thiosulfate solution.

C. Thiophenol in Dimethyl Sulfoxide.—DMSO liberated iodine from acid solutions of iodide and iodate so that this method of assaying was discarded. Equimolar amounts (0.00275–0.00500 mol) of the 2-bromopyridine and potassium thiophenoxide in DMSO were heated under nitrogen in sealed tubes. Aliquots were quenched in hydrochloric acid and the excess acid was back-titrated with baryta.

(23) C. W. L. Bevan and J. Hirst, *J. Chem. Soc.*, 254 (1956).

Registry No.—Thiophenoxide ion, 13133-62-5; 2-bromopyridine, 109-04-6; 2-bromo-3-methylpyridine, 3430-17-9; 2-bromo-5-methylpyridine, 3510-66-5; 2,3-dibromopyridine, 13534-89-9; 2,5-dibromopyridine, 624-28-2; 2-thiophenoxypyridine (picrate), 19520-21-9; 3-methyl-2-thiophenoxypyridine, 19520-22-0; 3-methyl-2-thiophenoxypyridine (picrate), 19520-23-1; 5-methyl-2-thiophenoxypyridine, 19541-52-7; 5-methyl-2-thiophenoxypyridine (picrate), 19520-24-2; 3-bromo-2-thiophenoxypyridine, 19520-25-3; 3-bromo-2-thiophenoxypyridine (picrate), 19520-26-4; 5-bromo-2-thiophenoxypyridine, 19520-27-5; 5-bromo-2-thiophenoxypyridine (picrate), 19520-28-6.

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Electronic Absorption and Fluorescence of Phenylethynyl-Substituted Acenes

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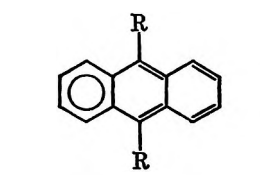
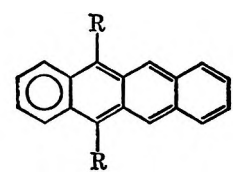
Substitution of acenes Ia, IIa and IIIa with the phenylethynyl group substantially increased quantum yields of fluorescence, and produced large shifts to longer wavelengths in the visible absorption and fluorescence spectra. A nearly constant displacement toward the red of 100 mμ in the fluorescence emission was observed for the *meso*-substituted bis(phenylethynyl)acenes Ib, IIb, and IIIb, when compared with the parent hydrocarbons. The spectral data indicate that the ethynyl group is a better conductor of electronic effects in the excited state than in the ground state.

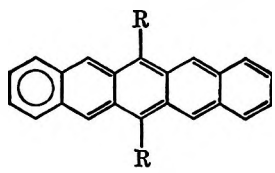
An extensive study of the fluorescence efficiencies of 9,10-disubstituted anthracenes has shown that the relative effectiveness of the phenyl group in intensifying fluorescence is considerably greater than that for such substituents as halo, hydroxy, alkoxy, alkyl, amino, acyl and nitro.[1] We have found that 9,10-bis(phenylethynyl)anthracene (Ib), a bright yellow-green fluorescer,[2] has an absolute fluorescence quantum yield (ϕ_F) = 0.96, which is even higher than ϕ_F = 0.84 for 9,10-diphenylanthracene (Ic). Thus the fluorescence efficiency of Ib is greater than any of the 9,10-disubstituted anthracenes previously reported. A comparison of the absorption and emission properties of Ib with those of the parent hydrocarbon, anthracene (Ia), shows that in addition to enhancing the fluorescence efficiency, the mild electron accepting phenylethynyl group[3] has also produced unusually large red shifts (see Table I).



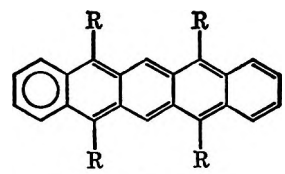
Ia, R = H
b, R = $-C{\equiv}CC_6H_5$
c, R = $-C_6H_5$
d, R = $-CH{=}CHC_6H_5$



IIa, R = H
b, R = $-C{\equiv}CC_6H_5$



IIIa, R = H
b, R = $-C{\equiv}CC_6H_5$



IVb, R = $C{\equiv}CC_6H_5$

To test the generality of the effect of phenylethynyl substitution on excited state behavior, phenylethynylacenes IIb, IIIb and IVb were prepared (see Table II for visible absorption spectra) and evaluated. 5,12-Bis(phenylethynyl)naphthacene (IIb), and 6,13-bis-

(1) M. Furst, H. Kallman, and F. H. Brown, *J. Chem. Phys.*, **26**, 1321 (1957).

(2). (a) A. Heller and G. Rio, *Bull. Soc. Chim. Fr.*, 1707 (1963); (b) A. Zweig, A. H. Maurer, and B. G. Roberts, *J. Org. Chem.*, **32**, 1322 (1967).

(3) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3452 (1953).

TABLE I

ABSORPTION AND FLUORESCENCE OF THE ACENES I–IV

Compd	Absorption,[a] Long-wavelength band, λ_{max}, mμ	Log ε	Δλ, mμ	Fluorescence,[a] short-wavelength band, λ_{max}, mμ	Δ λ_{max}	Quantum yields (ϕ_F), einstein/mol
Ia	382	3.80		388		0.25
Ib	455	4.52	73	486	98	0.96
Ic	395	4.13	13	407	19	0.84
IIa	476	3.98		483		0.21
IIb	548	4.37	72	580	97	0.66
IIIa	576	3.72		578		<0.01
IIIb	655	4.41	79	680	102	0.34
IVb[b]	705	4.43	129	740	162	0.08

[a] Solvent was benzene. [b] Solvent was *o*-dichlorobenzene.

TABLE II

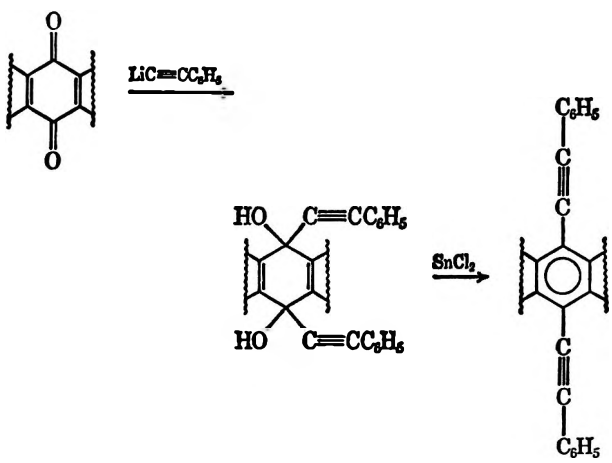
VISIBLE ABSORPTION SPECTRA OF PHENYLETHYNYL-SUBSTITUTED ACENES[a]

Compd	λ_{max}, mμ (log ε)
Ib	439 (4.50), 455 (4.52)
IIb	478 (3.90), 512 (4.24), 548 (4.37)
IIIb	560 (3.74), sh 604 (4.16), 655 (4.41)
IVb[b]	430 (3.60), 461 (3.46), 597 (371), 645 (4.18), 705 (4.43)

[a] Determined in benzene with a Cary 15 spectrophotometer. [b] Solvent was *o*-dichlorobenzene.

(phenylethynyl)pentacene (IIIb), and 5,7,12,14-tetrakis(phenylethynyl)pentacene (IVb), were prepared from 5,12-naphthacenequinone,[4] 6,13-pentacenequinone[5] and 5,7,12,14-pentacenediquinone,[6] respectively, according to the procedure described by Ried for making Ib—phenylethynylation with lithium phenylacetylide, followed by reduction of the corresponding quinols with stannous chloride[7] (see Scheme I).

SCHEME I



The spectral data presented in Table I point out the generality of the large shifts to longer wavelengths and the increased fluorescence efficiencies. In particular, the fluorescence emission of *meso*-substituted acenes Ib, IIb and IIIb is displaced from that of the parent hydrocarbons by a nearly constant value of 100 mμ. Substitution of four phenylethynyl groups in the 5, 7, 12, and 14 positions of pentacene (*i.e.*, IV), however, gave a bathochromic shift of only 162 mμ.

Comparison of the yellow-green fluorescence of Ib with the observed blue fluorescence of 9,10-diethynylanthracene[8] illustrates the essential character of the phenyl group in causing a bathochromic shift. The large spectral shifts in the phenylethynyl-substituted acenes indicate substantial electron delocalization through the -C≡C- group in the excited state, and a significant lowering of the first excited singlet relative to the ground state. This observation is in direct contrast to the proposal that the delocalized system of γ-phenylpropargyl radical does not include the benzene ring,[9] and points out the difference in the conjugative characteristics of the -C≡C- group in excited and ground-state systems.

The absence of a sizable red shift in the absorption and fluorescence spectra of 9,10-diphenylanthracene reflects the noncoplanarity of the phenyl groups with the anthracene ring in the ground and excited states. Similarly, steric effects appear to account for the small red shift in the absorption spectrum of *trans,trans*-9,10-distyrylanthracene (Id), which has a single broad band centered at 410 mμ. The steric strain in the vibrationally equilibrated first excited singlet state of Id evidently is relieved by a conformational change, as indicated by a substantial shift in fluorescence (λ_{max} 615 mμ, shoulder at 560 mμ). In the related phenylethynylacene Ib, it is clear from the absorption and fluorescence spectra that neither the ground nor excited state is sterically hindered. Moreover, it is apparent that the -CH=CH- group is a better conductor of electronic effects in the excited state than is -C≡C-, since the yellow-orange fluorescence of 9,10-distyrylanthracene (ϕ_F = 0.23) is at longer wavelengths than the fluorescence of Ib, which is centered at 513 mμ. This is qualitatively in agreement with the conclusion that acetylenes have a lower aptitude than ethylenes for conjugation with electron deficient systems in the ground state.[3]

Experimental Section

9,10-Dihydroxy-9,10-bis(phenylethynyl)-9,10-dihydroanthracene.—Recrystallization of the product obtained from the reaction of 9,10-anthraquinone and lithium phenylacetylide[10] from acetonitrile gave colorless crystals, mp 220° (lit.[10] mp 206–207°). The two peaks at 3550 and 3410 cm^{-1} in the infrared spectrum ($CHCl_3$) established the *cis* relationship of the two hydroxy groups.

9,10-Bis(phenylethynyl)anthracene (Ib).—The procedure described by Ried, Donner, and Schelegelmilch[10] was used without modification.

(4) L. Fieser, *J. Amer. Chem. Soc.*, **53**, 2329 (1931).

(5) V. Bruckner, A. Karczag-Wilhelm, K. Kormendy, M. Meszaros, and J. Tomasz, *Acta. Chim. Acad. Sci. Hung.*, **22**, 433 (1960); *Chem. Abstr.*, **55**, 8367i (1961).

(6). W. H. Mills and M. Mills, *J. Chem. Soc.*, 2194 (1912).

(7) W. Ried, "Neure Methoden Der Praparativen Organischen Chemie," Band IV, Verlag Chemie Gmb. H., Weinheim/Bergstr., 1966, p 88.

(8) W. Ried, H. Schmidt and A. Urschel, *Chem. Ber.*, **91**, 2472 (1958).

(9) M. M. Martin and E. B. Sanders, *J. Amer. Chem. Soc.*, **89**, 3777 (1967).

(10) W. Ried, W. Donner, and W. Schlegelmilch, *Ber.*, **94**, 1051 (1961).

5,12-Dihydroxy-5,12-bis(phenylethynyl)-5,12-dihydronaphthacene.—To lithium phenylacetylide, made from 14.85 g (0.146 mol) of phenylacetylene and 2.80 g (0.122 mol) of lithium amide in 100 ml of dioxane, was added 15.7 g (0.061 mol) of 5,12-naphthacenequinone[4] in 150 ml of dioxane. The mixture was refluxed for 4 hr, then cooled and treated with 350 ml of 0.5 *M* aqueous ammonium chloride solution. Recrystallization of the product from benzene gave 15.95 g (57%) of colorless crystals, mp 216.5–218° dec. The infrared spectrum ($CHCl_3$) had a single peak at 3610 cm^{-1} for *trans* OH, and two peaks at 3550 and 3400 cm^{-1} corresponding to *cis*-hydrogen-bonded OH. The ratio of *cis* to *trans* was 4:1.

Anal. Calcd for $C_{34}H_{22}O_2$: C, 88.31; H, 4.77. Found: C, 87.97; H, 4.83.

5,12-Bis(phenylethynyl)naphthacene (IIb).—To 29 g of stannous chloride dihydrate in 200 ml of 50% aqueous acetic acid was slowly added 14.4 g of 5,12-dihydroxy-5,12-bis(phenylethynyl)-5,12-dihydronaphthacene in 300 ml of dioxane. The mixture was stirred at room temperature for 2 hr, then diluted to a volume of 1500 ml with water. Recrystallization of the crude product from benzene gave 8.1 g (63%) of dark red-purple needles, mp 248° dec.

Anal. Calcd for $C_{34}H_{20}$: C, 95.33; H, 4.67. Found: C, 95.45; H, 4.78.

6,13-Dihydroxy-6,13-bis(phenylethynyl)-6,13-dihydropentacene.—To lithium phenylacetylide, made from 10.20 g (0.10 mol) of phenylacetylene and 2.30 g (0.10 mol) of lithium amide in 100 ml of anhydrous dioxane, was added 3.08 g (0.01 mol) of 6,13-pentacenequinone[5] in 100 ml of dioxane. The mixture was refluxed for 4 hr, then treated with 600 ml of 0.5 *M* aqueous ammonium chloride solution. The crude product was washed with benzene, then washed with water. Recrystallization in chloroform gave 3.47 g (68%) of colorless solid, mp 230° dec. The infrared spectrum ($CHCl_3$) had a single peak at 3610 cm^{-1} for *trans* OH, and two peaks at 3550 and 3400 cm^{-1} corresponding to *cis*-hydrogen-bonded OH. The ratio of *cis* to *trans* was 1:1.

Anal. Calcd for $C_{38}H_{24}O_2$: C, 89.06; H, 4.69. Found: C, 89.32; H, 4.80.

6,13-Bis(phenylethynyl)pentacene (IIIb).—To 30 g of stannous chloride dihydrate in 25 ml of 50% aqueous acetic acid was added 1.38 g of 6,13-dihydroxy-6,13-bis(phenylethynyl)-6,13-dihydropentacene in 90 ml of dioxane and the mixture was stirred at room temperature for 2 hr. Dilution with water gave 1.18 g of crude product. Recrystallization from xylene gave 0.91 g (63%) of deep blue crystals, which sublimed at 195°.

Anal. Calcd for $C_{38}H_{22}$: C, 95.39; H, 4.60. Found: C, 95.23; H, 4.75.

5,7,12,14-Tetrahydroxy-5,7,12,14-tetrakis(phenylethynyl)-5,7,12,14-tetrahydropentacene.—A mixture of 10.20 g (0.10 mol) of phenylacetylene, 2.30 g (0.10 mol) of lithium amide and 75 ml of anhydrous dioxane was refluxed for 1 hr. More dioxane (100 ml) was added to the cooled mixture. 5,7,12,14-Pentacenediquinone[6] (1.69 g, 0.005 mol) was added all at once and the mixture was refluxed for 4.5 hr. Aqueous ammonium chloride solution (0.2 *N*, 400 ml) was added, followed by an addition of 200 ml of benzene. A tan solid, mp 400°, was collected after stirring the aqueous and benzene layers for 15 min. Recrystallization from chloroform gave 2.77 g (72%) of colorless crystals, infrared 3300 cm^{-1} (Nujol).

Anal. Calcd for $C_{64}H_{34}O_4$: C, 86.86; H, 4.56. Found: C, 87.16; H, 4.52.

5,7,12,14-Tetrakis(phenylethynyl)pentacene (IVb).—To a solution of 1.69 g (7.5 mmol) of stannous chloride dihydrate in 15 ml of 50% acetic acid was added 1.12 g (1.5 mmol) of the tetrol in 50 ml of dioxane. A dark green color formed as the mixture was stirred at room temperature for 5 hr. Filtration gave 0.98 g of solid which was insoluble in most organic solvents. Recrystallization from 1,2,4-trichlorobenzene gave dark green needles, mp >300°.

Anal. Calcd for $C_{64}H_{30}$: C, 95.58; H, 4.42. Found: C, 95.50; H, 4.28.

Fluorescence Measurements.—The techniques and instrumentation used for obtaining absolute emission intensities, spectra and quantum yields in the visible region have been described elsewhere.[11a] An instrument similar in design, but with sensitivity out to 1.0 μ, was constructed and used to obtain fluorescence data in the long-wavelength visible and near-infrared regions.[11b]

Registry No.—Ia, 120-12-7; Ib, 10075-85-1; Ic, 1499-10-1; Id, 10273-82-2; IIa, 92-24-0; *cis*-5,12-dihydroxy-5,12-bis(phenylethynyl)-5,12-dihydronaphthacene, 18826-28-3; *trans*-5,12-dihydroxy-5,12-bis(phenylethynyl)-5,12-dihydronaphthacene, 18826-65-8; IIb, 18826-29-4; IIIa, 135-48-8; *cis*-6,13-dihydroxy-6,13-bis(phenylethynyl)-6,13-dihydropentacene, 18826-30-7; *trans*-6,13-dihydroxy-6,13-bis(phenylethynyl)-6,13-dihydropentacene, 18826-66-9; IIIb, 18826-31-8; 5,7,12,14-tetrahydroxy-5,7,12,14-tetrakis(phenylethynyl)-5,7,12,14-tetrahydropentacene, 18841-60-6; IVb, 18826-38-5.

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(11) (a) B. G. Roberts and R. C. Hirt, *Appl. Spectr.*, **21**, 250 (1967); (b) M. M. Rauhut, B. G. Roberts, D. R. Maulding, W. Bergmark, and R. Coleman, submitted for publication.

Reactions of Pentafluorophenylcopper Reagent

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A pentafluorophenylcopper reagent containing magnesium halide was prepared from the reaction between pentafluorophenylmagnesium bromide and cuprous chloride. The reagent underwent reactions representative of both organocopper and perfluoroaryl organometallic compounds. Reactions with H_2O, CO_2, O_2, C_6H_5I, p-$C_6F_5OC_6F_4Br$, p-$CH_3OC_6F_4I$, $CF_2{=}CFI$, and $C_7F_{15}I$ have been studied. The effect of the magnesium halide content on the reactivity of the pentafluorophenylcopper reagent was examined.

The method for the preparation of decafluorobiphenyl from bromopentafluorobenzene and copper–bronze[1] suggests the intervention of a pentafluorophenylcopper intermediate. Reports have indicated that pentafluorophenylmercury,[2] zinc,[3] and cadmium[4] and more recently perfluoroalkylcopper compounds[5]

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(2) R. D. Chambers, G. E. Coates, J. G. Livingstone, and W. K. R. Musgrave, *ibid.*, 4367 (1962).

(3) J. G. Noltes and J. W. G. Van den Hurk, *J. Organometal. Chem.*, **1**, 337 (1964).

(4) M. Schmeisser and M. Weidenbruch, *Chem. Ber.*, **100**, 2306 (1967).

(5) (a) I. M. White, J. Thrower, and V. C. R. McLoughlin, 4th International Fluorine Symposium, Estes Park, Colo., 1967; (b) J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *Chem. Commun.*, 1259 (1967).

TABLE I

REACTIONS OF THE REAGENT PREPARED FROM C_6F_5MgBr + CuCl WITH RX[a]

RX	Solvent	Temp, °C	Time, hr	Products, % C_6F_5R	$(C_6F_5)_2$	C_6F_5X	Other, %
C_6F_5I	THF	66	10	74	74		
	DMAC	60	18	78	78		
p-$C_6F_5OC_6F_4Br$	DMAC	60	1.5	0	0	20	p-$C_6F_5OC_6F_4H$[b] (22)
							p-$C_6F_5OC_6F_4Br$ (30)
	THF	66	60	5	5	18	p-$C_6F_5OC_6F_4H$[b] (18)
							p-$C_6F_5OC_6F_4Br$ (50)
							p-$(C_6F_5OC_6F_4)_2$ (2)
p-$MeOC_6F_4I$	THF	66	20	70	12	~2	p-$MeOC_6F_4H$,[b]
							p-$(MeOC_6F_4)_2$
	Bu_2O	70	48	45	<1	0	
C_6H_5I	THF	66	168	71	0	0	
CF_2=CFI	THF	25–55	5	55	<1	<2	
$C_7F_{15}I$	DMAC	60	5	0	25	15	

[a] The ratio of reactants was 1:1; the concentration of the organocopper species varied from *ca.* 0.2 to 0.3 mol/l. (see Experimental Section). [b] After aliquot hydrolysis.

are easily prepared and are more thermally stable than their corresponding hydrogen analogs. On this basis, attempts to prepare pentafluorophenylcopper[6] and study its reactions seemed feasible.

Synthesis and Reactions

A pentafluorophenylcopper reagent[7] containing halide ion was prepared by the reaction between pentafluorophenylmagnesium bromide and cuprous chloride in tetrahydrofuran (THF) (eq 1). Evaporation of the solvent *in vacuo* afforded a white solid that could be dissolved in most dipolar aprotic solvents. Reactions of the pentafluorophenylcopper species in THF [or N,N-dimethylacetamide (DMAC)] with oxygen and water yielded decafluorobiphenyl and pentafluorobenzene, respectively (eq 2–4). The yield of decafluorobiphenyl was not affected by refluxing the organometallic solution (THF) for 10 days prior to oxidation.[8] Carbonation of the THF solution of the reagent did not afford pentafluorobenzoic acid. When the same reaction was repeated and subsequently oxidized, the typical yield of decafluorobiphenyl was obtained. Carbonation of the same reagent in DMAC, however, afforded pentafluorobenzoic acid (eq 5 and 6).

$$C_6F_5MgBr + CuCl \xrightarrow[25°,\ 24\ hr]{THF} \text{"}C_6F_5Cu(MgBrCl)\text{"} \quad (1)$$

$$\text{"}C_6F_5Cu(MgBrCl)\text{"} \xrightarrow{H_3O^+,\ DMAC\ or\ THF} C_6F_5H\ (80\%) \quad (2)$$

$$\text{"}C_6F_5Cu(MgBrCl)\text{"} \xrightarrow[DMAC\ or\ THF]{O_2} C_6F_5C_6F_5\ (75\%) \quad (3)$$

$$\text{"}C_6F_5Cu(MgBrCl)\text{"} \xrightarrow[2.\ O_2]{1.\ THF,\ 65°,\ 10\ days} C_6F_5C_6F_5\ (72\%) \quad (4)$$

$$\text{"}C_6F_5Cu(MgBrCl)\text{"} \xrightarrow[H_3O^+]{THF,\ CO_2} C_6F_5CO_2H\ (0\%) \quad (5)$$

$$\text{"}C_6F_5Cu(MgBrCl)\text{"} \xrightarrow[H_3O^+]{DMAC,\ CO_2} C_6F_5CO_2H\ (36\%) \quad (6)$$

The stability and solubility of the perfluoroarylcopper reagent seem characteristic for perfluorinated copper(I) compounds,[5] whereas its reactions (oxidation and hydrolysis) are characteristic of copper(I) organometallics in general.[9] The fact that the organometallic copper species can be carbonated in DMAC and not in THF presumably reflects the greater carbanion character in the more complexing solvent.

Results of the reactions of the organocopper reagent with various halogen compounds are presented in Table I. Apparently, this reagent reacts *via* two basic pathways; path I is representative of organocopper species,[10a] and path II is characteristic of perfluoroaryl organometallic species.[10b]

Variation of the solvent effects the course of reaction; *e.g.*, when the copper reagent is allowed to react with p-$C_6F_5OC_6F_4Br$ in DMAC, path II occurs specifically whereas in THF paths I and II are competitive. Similarly, p-$MeOC_6F_4I$ in dibutyl ether specifically reacts with the copper reagent by way of path I while in THF paths I and II are competitive.

The rates of reaction between the copper reagent and various substrates leading to coupled products (C_6F_5R, see Table I) qualitatively decrease in the series perfluoroaromatic ~ perfluoroolefin > aromatic > perfluoroalkyl halide with iodine being a more effective leaving group than bromine. Under our experimental conditions, reactions with perfluoroalkyl iodides failed to yield appreciable amounts of coupled products in either DMAC or THF.

A four-centered transition state where carbon–carbon bond making and carbon–halogen bond breaking are concerted has been proposed for the reactions of cuprous acetylides[11] or salts[12] with aryl halides. Our halogen mobilities are consistent with these proposals. However, the fact that perfluoroaromatics (and olefins) are more reactive toward the copper reagent than hydrocarbon aromatics may suggest that in the transition state of the former, carbon–carbon bond making may proceed to a greater extent than carbon–halogen bond breaking. This could conceivably lower the energy gap between fluoroaromatic ground and transition states by delocalization of negative charge throughout the fluoroaromatic ring. Quantitative data would be necessary to distinguish these possibilities.

(6) Since our work began, the synthesis and certain reactions of pentafluorophenylcopper have been reported: see (a) A. Cairncross and W. A. Sheppard, *J. Amer. Chem. Soc.*, **90**, 2186 (1968); (b) S. S. Dua, A. E. Jukes, and H. Gilman, *J. Organometal. Chem.*, **12**, P24 (1968); (c) A. E. Jukes, S. S. Dua, and H. Gilman, *ibid.*, **12**, P44 (1968).

(7) Since the structure of this compound has not been determined as yet, the reagent will be designated by the general formula "$C_6F_5Cu(MgX_2)$." Qualitative analysis of the reagent indicated the presence of Cu, Mg and halide ions.

(8) Pentafluorophenylmagnesium bromide on the other hand decomposes to a hard, intractable "perfluorophenylene" under reflux conditions.

(9) G. M. Whitesides, J. San Filippo, Jr., C. P. Casey, and E. J. Panek, *J. Amer. Chem. Soc.*, **89**, 5302 (1967).

(10) (a) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967); (b) R. J. De Pasquale *J. Organometal. Chem.*, **15**, 233 (1968).

(11) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, **28**, 3313 (1963).

(12) (a) R. G. R. Bacon and H. O. A. Hill, *J. Chem. Soc.*, 1097 (1964); (b) L. J. Belf, M. W. Buxton, and G. Fuller, *ibid.*, 3372 (1965).

Path II (eq 8) is considerably more sensitive to the complexing ability of the solvent (DMAC > THF > Bu_2O) than path I (eq 7, X = Br, I). Since this type of equilibrium (path II) is characteristic of perfluoro-

$$C_6F_5Cu(MgBrCl) + RX \longrightarrow C_6F_5R + CuX(MgBrCl) \quad (7)$$

$$C_6F_5Cu(MgBrCl) + RX \rightleftharpoons C_6F_5X + RCu(MgBrCl) \quad (8)$$

$$\downarrow O_2$$

$$C_6F_5C_6F_5 + C_6F_5R + RR$$

aryllithium and magnesium reagents,[10b] suspicion is aroused regarding the nature of the organometallic involved in this process. To clarify this situation, hopefully magnesium halide was partially precipitated from the reagent with dioxane, and the reactions of the resulting reduced halide–organometallic solutions were investigated for comparison.[13]

Reactivity of the Pentafluorophenylcopper Reagent *vs.* Magnesium Halide Content.—The halide-reduced organometallic solution was allowed to react with *p*-$MeOC_6F_4I$ and *p*-$C_6F_5OC_6F_4Br$ in the presence and the absence of an added equivalent of magnesium bromide. These results along with the reactions of the reagent prepared from C_6F_5MgBr + CuCl are shown in Tables II and III.

Table II

Reactions of "RCu" with *p*-$C_6F_5OC_6F_4Br$ in DMAC at 60 ± 2° [a]

Reagent	RCu, initial concn,[b] mol/l.	Time, hr	Ratio of C_6F_5Br/ *p*-$C_6F_5OC_6F_4H$/ *p*-$C_6F_5OC_6F_4Br$	Starting material accounted for, %
5.5C_6F_5Cu–$MgBr_2$	0.22	0.08	4:7:10	
		3.0	3:6:2	95
C_6F_5Cu–1.18$MgBr_2$	0.22	0.08	1:1.8:15.5	
		3.0	1:1.4:1.2[c]	80
C_6F_5MgBr + CuCl	0.31	1.5	2:3:4[c]	79[d]

[a] Under these conditions, coupled products, *e.g.*, $(C_6F_5)_2$ or *p*-$C_6H_5OC_6F_4C_6H_5$, were not observed. [b] Obtained by determining C_6F_5H after aliquot hydrolysis. [c] Prior to oxidation. [d] After oxidation.

Table III

Reactions of "RCu" with *p*-$MeOC_6F_4I$ in THF at 66°

Reagent	RCu, initial concn,[a] mol/l.	Time, hr	Ratio of $(C_6F_5)_2$/ *p*-$C_6F_5C_6F_4OMe$	Completion,[b] %
5.5C_6F_5Cu–$MgBr_2$	0.22	3	1:3.5[c]	80
C_6F_5Cu–1.18$MgBr_2$	0.22	18	1:4.4[c]	80
C_6F_5MgBr + CuCl	0.24	20	1:6	85

[a] Obtained by determining C_6F_5H after aliquot hydrolysis. [b] Obtained from unreacted *p*-$MeOC_6F_4I$; further reaction time drove reactions to >90% completion. [c] Duplicate experiments.

From the data several points emerge; solutions studied containing various ratios of $MgBr_2$–arylcopper species undergo similar types of reactions, but with different rates and product distributions. The variation of the latter with $MgBr_2$ concentration strongly suggests that there is more than one reactive organocopper species present. Costa, *et al.*,[14] have recently discussed the various complexes formed in their synthesis of phenylcopper. Such complexes will vary in composition with change in stoichiometry and solvent.

It could be argued that a perfluoroaryl Grignard reagent is present from incomplete initial reaction (eq 1) or is formed by a reversible process inherent in the organocopper preparation. The perfluororarylmagnesium compound could then be the species responsible for the exchange process indicated by eq 8. This possibility, however, is inconsistent with the following observations. (a) Concerning the reversibility, the Grignard source could reasonably be formed from the complex given in eq 9. By mass law, added magnesium

$$"C_6F_5Cu(MgX_2)" \rightleftharpoons C_6F_5MgX + CuX \quad (9)$$

halide should enhance the Grignard concentration and thereby accelerate reactions involving this species. This reasoning, however, is not consistent with the results in Tables II and III, namely, that the halide-reduced copper reagent exchanges halogen at the faster rate. (b) Pentafluorophenylmagnesium compounds decompose after several hours at THF reflux temperature, affording a "perfluoropolyphenylene".[15] In contrast, the organocopper reagent prepared from C_6F_5MgBr + CuCl is stable after 10 days at THF reflux temperature. (c) Pentafluorophenylmagnesium halides react irreversibly with CO_2[16] (THF) and N-methylformanilide[17] (Et_2O), whereas the copper reagent prepared above is not reactive in similar instances.

In view of these data, the reagent prepared from pentafluorophenylmagnesium bromide and cuprous halide seems to undergo reactions representative of a complexes pentafluorophenylcopper species. The variation of reaction rate with solvent (carbonation and rapid exchange in DMAC and not in THF; heterolytic decomposition in DMAC, see below) is probably typical of weakly ionized organometallics.[18] Even though the exact structure of the copper complexes prepared from the metathetical reaction of perfluoroaryl Grignards and cuprous halides is not known, the reagent is versatile and its modes of reaction are predictable.

Stability of "$C_6F_5Cu(MgBrCl)$" in DMAC.—The decomposition (100°, DMAC) of the perfluoroarylcopper reagent was monitored by the decrease in pentafluorobenzene (formed on hydrolysis of aliquot samples) with time. After 8 hr, approximately 50% of the organometallic reagent had decomposed to an intractable material suspected to be a "perfluoropolyphenylene".[15] Products derived from the reaction of a copper species with DMAC were not observed. The decomposition was repeated in the presence of decafluorobiphenyl, and in another experiment with naphthalene. In the presence of decafluorobiphenyl, 62% of the organometallic reagent had decomposed after 1 hr yielding perfluoroterphenyl and perfluoroquaterphenyl along with the previously isolated "perfluoropolyphenylene." The decomposition of the organometallic was unaffected by the presence of naphthalene. Decafluorobiphenyl readily undergoes nucleo-

(13) Halide-free pentafluorophenyl copper has been recently prepared, see ref 6a.

(14) G. Costa, A. Camus, L. Gatti, and N. Morsich, *J. Organometal. Chem.*, **5**, 568 (1966).

(15) This material was initially characterized by J. Thrower and M. A. White, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, 19K.

(16) R. J. Harper and C. Tamborski, *Chem. Ind.* (London), 1824 (1964).

(17) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961).

(18) A recent paper reported that the acid–base reaction between diethylcadmium and phenylacetylene is extremely solvent dependant: O. Yu. Okhlobystin and L. I. Zakharkin, *Zh. Obshch. Khim.*, **36**, 1734 (1966).

philic substitution reactions[19] and naphthalene is an effective radical scavenger.[20] Decafluorobiphenyl accelerated the decomposition of the organometallic whereas naphthalene did not afford a naphthylpentafluorophenyl adduct. These facts strongly suggest that under our conditions, the organocopper reagent is decomposing by a heterolytic rather than a homolytic mechanism.

Experimental Section

Fluoroaromatics used in this work were either purchased from Imperial Smelting (N. S. C) Ltd., Avonmouth, England, or prepared from published procedures. Solvents were purified and dried by conventional methods and distilled prior to use. Reactions involving organometallic reagents were carried out under dry nitrogen with the usual precautions for the rigorous exclusion of moisture and air. Melting points were determined with a "Mel-Temp" apparatus and are uncorrected. The ^1H and ^{19}F nmr spectra were recorded on a Varian A 56-60 spectrometer in carbon tetrachloride as solvent; chemial shifts are reported in parts per million from internal tetramethylsilane or trichlorofluoromethane. Infrared spectra were run on a Perkin-Elmer "Infracord" spectrometer as KBr pellets (solids) of films (liquids.) Vpc analysis were performed on F & M Model 500 or 810 instruments using a 6 ft × 0.25 in. column, 20% Apiezon L (F & M Model 500) and a 11 ft × 0.25 in. column, 20% polyphenyl ether (six ring) on 60–80 mesh Chromosorb W (F & M Model 810). The mass spectral analysis were performed on a CEC-21-110B mass spectrometer.

A. Preparation of Pentafluorophenylcopper Reagent Containing Magnesium Halide.—Ethylmagnesium bromide (0.101 g, 80.0 ml in THF) was added to a stirred solution containing bromopentafluorobenzene (25.0 g, 0.101 mol) dissolved in THF (170 ml) containing *t*-butylbenzene (2.5 g) as an internal vpc standard.[21] The rate of addition was such that the temperature of the reaction did not exceed 30°. After the completion of addition, the reaction mixture was stirred for 0.5 hr at room temperature. On rapid addition of cuprous chloride (10.0 g, 0.101 mol), the reaction temperature rose to 35°. The resulting mixture was allowed to stir at room temperature for 18 hr. The precipitate was allowed to settle and an aliquot sample of the supernatant liquid was withdrawn, hydrolyzed, extracted with pentane and analyzed by vpc. The yields of pentafluorobenzene thus obtained ranged from 76 to 85%. Small amounts of decafluorobiphenyl[22] were detected in solution. The supernatant liquid showed little change after being stored for 2 weeks under nitrogen and was used for the following experiments.

Oxidation.—A 50-ml aliquot (0.015 mol) of the supernatant liquid prepared as described above was pipeted into a dry flask. Anhydrous oxygen was bubbled through the solution for 1.5 hr producing a dark mixture. An aliquot sample which was withdrawn and analyzed by vpc revealed that decafluorobiphenyl (70–80%) was the major volatile product. From the reaction mixture, decafluorobiphenyl was isolated *via* alumina chromatography and its structure was verified by spectral comparisons with an authentic sample. The quantity of "C_6F_5Cu" in solution prepared as described above was estimated by averaging the yields of C_6F_5H and $(C_6F_5)_2$ obtained on hydrolysis and oxidation, respectively.

Carbonation.—A 50-ml aliquot (0.015 mol) was stirred at 25° for 2 hr while carbon dioxide was bubbled through the solution. Conventional work-up of the reaction mixture did not afford pentafluorobenzoic acid. The experiment was repeated and after carbonation the solution was oxidized by passing dry oxygen through the reaction mixture for 1.5 hr. Work-up of the reaction mixture afforded 2.5 g (75% yield) of decafluorobiphenyl.

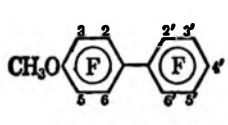
Another 50-ml aliquot (0.015 mol) of the THF solution was concentrated *in vacuo* producing a white residue which was then dissolved in 50 ml of dimethylacetamide (DMAC). The solution was carbonated as described above and yielded 1.5 g of pentafluorobenzoic acid (36% yield).

Reaction with Iodopentafluorobenzene.—Iodopentafluorobenzene (2.5 g, 8.6 mmol) was added to 25 ml of the THF solution of pentafluorophenylcopper reagent (8.6 mmol). The reaction mixture was heated at 66° for 10 hr. The precipitate that formed was filtered under nitrogen and the filtrate was quenched with 25 ml of water. The resulting mixture was extracted with two 25-ml portions of petroleum ether (bp 30–60°). The petroleum ether solution was concentrated leaving 3.3 g of an oil which solidified on standing. Recrystallization of this material from methanol afforded 2.1 g (74% yield) of decafluorobiphenyl. The above reaction was repeated in DMAC with similar results.

Reaction with 4-Pentafluorophenoxybromotetrafluorobenzene. DMAC Solvent.—A 50-ml quantity of the THF solution containing pentafluorophenylcopper reagent (0.015 mol) was concentrated to remove all the THF. To this solid was added 50 ml of DMAC and 4-pentafluorophenoxybromotetrafluorobenzene (6.30 g, 0.015 mol). After heating this solution at 60° for 1.5 hr, an aliquot sample was removed, worked up as previously described and analyzed by vpc. The analysis indicated C_6F_5Br, p-$C_6F_5OC_6F_4H$, p-$C_6F_5OC_6F_4Br$ in a 2:3:4 area ratio, respectively.[23] The reaction mixture was then oxidized by passing dry oxygen throgh the mixture for 3 hr at 60°. The reaction was hydrolyzed and analyzed by vpc indicating six compounds: C_6F_5Br (20%), $(C_5F_5)_2$ (6%), p-$C_6F_5OC_6F_4H$ (6%), p-$C_6F_5OC_6F_4Br$ (30%), p-$C_6F_5OC_6F_4C_6F_5$ (8%), and p-$(C_6F_5OC_6F_4)_2$ (9%).

THF Solvent.—4-Pentafluorophenoxybromotetrafluorobenzene (6.30 g, 0.015 mol) was added to 50 ml of a THF solution of pentafluorophenylcopper reagent (0.015 mol), the reaction mixture heated at 66° for 1.5 hr and a sample was removed for vpc analysis. At this time, no appreciable reaction had occurred so the reaction was allowed to proceed for an additional 20 hr. Analysis by vpc indicated the following compounds: C_6F_5Br, $(C_6F_5)_2$, p-$C_6F_5OC_6F_4H$, p-$C_6F_5OC_6F_4Br$ and p-$C_6F_5OC_6F_4C_6F_5$ in 1:1:1:-20:1 are a ratio, respectively. After 2.5 days of additional heating at 66°, an additional product appeared, p-$(C_6F_5OC_6F_4)_2$. The products identified in increasing vpc retention time were C_6F_5Br (18%), $(C_6F_5)_2$ (5%), p-$C_6F_5OC_6F_4H$ (18%), p-$C_6F_5OC_6F_4Br$ (50%), p-$C_6F_5OC_6F_4C_6F_5$ (5%) and p-$(C_6F_5OC_6F_4)_2$ (2%).

Reaction with 4-Methoxyiodotetrafluorobenzene. THF Solvent.—4-Methoxyiodotetrafluorobenzene (3.7 g, 0.012 mol) was added to 50 ml of the THF solution of pentafluorophenylcopper reagent (0.012 mol). The reaction mixture was stirred and heated at 66° for 20 hr. Analysis of the reaction mixture by vpc and mass spectroscopy indicated four products, p-$CH_3OC_6F_4H$, $(C_6F_5)_2$, p-$CH_3OC_6F_4C_6F_5$ (70% yield), and p-$(CH_3OC_6F_4)_2$ in a 1:1:6:1 area ratio, respectively. Mass spectral analysis provided the parent ion peaks m/e 180, 334, 346 and 358, respectively. The major product, p-$CH_3OC_6F_4C_6F_5$, was isolated by preparative vpc in a 70% yield, mp 58–60°, m/e 346. Its ^1H nmr spectrum exhibited a triplet (J = 2 Hz) at 4.2 ppm. The ^{19}F nmr spectrum indicated five regions: +137.6 (m, 2), +139.6 (m, 2), +150.9 (t of t, 1, $J_{4'5'}$ = 21 Hz, $J_{4'6'}$ = 1.5 Hz), +156.9 (one-half AA'XX', 2), +160.9 (m, 2). These were assigned the fluorine atoms at the 2–6 (or 2'–6'), 4', 3–5, and 3'–5' positions, respectively.



(n-C_4H_9)$_2$O Solvent.—A 50-ml aliquot of pentafluorophenylcopper reagent (0.015 mol)–THF solution was heated *in vacuo* to dryness. To this solid was added *n*-dibutyl ether (70 ml) and the reaction mixture was stirred and heated at 70° for 2 days. Analysis of the reaction mixture by vpc indicated p-$CH_3OC_6F_4C_6F_5$ (45%) as a major reaction product with p-$CH_3OC_6F_4I$ (50%) remaining unreacted. Only a trace of $(C_6F_5)_2$ was formed.

Reaction with Iodobenzene.—Iodobenzene (1.6 g, 7.9 mmol) was added to 25 ml of the THF solution of pentafluorophenylcopper reagent (7.9 mmol) and the reaction mixture was heated at 66°. The reaction was monitored by vpc analysis which indicated that the reaction proceeded very slowly. After 7 days at 66°, vpc analysis indicated $C_6F_5C_6F_5$ (71%) as the only reaction product. There was no $(C_6H_5)_2$ or $(C_6F_5)_2$ present. The

(19) (a) R. J. De Pasquale and C. Tamborski, *J. Org. Chem.*, **32**, 3163 (1967); (b) J. Thrower and M. A. White, private communication, May 1964.

(20) D. H. Heg and G. H. Williams, *Discussions Faraday Soc.*, **14**, 216 (1953).

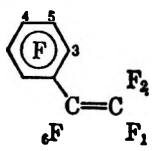
(21) The yields were obtained by the vpc method using an internal standard unless otherwise stated.

(22) In the reactions where decafluorobiphenyl was the reaction product, the yield of decafluorobiphenyl was determined by subtracting the initial concentration formed during the preparation of pentafluorophenylcopper reagent (blank) from the observed value.

(23) Pentafluorobenzene, the other product of this reaction, was not determined in the vpc analysis.

reaction mixture was hydrolyzed and the crude product (1.6 g) was recrystallized from the CH_3OH/C_6H_6 mixture, mp 109–111°, with an infrared spectrum identical with that of an authentic sample.

Reaction with Iodotrifluoroethylene.—Freshly distilled iodotrifluoroethylene (8.7 g, 0.042 mol) was added to 150 ml of the THF solution of pentafluorophenylcopper reagent (0.042 mol). The reaction flask, equipped with a methanol–ice condenser, was heated gradually from 25 to 55°. After 5 hr at 55°, the reaction mixture was cooled and analyzed by vpc. Analysis indicated the presence of two products, $C_6F_5CF{=}CF_2$[24] and C_6F_5I, in a 20:1 area ratio, respectively. The solution was decanted from the precipitate, hydrolyzed with water (5 ml), filtered, dried ($CaCl_2$) and distilled. The fraction with bp 124–125° was further analyzed by vpc and indicated a purity of 98%. The perfluorostyrene had a characteristic C=C absorption in the infrared spectrum at 5.65 μ. Its ^{19}F nmr spectrum shown multiplets at +97, +113, +138, +150, +162 and +171 ppm which were assigned the F_1–F_6, respectively. The experimentally derived coupling constants were $J_{1,2} = 63$, $J_{1,6} = 36$, $J_{1,3} = 2.5$, $J_{1,4} = 1$, $J_{2,6} = 117$, $J_{2,3} = 10.5$, $J_{2,4} = 1.5$, $J_{4,5} = 20$ Hz.



Reaction with Perfluoroheptyl Iodide.—*n*-Perfluoroheptyl iodide (6.6 g, 0.013 mol) was added to 50 ml of the supernatant THF solution of pentafluorophenylcopper reagent (0.013 mol). The resulting solution was stirred at 25° for 3 hr. Analysis by vpc indicated the formation of two products ($C_6F_5)_2$ (4%) and C_6F_5I (3%). The reaction mixture was then heated to 60° for 5 hr. The two products increased in concentration to 25 and 15%, respectively. After hydrolysis of the reaction mixture, C_6F_5H (47%) was also observed. None of the desired product perfluoro-*n*-heptylbenzene[25] was detected. When the reaction was repeated in DMAC as the solvent, analogous results were obtained.

B. Preparation of Halide-Reduced Pentafluorophenylcopper Reagent.—The organocopper reagent was prepared as described above from pentafluorophenylmagnesium bromide (0.101 mol in 250 ml of THF) and cuprous bromide (14.5 g, 0.10 mol). After the reaction mixture was stirred overnight, 10.0 ml of anhydrous dioxane was added and the precipitate was filtered under dry nitrogen. A 1-ml aliquot was removed from the filtrate and analyzed for bromide ion by quenching in 3 ml of 3 *N* HNO_3 and titrating the resulting solution potentiometrically with silver nitrate. The concentration of bromide ion in solution was determined as 0.33 mequiv/ml. The filtered THF solution of pentafluorophenylcopper reagent was used in the following experiments.

Reaction with 4-Pentafluorophenoxybromotetrafluorobenzene.—A 50-ml sample of the above THF solution was gently heated to dryness *in vacuo*. To this dry residue was added 50 ml of DMAC and cumene (0.40 g) as an internal standard. An aliquot sample was removed, hydrolyzed and analyzed for pentafluorobenzene in order to determine the concentration of the pentafluorophenylcopper reagent. The DMAC solution was divided into two equal fractions (A and B). To fraction A was added *p*-$C_6F_5OC_6F_4Br$ (2.24 g, 5.45 mmol) and the mixture was heated to 60 ± 2°. After 5 min, an aliquot sample was removed, worked up and indicated the products C_6F_5Br–*p*-$C_6F_5OC_6F_4H$–*p*-$C_6F_5OC_6F_4Br$ in a 4:7:10 area ratio, respectively; after 3 hr, the ratio of products was 3:6:2 with *ca.* 95% of the material accounted for. To fraction B was added an ether solution (2.30 ml, 5.45 mmol) of magnesium bromide and *p*-$C_6F_5OC_6F_4Br$ (2.24 g, 5.45 mmol). The reaction mixture was stirred and heated at 60 ± 2°. After 5 min, an aliquot was worked up, analyzed and indicated the products C_6F_5Br–*p*-$C_6F_5OC_6F_4H$–*p*-$C_6F_5OC_6F_4Br$ in a 1:1.8:15.5 area ratio, respectively; after 3 hr, the ratio of products was 1:1.4:1.2 with *ca.* 80% of the material accounted for.

Reaction with 4-Methoxyiodotetrafluorobenzene.—A 25-ml sample (5.5 mmol) of the above THF solution was allowed to react with *p*-$CH_3OC_6F_4I$ (1.7 g, 5.5 mmol) at 66°. After 3 hr, the reaction was 80% complete and analysis of the reaction mixture indicated two major components, $(C_6F_5)_2$ and *p*-$CH_3OC_6F_4$-C_6F_5, in a 1:3.5 area ratio. After 4 hr, the reaction was nearly completed. To another 25-ml sample (5.5 mmol) of the above THF solution was added an ether solution of magnesium bromide (2.3 ml, 5.5 mmol) and *p*-$CH_3OC_6F_4I$ (1.7 g, 5.5 mmol). The reaction was heated at 66° and after 18 hr (80% completion), the ratio of $(C_6F_5)_2$–*p*-$CH_3OC_6F_4C_6F_5$ was 1:4.4.

C. Thermal Stability of Pentafluorophenylcopper Reagent. THF Solution.—A THF solution of pentafluorophenylcopper reagent (prepared as described in A above) was hydrolyzed and analyzed by vpc, indicating a 74% yield of C_6F_5H. The supernatant solution was then heated at 66° for 10 days, cooled to room temperature and oxidized yielding decafluorobiphenyl (74%).

DMAC Solution.—A 25-ml aliquot of the supernatant THF solution was heated *in vacuo* until dryness. The solid residue was dissolved in DMAC (25 ml) and heated to 100°. At intervals, samples were witdrawn and analyzed by vpc for C_6F_5H. From the decrease of C_6F_5H with time, the per cent decomposition of the organocopper reagent was determined (2 hr, 22%; 4.5 hr, 38%; 8 hr, 47%). After 8 hr, the reaction mixture was hydrolyzed with 3 *N* HCl (20 ml). The residue was filtered and triturated with hot THF, dried and yielded 0.25 g of a solid, mp >400°. The infrared spectrum of this material was identical with that of perfluoropolyphenylene.

DMAC and Decafluorobiphenyl.—The above experiment was repeated in the presence of 0.5 mol quantity of decafluorobiphenyl. After 1 hr, 62% of the organocopper reagent had decomposed (38% of decafluorobiphenyl remained). Also detected by the vpc analysis were two other components in a 4:1 area ratio. The molecular weights of these compounds, *m/e* 482 and 630, and their vpc retention time suggest the compounds perfluorotriphenyl and perfluoroquaterphenyl, respectively.

DMAC and Naphthalene.—The above experiment was repeated in the presence of naphthalene (*ca.* 4 mol quantity). Analysis of aliquot samples indicated a per cent decomposition of the organocopper reagent: 1 hr, 12%; 5.5 hr, 40%. There was no perfluorotriphenyl-, perfluoroquaterphenyl- or pentafluorophenylnaphthalene found in vpc analysis of the reaction mixture. Within the experimental error, no naphthalene was consumed during the course of the reaction.

Registry No.—Iodopentafluorobenzene, 827-15-6; 4-pentafluorophenoxybromotetrafluorobenzene, 14055-44-8; 4-methoxyiodotetrafluorobenzene, 1744-45-2; iodobenzene, 591-50-4; iodotrifluoroethylene, 359-37-5; perfluoroheptyl iodide, 335-58-0.

Acknowledgment.—We wish to express our appreciation to Lee D. Smithson of the Air Force Materials Laboratory for performing the mass spectral analysis.

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Proximity Effects in *peri*-Substituted Naphthalenes. I. Some 8-Substituted 1-Hydroxymethyl- and 1-Chloromethylnaphthalenes[1]

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The methylene signals in the nmr spectra of a series of 8-substituted 1-hydroxymethyl- and 1-chloromethylnaphthalenes were analyzed. The greater deshielding observed for the chlorides over the alcohols is explained as due to differences in conformational preferences. Intramolecular hydrogen bonding in the alcohols may lead to greater populations of conformers in which the hydrogens are further removed from the naphthalene ring's maximum deshielding region than in the chlorides. Solvolysis of the chlorides in 80% aqueous acetone revealed a good Hammett $\sigma\rho$ plot when the unsubstituted compound was omitted from consideration. Steric acceleration can explain the faster rates for the substituted compounds.

The spatial proximity of substituents in naphthalene's 1 and 8 positions, the *peri* positions, is revealed by the appearance of several unique physical and chemical properties.[2] Our studies in *peri*-substituted naphthalenes have stemmed from similar studies accomplished and in progress on eclipsed groups in the norbornane system.[3] From a geometrical consideration *peri* substituents are much closer to one another than identical *ortho* substituents, and steric interactions and field effects should be more severe. Since such substituents are separated by three carbon atoms, they may be likened to *meta* substituents in their ability to transmit inductive and resonance effects between one another. However, imposition of one-third double bond character or less to the 8,9 and 9,1 bonds[4] should decrease the ability of the system to transmit such effects.

Relative magnitudes of proximity effects of *peri* substituents were to be studied by measurements of (a) pK_a values of 8-substituted 1-naphthoic acids, (b) frequency shifts in the infrared and shifts in the chemical shifts in the nmr spectrum associated with intramolecular and intermolecular hydrogen bonding in 8-substituted 1-hydroxymethylnaphthalenes, (c) chemical shift differences of the methylene hydrogens of the aforementioned alcohols and their corresponding chlorides, and (d) solvolysis rates of the chlorides. The present paper deals with the determination and evaluation of the latter two measurements.

The 8-substituted 1-hydroxymethylnaphthalenes were prepared by either lithium aluminum hydride or diborane reduction of the known corresponding acids. The desired chlorides were obtained *via* their alcohols by reaction either with thionyl chloride by the method of Kirner and Windus[5] or with gaseous hydrogen chloride by the method of Shoesmith and Rubli.[6]

Interpretation of Nmr Spectra.—The nmr spectra of the hydroxymethylnaphthalenes and chloromethylnaphthalenes were thoroughly analyzed in the region of the methylene hydrogen signals. The data are summarized in Table I. Normally the α-hydrogen signals of primary alcohols appear at lower fields than those of the corresponding chlorides.[7] When a phenyl substituent is present in the α position, both methylene signals undergo a paramagnetic shift presumably due to a combination of inductive and anisotropic effects. Still the methylene signal for the alcohol appears further downfield (line 7, Table I).

Fundamental to the meaningful interpretation of the relevancy of chemical shift positions of any aryl-substituted compound is that data be obtained in solutions sufficiently dilute so that further dilution does not alter the positions. In these dilute solutions intermolecular association of solute will be minimal, as will the mutual shielding of hydrogen nuclei by the induced ring current of the benzene ring of adjacent molecules.[8] The methylene signals for benzyl alcohol and benzyl chloride in 5 and 6% solutions in CCl_4 are reported to be 4.40 and 4.50 ppm, respectively,[9] a reversal of order in comparison with our data on these two compounds obtained at infinite dilution. Evidently greater association in benzyl alcohol is possible *via* intermolecular hydrogen bonding in which the methylene protons lie in the shielding cone of a neighboring benzene ring.

The expected lower field methylene chemical shift for the alcohol is observed with the simple 1-substituted naphthalene compounds (line 1, Table I). However, when the 8 position is substituted the reverse is generally true. This reversal is attributed to changes in the conformational preferences between the alcohols and their chlorides. For 1-chloromethylnaphthalene potential-energy functions governing internal rotation have been estimated from van der Waals interaction data[10] and the equation of Hill.[11] The potential (E_v) minimum was calculated to be 70–80°. The 60° rotomer (**1**) for the chloride is depicted below.

The negative $\Delta\delta$'s in Table I for the 8-substituted compounds may be explained as follows. If the population of conformations approaching **2**, the 180°

(1) Grateful acknowledgement is made to the National Science Foundation for a research grant (NSF-GP-1574) which supported a large portion of this work.

(2) For a recent review of naphthalene *peri* interactions see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(3) D. C. Kleinfelter, *J. Org. Chem.*, **32**, 3526 (1967), and references therein.

(4) *Cf.* D. W. J. Cruickshank, *Acta Cryst.*, **10**, 504 (1957).

(5) W. R. Kirner and W. Windus, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 136.

(6) J. B. Shoesmith and H. Rubli, *J. Chem. Soc.*, 3098 (1927).

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 54.

(8) A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.*, **26**, 1651 (1957).

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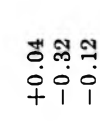
TABLE I

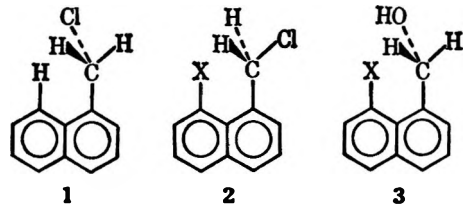
NMR SPECTRAL DATA FOR SOME 1-HYDROXYMETHYLNAPHTHALENES AND 1-CHLOROMETHYLNAPHTHALENES[a]

	Registry no.	δ(CCl4)	δ(CHCl3)
X = H	4780-79-4	5.04	5.18
X = OCH_3	19190-42-2	4.94	5.08
X = Br	14038-58-0	5.40	5.51
X = Cl	10446-06-7	5.37	5.47
X = CH_3	10336-29-5	5.09	5.23
X = NO_2	19190-46-6	4.86	5.00
Benzyl alcohol	100-51-6	4.60	4.70
o-Methoxybenzyl alcohol	612-16-8	4.58	4.72



	Registry no.	δ(CCl4)	δ(CHCl3)	Δδ(CCl4)[b]
X = H	86-52-2	5.00	5.08	+0.04
X = OCH_3	19190-47-7	5.26	5.33	−0.32
X = Br	19190-48-8	5.52	5.59	−0.12
X = Cl	19190-49-9	5.47	5.53	−0.10
X = CH_3	15675-12-4	5.14	5.23	−0.05
X = NO_2	19190-51-3	4.90	4.98	−0.04
Benzyl chloride	100-44-7	4.53	4.61	+0.07
o-Methoxybenzyl chloride	7035-02-1	4.57	4.67	+0.01

[a] Chemical shifts (δ) are for very dilute solutions in which no shifts in δ upon further dilution were observed, and are presumed correct to ±0.01 ppm. [b] Δδ is the difference between the δ for the alcohol and the corresponding chloride in CCl_4; negative values imply the alcohol signal is upfield from the chloride.



1 2 3

rotomer, is preferred for the 8-substituted 1-chloromethylnaphthalenes, then the methylene hydrogens reside more within a region of high anisotropic deshielding, *i.e.*, near the plane of the naphthalene ring at the fusion point. Conversely, if conformations approaching **3** are preferred for the 8-substituted 1-hydroxymethylnaphthalenes, then the methylene hydrogens, on the average, are further removed from the region of highest anisotropic deshielding. The α- and β-proton resonances for naphthalene are known to be 7.80 and 7.44 ppm, respectively.[12] Extension to the α- and β-methyl derivatives gives methyl resonances of 2.64 and 2.48 ppm.[13-16] The methylene signal of α-hydroxymethylnaphthalene of 5.04 ppm in CCl_4, corresponds to a downfield shift of 0.26 ppm relative to the β isomer.[17] All these differences may be largely attributed to the exertion of greater anisotropic deshielding at the α position.

Conformations approaching **3** would be preferred for those alcohols in which significant intramolecular hydrogen bonding to the 8 substitutent occurs. The greatest Δδ is observed for the 8-methoxy compound in which ir and nmr data have revealed the predominance of OH···O bonding.[18] In the 8-halogen compound OH···X bonding is less prevalent and the Δδ is correspondingly less.

In order to substantiate the assignments of preferred conformations from the nmr work and because such assignments are presumed important to the solvolytic study (*vide infra*), E_v calculations on the 8-substituted 1-chloromethylnaphthalenes have been performed. In these calculations an arbitrary value of 2.50 Å (an average value for the C_4–C_5 and C_1–C_8 distances in 3-bromo-1,8-dimethylnaphthalene of 2.44 and 2.56 Å, respectively[19]) was chosen as the mean C_8–X, C_1–CH_2 interplanar distance. Serious steric interactions between *peri* substituents would cause in-plane and out-of-plane deformations[20] and would magnify this value. Assuming the *o*-methyl group is held in the "anti" orientation, the C···O interaction for the 8-methoxy compound is calculated to be only *ca.* 0.6 kcal/mol. Therefore, the calculated E_v minima at *ca.* 110 and 180° should be significant. The 0.8-kcal difference between these minima for 1-chloromethylnaphthalene is decreased to 0.3 kcal for the 8-methoxy derivative.[21] Such calculations are only qualitatively significant for the more bulky 8 substituents in that appreciable distortions of the *peri* groups will be involved. Cal-

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(20) Reference 2, p 568.

(21) The absolute values for 110 and 180° are 1.7 and 2.0 kcal/mol, respectively.

TABLE II

SOLVOLYTIC DATA OF 8-SUBSTITUTED 1-CHLOROMETHYLNAPHTHALENES IN 80% AQUEOUS ACETONE

Substituent	$k_1 \times 10^6$ sec^{-1} [a] (75.0 ± 0.1°)	$k_1 \times 10^5$ sec^{-1} [a]	ΔH^*, kcal mol^{-1} (75.0°)	ΔS^*, eu (75.0°)	Rate relative to H (75.0°)
H	5.08	4.65 (100°)	22.2	−21.2	1.00
Cl	3.23	3.53 (100°)	23.8	−15.4	0.645
Br	4.38	3.65 (100°)	21.9	−22.5	0.862
OCH_3	30.0	11.5 (90°)	21.9	−16.9	5.91
CH_3	108	56.9 (95°)	20.5	−18.2	21.3
NO_2	0.525[b]	0.625 (100°)	24.3	−17.7	0.104

[a] Average value from two runs. [b] Estimated from 85.0 and 100.0° by graphic method.

culations on these compounds indicate the lower energy minima now lie at *ca.* 180°, with the energy difference between them and the other minima at *ca.* 105° to be 11 kcal/mol and greater. Hence, bulky substituents alter the populations of the preferred conformations.

Some further comments should be made concerning the chemical shifts of the 8-substituted compounds relative to the unsubstituted parent compounds. The methylene signals for the 8-bromo and 8-chloro compounds are considerably downfield from those of the parent compounds. The methyl group signals for *o*-chloro- and *o*-bromotoluenes[22] do not significantly differ from that in toluene itself. Evidently the change in geometry to the *peri* positions permits the halogens to exert their anisotropic deshielding effect[23] due to the closer proximity of the halogen to the methylene hydrogens. Again, some of the greater downfield shifts for the 8-halo-1-chloromethylnaphthalenes relative to the alcohols may be due to the greater contributions of conformation **2** in which the maximum anisotropic effect of the halogen substituent may be experienced. A deshielding electrostatic effect of oxygen on the methylene hydrogens may be more important in 8-methoxy-1-chloromethylnaphthalene, relative to the corresponding alcohol. The methylene signal positions for *o*-methoxybenzyl alcohol and its chloride are approximately the same.

That the methylene signals for the 8-methyl compounds are downfield relative to the unsubstituted compounds is not surprising in light of known data on the methylnaphthalenes. The values for 1-methylnaphthalene and 1,8-dimethylnaphthalene are 2.64 and 2.82 ppm, respectively.[13] This lower field shift of sterically hindered protons has been explained by Tiers[24] as being due to net electron displacement away from hydrogen nuclei induced by repulsive interactions with neighboring groups in the molecule.

Finally, the methylene signals of the 8-nitro compounds are upfield from those of the unsubstituted parent compounds. Such behavior has been noted previously by Wells.[25] Presumably the nitro group is twisted considerably from the plane of the naphthalene nucleus by rotation about the C–N bond. The plane of the nitro group may actually be nearly perpendicular to the naphthalene plane, which would cause a change over to the methylene hydrogens lying in the diamagnetic shielding region of the anisotropic grouping.

It is interesting to note that there is practically a constant chemical shift difference of 0.12 ± 0.02 and 0.08 ± 0.01 ppm between the methylene signals in CCl_4 *vs.* $CHCl_3$ (or $CDCl_3$) for the hydroxymethylnaphthalenes and their corresponding chloromethylnaphthalenes. Hydrogen bonding with chloroform would presumably be more important in the alcohols than in the chlorides. Chloroform is apparently not significantly affecting the conformational preference of the compounds even where intramolecular hydrogen bonding is involved.

Solvolysis of the 1-Chloromethylnaphthalenes.—The 1-chloromethylnaphthalenes were solvolyzed at two different temperatures in 80% aqueous acetone. First-order rate constants at each temperature and energies and entropies of activation at 75.0° are summarized in Table II. Among structural features which could presumably affect the solvolysis rates are polar effects, steric effects, resonance effects, and neighboring group participation. As mentioned previously resonance effects should be minimal since the 8 substituents may be likened to *meta* substituents.

Winstein and coworkers[26] have aptly demonstrated the importance of methoxy-assisted ionization (MeO participation) in the solvolyses of *o*-anisyl substituted tosylates in which the methoxy group is in a position proximate to the reaction sites. The hydrolysis rates of a number of -OCOR substituted benzyl and benzhydryl bromides have been determined.[27] Only in *o*-carbophenoxybenzydryl bromide was participation considered to be an important factor. Bender.[28] in his review of nucleophilic reactions of carboxylic acid derivatives, states that sterically favorable intramolecular reactions proceed more rapidly than the corresponding intermolecular processes, but that the intramolecular nucleophile must be a powerful one compared to external nucleophiles, and the potential interacting groups must be able to adopt the proper steric orientation.

Only in the 8-methoxy-1-chloromethylnaphthalene could the nonbonded p electrons of the 8 substitutent lie near to the *trans-anti*-parallel arrangement of the attacking intramolecular nucleophile. The p electrons of the other potential intramolecular nucleophiles would lie too far above the *peri* carbon atom for participation to occur. Even in the 8-methoxy derivative little significant participation might be anticipated, in that the geometry of the resonance stabilized oxonium ion

(22) Spectra No.'s 13M and 161M, The Sadtler Standard Spectra, N. M. R., Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1966.

(23) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, London, 1965, p 136.

(24) G. V. D. Tiers, *J. Amer. Chem. Soc.*, **78**, 2914 (1956); see also H. J. Bernstein and W. G. Schneider, *J. Chem. Phys.*, **24**, 468 (1956).

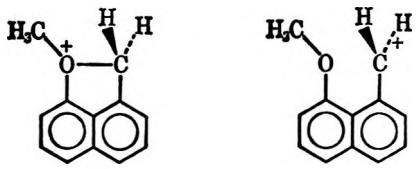
(25) P. R. Wells, *Aust. J. Chem.* **17**, 967 (1964).

(26) R. Heck, J. Corse, E. Grunwald, and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3278 (1957); S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1957), and numerous subsequent papers by S. Winstein and coworkers.

(27) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **84**, 1179 (1962).

(28) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

intermediate (**4a**) would be such that the vacant p orbital of contributor **4b** would lie perpendicular to the adjacent π cloud, and benzylic type resonance, known to be very important in this system,[29] would be precluded. One might not expect the contribution of **4a** to be sufficient to outweigh benzylic-type resonance.



4a **4b**

As to the question of the importance of polar effects in evaluating the factors influencing the solvolysis rates, whether such polar effects be of an inductive type transmitted through the bonding system or of a field type through space, the test is the classical Hammett $\sigma\rho$ treatment. In Figure 1 the logarithms of the rate constants have been plotted *vs.* the σ *meta* substituent constants. If one ignores the value for H, one obtains an excellent correlation according to Jaffé's standard.[30] Two explanations for the correlation may be suggested. (1) Polar effects operate in the expected manner, similar to those one would expect for *meta*-substituted benzyl chlorides, and steric acceleration contributes nearly an equal amount to increase the solvolysis rates regardless of the nature of the *peri* substituent. (2) There exists a collaboration of changing factors which fortuitously results in the Hammett correlation.

Steric acceleration has been invoked to explain results in other systems[31] and may offer an alternative explanation for the enhanced solvolysis rates of the *ortho*-substituted α-phenylalkyl chlorides previously attributed to polar effects of the methyl groups outweighting steric inhibition to resonance.[32] A substituent with a large E_s value[33a] could cause not only the ground state energy to be raised but also the transition state energy, with the latter increase resulting from the *peri* substituent causing steric inhibition to resonance stabilization of the developing positive charge in the transition state. The first explanation requires that

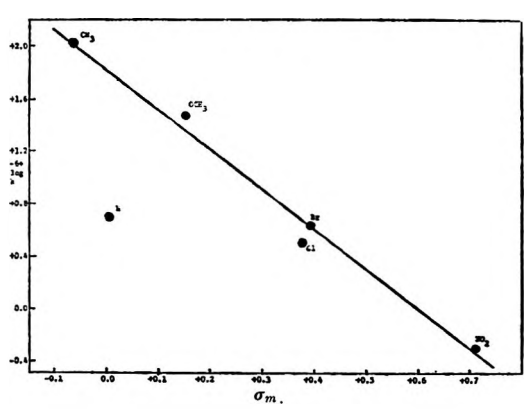


Figure 1.—Hammett plot for 1-chloromethylnaphthalenes (75°): $\rho = -3.01$; $r = 0.995$; $s = 0.0107$.

for a substituent with a small E_s value, *e.g.*, methoxy, steric contributions to the energies of the ground and transition states may not be raised so much, but the difference between the contributions (steric acceleration) remains the same as for a substituent with a larger E_s value. Hence, for the solvolysis reactions the *peri* substituent might be likened to a torque that maintains a constant energy difference between ground and transition states attributable to steric factors.

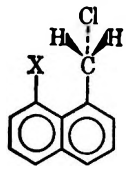
In considering the second explanation, which the authors tentatively favor, the E_s values for methyl and bromine are identical (0.00) so that these two substituents could be expected to contribute equally to steric acceleration in any case. The E_s value for the nitro group (-0.75) suggests a greater steric interaction. However, if the plane of the nitro group approaches a position perpendicular to the naphthalene ring, as suggested by the nmr data, then its effective size will be decreased[33b] and may approximate that of bromine and methyl. The E_s value for chlorine ($+0.18$) suggests a smaller contribution towards steric acceleration. This contribution seems to be substantiated by the fact that the 8-chloro compound solvolyzes more slowly than the 8-bromo analog, and the reverse would be expected from σ *meta* substituent constants. Finally, the E_s value for methoxy ($+0.99$) suggests a significantly smaller steric acceleration role and thereby a deviation from the Hammett plot, which deviation was not observed. For methoxy the smaller steric effect could be counterbalanced by rate enhancement due to some methoxy-assisted ionization. Further rate studies are planned to elucidate the roles of the *peri* substituents.

Solvolyses of benzyl systems have been referred to as "limiting" or borderline systems between SN1 and SN2 types of mechanisms; therefore, we feel that some defense must be offered for largely SN1 character for our solvolyses. An excellent analysis of the solvolysis reaction including borderline system evaluations may be found elsewhere.[34]

In a variety of solvent systems 1-chloromethylnaphthalene solvolyses at least twice as fact as benzyl chloride.[29] The enhancement of reactivity is associated with the increased opportunity for delocalization of positive charge in the carbonium ion of the naphthalene system. The magnitude of the reaction constant, ρ, has been proposed as a measure of the change in electronic charge on the benzenoid system between the ground and transition states.[35] The larger the ρ value, the greater is the positive charge on the system at the transition state. A plot of log k_1 for the benzyl chlorides *vs.* log k_1 for the benzyl tosylates has given a good straight line showing the correspondence in behavior between the two systems, although the ρ is less for the chlorides.[36] Since a ρ of *ca.* -2.20 has been obtained for the benzyl tosylates in *ca.* 50% aqueous acetone at 25.3°, and since the tosylates presumably involve a more complete breaking of the old bond in the transition state (*i.e.*, greater carbonium ion character), our ρ of -3.01 certainly suggests a large degree of positive charge in the transition state for the chloride solvolyses.

(29) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 177.
(30) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(31) Reference 29, p 92.
(32) G. Baddeley and J. Chadwick, *J. Chem. Soc.*, 368 (1951).
(33) (a) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., N. Y., 1956, Chapter 13, p 598; (b) ref 33a, p 651.
(34) See ref 29.
(35) C. G. Swain and W. P. Langsdorf, *J. Amer. Chem. Soc.*, **73**, 2813 (1951).
(36) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3445 (1953).

In addition, the steric difficulty in accomplishing an SN2-type displacement on the *peri* substituted 1-chloromethylnaphthalenes argues strongly in favor of the SN1 mechanism. The lowest energy conformer (**2a**, except for methoxy) should be an unreactive one for an SN2-type displacement since the *peri* substituent would block the approach of the nucleophile to the carbinyl C atom. Therefore, the lone possibility for SN2 displacement would be **5**, a conformer in which one of the hydrogen atoms would have to pass by the *peri* substituent in order to fulfill the inversion requirement of this reaction type. Presumably such a passage would involve severe atomic repulsions and a high activation energy relative to the unsubstituted "parent" compound.



5

Obviously there would be considerable steric strain in a planar carbonium ion intermediate for the *peri*-substituted compounds; however, a fairly large ρ is observed. As pointed out by Streitwieser,[37] the π overlap between two ρ orbitals is roughly proportional to the cosine of the angle between them, and hence, a carbonium ion may be twisted rather severely from the plane of an attached aromatic ring and still be able to distribute a considerable amount of positive charge to the ring.

In our system steric acceleration is invoked to explain the facilitation of the conversion of an sp^3 hybridized ground state carbon to an sp^2 hybridized intermediate. It is interesting that the counterpart, the conversion of an sp^2 hybridized ground state carbon to a tetrahedral sp^3 hydridized intermediate as in the saponification of *peri*-substituted esters,[38] is retarded. These may be general occurrences in such sterically hindered systems.

Experimental Section

Melting points were determined in soft capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are uncorrected. A Varian A-60 nmr spectrometer, calibrated with tetramethylsilane ($\delta = 0$) and chloroform ($\delta =$ 436.5 cps), was used for the nmr determinations. Chemical shifts are presumed correct to ± 0.01 ppm. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Weiler and Strauss Microanalytical Laboratory, Oxford, England.

Naphthoic Acids.—Methods of preparation of these acids appear in the literature. The α-naphthoic acid was a commercial sample,[39] the 8-methyl-1-naphthoic acid was prepared by the method of Cason and Wordie,[40] and 8-nitro-1-naphthoic acid was prepared by the method of Ekstrand.[41] The 8-bromo-, 8-chloro-, and 8-methoxy-1-naphthoic acids were prepared by the procedure of Rule and Barnett.[42]

Hydroxymethylnaphthalenes.—Lithium aluminum hydride reduction in the standard manner[43] was employed for reduction of α-naphthoic acid and 8-methyl-1-naphthoic acid. With the remaining acids the externally generated diborane reduction in diglyme of Brown and Subba Rao[44] was used. The percentage yields, physical constants, recrystallizing solvents, and analytical data (where appropriate) for these alcohols are as follows: 1-hydroxymethylnaphthalene (81%, mp 60–62°[45] from ether–ligroin); 8-chloro-1-hydroxymethylnaphthalene [92%, mp 81.5–83° from methanol (*Anal.* Calcd for $C_{11}H_9OCl$: C, 68.58; H, 4.71; Cl, 18.41. Found: C, 68.36; H, 4.60; Cl, 18.13)]; 8-bromo-1-hydroxymethylnaphthalene [92%, mp 88–89° from methanol[46] (*Anal.* Calcd for $C_{11}H_9OBr$ C, 55.72; H, 3.82; Br, 33.71. Found: C, 55.38; H, 3.73; Br, 33.72)]; 8-methoxy-1-hydroxymethylnaphthalenes [82%, mp 88–89° from ethanol–water (*Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.32; H, 6.42)]; 8-methyl-1-hydroxymethylnaphthalene [74%, mp 93–94.5° from ether–ligroin (*Anal.* Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.67; H, 7.04)]; 8-nitro-1-hydroxymethylnaphthalene [38%, mp 72–73° from ether–ligroin (*Anal.* Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.84; H, 4.61; N, 6.70)].

Chloromethylnaphthalenes.—For the preparation of 1-chloromethylnaphthalene and 8-methoxy-1-chloromethylnaphthalene the method of Shoesmith and Rubli[6] involving passage of hydrogen chloride gas into benzene solution was employed. The remaining chlorides were obtained by addition of a thionyl chloride solution to the alcohol dissolved in chloroform.[5] The percentage yields, physical constants, recrystallizing solvents, and analytical data (where appropriate) for these chlorides are as follows: 1-chloromethylnaphthalene [45%, bp 137–139° (5.0 mm)[47]]; 8-chloro-1-chloromethylnaphthalene [86%, mp 47–48° from ligroin (*Anal.* Calcd for $C_{11}H_8Cl_2$: C, 62.58; H, 3.82; Cl, 33.59. Found: C, 62.39; H, 3.66; Cl, 33.36)]; 8-bromo-1-chloromethylnaphthalene [55%, mp 64–66° from ligroin (*Anal.* Calcd for $C_{11}H_8BrCl$: C, 51.70; H, 3.15; Cl, 13.88. Found: C, 51.58; H, 3.20; Cl, 13.65)]; 8-methoxy-1-chloromethylnaphthalene [55%, mp 46–47.5° from ligroin (*Anal.* Calcd for $C_{12}H_{11}ClO$: C, 69.73; H, 5.37; Cl, 17.16. Found: C, 69.93; H, 5.32; Cl, 16.95)]; 8-methyl-1-chloromethylnaphthalene [75%, mp 62.5–63.5° from ether–ligroin (*Anal.* Calcd for $C_{12}H_{11}Cl$: C, 75.59; H, 5.81; Cl, 18.60. Found: C, 75.37; H, 5.78; Cl, 18.90)]; 8-nitro-1-chloromethylnaphthalene [60%, mp 102–103.5° from ether–ligroin (*Anal.* Calcd for $C_{11}H_8O_2ClN$: C, 59.60; H, 3.64; Cl, 16.00; N, 3.32. Found: C, 59.87; H, 3.76; Cl, 15.72; N, 6.52)].

Solvolysis Procedure.—Approximately 0.15–0.20 g of the chloromethylnaphthalene weighed to the nearest 0.00002 g was diluted to 50.0 ml with 80% aqueous acetone, divided into nine 10-ml vials, and heated in a temperature bath maintained constant to $\pm 1°$. At appropriate time intervals the sample vials were removed from the temperature bath and swirled in an ice bath to stop the reaction. Exactly 5.00 ml of solution was pipeted into an erlenmeyer flask, and *ca.* 5 ml of 80% aqueous acetone was added to this solution. Titration of the hydrochloric acid that formed was accomplished with a standard sodium hydroxide solution to a blue lacmoid[48] end point (pH 4.4, red; pH 6.2, blue). The reaction solutions often became colored (amber to deep yellow) when solvolyzed longer than one or two half-lives. Hence, calculated infinity titers were used for calculating rate constants. Data for the solvolysis of 8-methyl-1-chloromethylnaphthalene, a typical example, are as follows: sample weight, 0.6855 g; base normality 0.01906; calcd infinity titer, 4.638 ml; 600 sec, 0.498 ml, 1.10 ($k_1 \times 10^4$ sec^{-1}); 1200 sec, 0.760 ml, 1.10; 2400 sec, 1.218 ml, 1.07; 3600 sec, 1.638 ml, 1.08; 5400 sec, 2.130 ml, 1.05; 7200 sec, 2.557 ml, 1.05; 10800 sec, 3.210 ml, 1.05; mean $k_1 \times 10^4$, 1.07 $\pm$ 0.02; average for two runs, 1.08 $\pm$ 0.02.

Acknowledgment.—We are grateful to Dr. J. F. Eastham of our own department for valuable discussions concerning this research.

(37) Reference 29, p 94.

(38) A. Fischer, J. D. Murdoch, J. Packer, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.*, 4358 (1957); A. Fischer, H. M. Fountain, and J. Vaughan, *ibid.*, 1310 (1959).

(39) Distillation Products Industries, Rochester 3, N. Y.

(40) J. Cason and J. D. Wordie, *J. Org. Chem.*, **15**, 608 (1950).

(41) J. Elkstrand, *J. Prakt. Chem.*, **38**, 154 (1888).

(42) H. G. Rule and A. J. G. Barnett, *J. Chem. Soc.*, 175 (1932).

(43) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley & Sons, Inc., New York, N. Y., 1951, pp 469–509.

(44) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

(45) K. Ziegler [*Ber.*, **54**, 737 (1921)] reported mp 59–60°.

(46) R. G. Gay and C. R. Hauser [*J. Amer. Chem. Soc.*, **89**, 2297 (1967)] reported mp 87–88.5° from hexane.

(47) H. W. Coles and M. L. Dodds, [*J. Amer. Chem. Soc.*, **60**, 853 (1938)] reported a bp 134° (3 mm).

(48) B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 287 (1956).

Photodecomposition of the Dianions of the Di-*p*-tosylhydrazones of Biacetyl and Benzil

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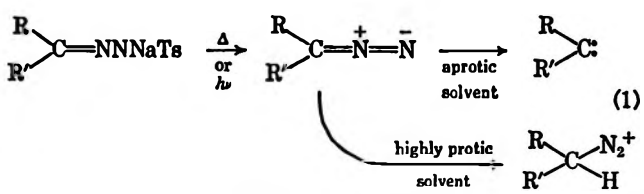
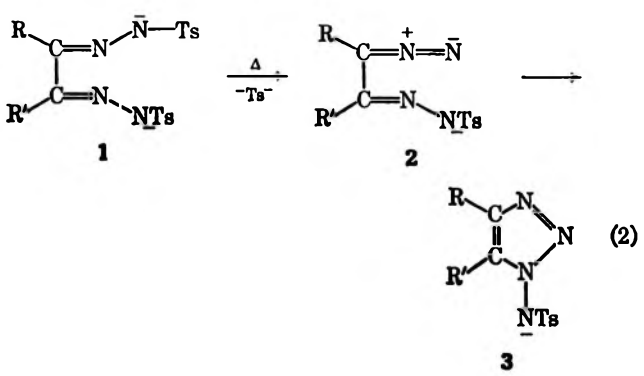
Irradiation of biacetyl di-*p*-tosylhydrazone dianion through Vycor gives 2-butyne as the only volatile product. The formation of 2-butyne is shown to arise *via* intermediate formation of the anion of 4,5-dimethyl-1-toluene-*p*-sulfonamido-1,2,3-triazole, which was isolable in the acid form in 81% yield when the irradiation was carried out employing a Corex filter. Irradiation of benzil di-*p*-tosylhydrazone dianion through Vycor gave a 74% yield of *cis*- and *trans*-α-methoxystilbene formed in the ratio 38:62. 4,5-Diphenyl-1-toluene-*p*-sulfonamido-1,2,3-triazole was isolated in 25% yield when the irradiation was carried out employing a Corex filter.

The course of the thermal decomposition of mono-*p*-tosylhydrazone salts has been well established.[1-6] *p*-Toluenesulfinate anion is eliminated in an initial step with resultant formation of a diazo compound. Depending on the choice of reaction conditions, the diazo compound may either be isolated[1b,3] or subsequently decomposed *in situ via* carbenoid or cationoid pathways.[1a,2,4,6] Dauben and Willey[7] have shown that the decomposition can also be effected photochemically. The evidence indicates that, in this case too, a fragmentation occurs first to give the diazo compound



(1)

(reaction 1). Bamford and Stevens[5] discovered that the dianions of the di-*p*-tosylhydrazones of 1,2-diketones (**1**) decompose thermally to give derivatives of 1-toluene-*p*-sulfonamido-1,2,3-triazole anion (**3**). Apparently in this instance, the decomposition involves the loss of one toluenesulfinate anion thereby forming an intermediate α-diazotosylhydrazone anion (**2**) which then cyclizes to give **3** (reaction 2). Theoretical



(2)

considerations which are presented below indicated to us that compounds with structure **1** might decompose photochemically by a different route from the one above to give alkynes instead of **3**. These considerations provided the necessary impetus for the investigation of the photochemistry of **1**.

A comparison of the molecular orbital nodal patterns in mono- and 1,2-ditosylhydrazone anions[8] suggests that the latter might decompose photolytically by way of a bis elimination process. The lowest energy electronic transition (ψ_6–ψ_6, Figure 1a) in a simple monotosylhydrazone anion should be accompanied by a

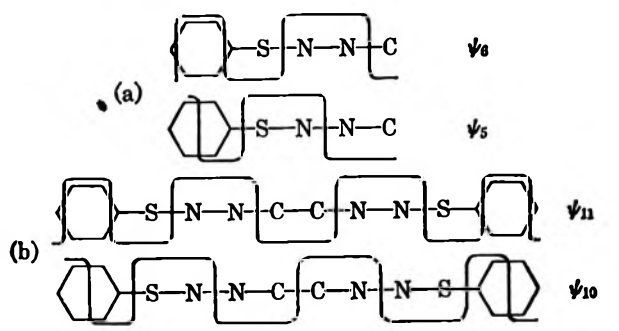


Figure 1.—Comparison of the nodal patterns in the highest energy bonding and lowest energy antibonding molecular orbitals for anions of (a) monotosylhydrazones and (b) 1,2-ditosylhydrazones.

decrease in the sulfur–nitrogen bond order. The initial fragmentation to give the diazo compound (reaction 1) is due to bond breaking at this position. Analogously, in the 1,2-ditosylhydrazone dianions, the bond order at both sulfur–nitrogen bonds is predicted to decrease on photoexcitation to the first excited state (ψ_{10}–ψ_{11}, Figure 1b). Possibly in this case, irradiation might effect the simultaneous elimination of two toluenesulfinate anions resulting in the formation of a didiazo compound (**4**, reaction 3). Regarding the fate of **4**, a consideration of molecular orbital nodal patterns[9] suggests that this type of compound might also decompose photolytically by way of a bis elimination process generating either a diradical or an alkyne depending on the spin multiplicity of the reactive intermediate. Possibly, the same species could result directly from **1** if cleavage at all four sites (*i.e.*, two S–N bonds and

(1) (a) J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Amer. Chem. Soc.*, **90**, 531 (1968); (b) G. Kaufman, F. Cook, H. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89**, 5736 (1967).

(2) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *ibid.*, **89**, 471, 1442 (1967).

(3) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *ibid.*, **87**, 935 (1965).

(4) L. Friedman and H. Shechter, *ibid.*, **81**, 5512 (1959).

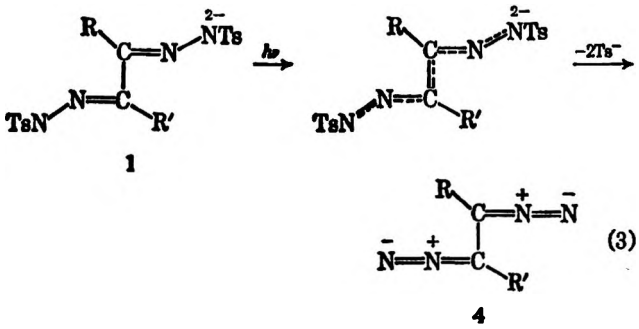
(5) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(6) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

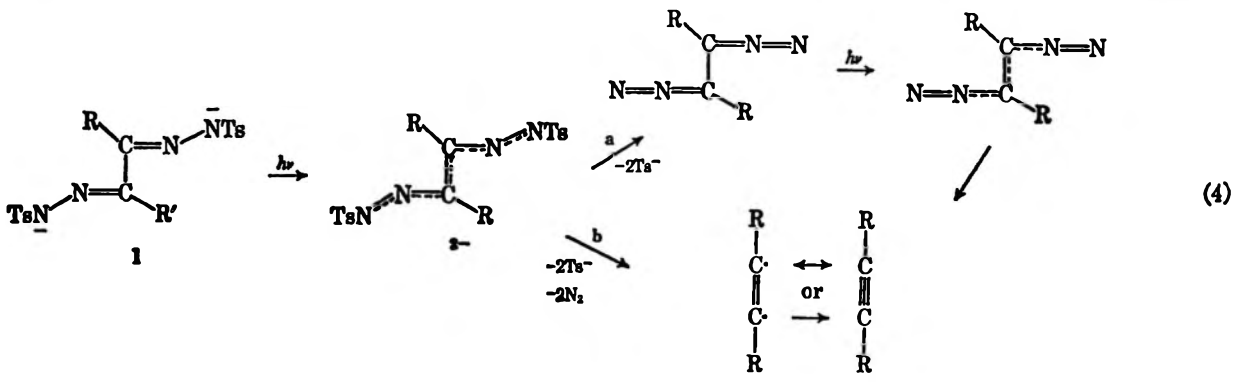
(7) W. G. Dauben and F. G. Willey, *J. Amer. Chem. Soc.*, **84**, 1497 (1962).

(8) The molecular orbital nodal patterns for mono- and 1,2-ditosylhydrazones shown in Figure 1 were adapted from the nodal patterns for 1-phenylbutadiene and 1,8-diphenyloctatetraene, respectively. See C. Coulson and A. Streitwieser, Jr., "Dictionary of π-Electron Calculations," W. H. Freeman and Co., San Francisco, Calif., 1965. Nodal positions in the corresponding species should be identical.

(9) The highest energy occupied molecular orbital ψ_4 in **4** is bonding at both C–N linkages and antibonding at C–C, while in the lowest energy unoccupied orbital, ψ_5, nodes occur at both C–N positions with bonding at the C–C linkage.

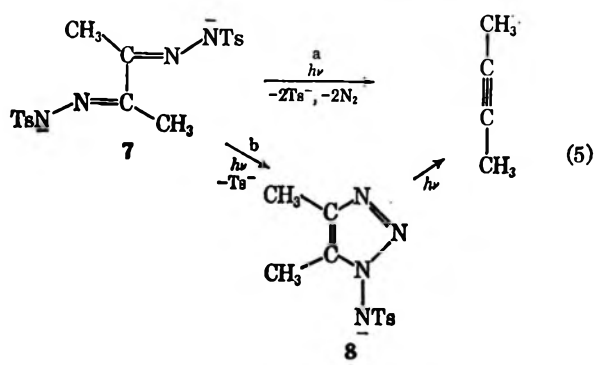


two C–N bonds) occurred simultaneously without intervention of **4** (reaction 4b).



Results and Discussion

The photochemistry of biacetyl and benzil ditosylhydrazone dianions was investigated. These two species seemed especially appropriate in view of the fact that their behavior on thermal decomposition had previously been studied.[5] Biacetyl ditosylhydrazone dissolved in methanolic sodium methoxide solution giving lemon yellow solutions of the dianion **7**. Irradiation at room temperature with a 450-W Hanovia lamp, employing a Vycor filter, effected a smooth decomposition producing 2-butyne as the only volatile product. While this result is in line with our ideas based on molecular orbital nodal patterns, recent work of Willey[10] has shown that 4,5 dialkyl- and 4,5-diaryl-1-toluene-*p*-sulfonamido-1,2,3-triazole derivatives decompose photolytically in basic media giving alkynes, which raises the question as to whether 4,5-dimethyltoluene-*p*-sulfonamido-1,2,3-triazole anion (**8**) might be an intermediate in the photodecomposition of **7**. Indeed, when the irradiation was interrupted and recovered solid material analyzed by column chromatography, the triazole corresponding to **8** was isolated. A means of determining the relative importance of pathways a (bis elimination) and b (reaction *via* **8**) in reaction 5 was suggested on examination of the ultraviolet absorption curves for **7** and **8** (Figure 2). While the curve for **7** exhibits a prominent maximum at 307 mμ, the curve for **8** shows little absorption at wavelengths greater than 260 mμ. By employing an appropriate filter, it appeared that it might be possible to decompose **7** selectively without destroying **8**. When the irradiation was carried out employing a Corex filter, which transmits light of wavelength greater than 260 mμ, very little gas evolution was noted, and, after 2 hr, analysis of the reaction mixture revealed that nearly all of the dianion had been converted into **8** as indicated by the



isolation of 4,5-dimethyl-1-toluene-*p*-sulfonamido-1,2,3-triazole in 81% yield. By far the most important source of 2-butyne, then, is **8** (reaction 5b). Instead of cleaving the dianion directly in a bis elimination process, the photoexcitation process seems to weaken only the sulfur–nitrogen bonds. Apparently, cleavage of a single sulfur–nitrogen bond is then followed by cyclization (reaction 2).[11]

The behavior of benzil ditosylhydrazone dianon (**9**) on pyrolysis stands apart from the behavior of the ditosylhydrazone dianions derived from aliphatic 1,2-diketones. Bamford and Stevens[5] have reported that **9** gives a 73% yield of diphenylacetylene. No mention was made of the formation of any 4,5-diphenyl-1-

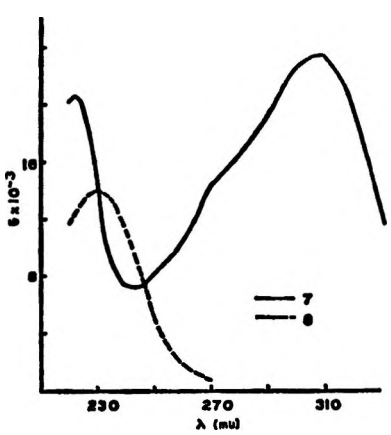
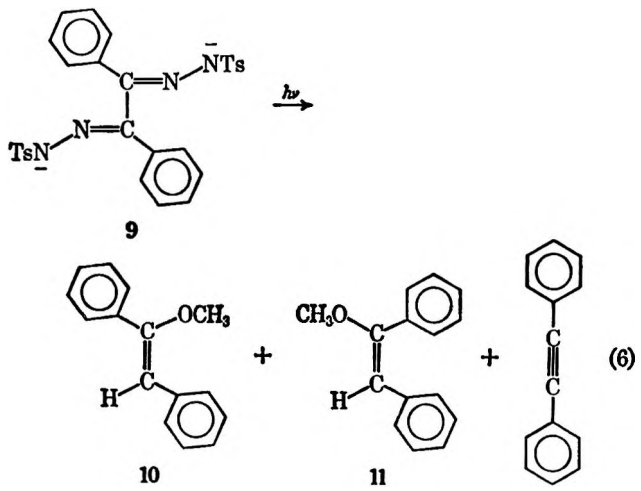


Figure 2.—Comparison of the ultraviolet absorption curves for the sodium salts of biacetyl ditosylhydrazone and 4,5-dimethyl-1-toluene-*p*-sulfonamide-1,2,3-triazole.

(10) F. Willey, *Angew. Chem. Intern. Ed. Engl.*, **3**, 138 (1964).

(11) This assumes that the *p*-toluenesulfinate anion(s) is (are) lost from an excited state in the *s-trans* conformation. A second consideration is that it is not inconceivable that the excited state actually loses two toluenesulfinate anions, cyclization occurs, and one toluenesulfinate ion is reincorporated to yield triazole anion **8**.

toluene-*p*-sulfonamido-1,2,3-triazole.[12] Rather unexpected behavior was also shown on irradiation (Vycor). Instead of producing diphenylacetylene as the major product, photodecomposition of benzil ditosylhydrazone in methanolic sodium methoxide gave a 74% yield of the two isomeric α-methoxystilbenes **10** and **11** formed in the ratio 62:38 (reaction 6). The gross structure of these



9

10 **11** (6)

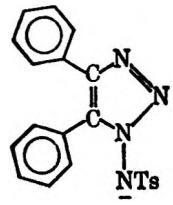
compounds was established by their facile hydrolysis to deoxybenzoin. The stereochemical assignment was complicated by the difficulty encountered in obtaining one of the isomers free from contaminating diphenylacetylene (formed in 20% yield). The infrared and ultraviolet spectra of the two isomers were quite similar; however, a choice can be made by consideration of the nmr spectra. Assuming an angle of twist out of the plane of the double bond of 40° for the phenyl groups of both isomers[13] and using the data of Johnson and Bovey,[14] it can be calculated that the olefinic hydrogen of the *trans* isomer should be deshielded to a greater extent than that of the *cis* isomer, while the methoxyl of the *cis* derivative should be deshielded to a greater extent than that of the *trans*. On this basis, the predominant stilbene component (=CH, τ 3.92; OCH_3, 6.42) was assigned the *trans*-α-methoxystilbene structure and the minor component (=CH, τ 4.20; OCH_3 6.26) the *cis* structure. Isomeric α-methoxystilbenes **10** and **11** were shown to be primary reaction products rather than secondary products formed by the photoaddition of methanol to diphenylacetylene. When diphenylacetylene was irradiated under the conditions of the original experiment, a nearly quantitative yield of unchanged starting material was recovered from the reaction.

The behavior of **9** on irradiation is similar to **7** in that a toluenesulfonamidotriazole anion (**12**) is formed as an intermediate in the reaction. Irradiation through Corex, however, resulted in a smaller yield (25% maximum) of **12**. The phenyl substituents in **12** extend the length of conjugation so that this anion shows considerable ultraviolet absorption at wavelengths greater than 260 mμ (Figure 3). Photodecomposition of **12** as well as of **9** is then to be expected under these conditions.

(12) Willey[10] indicates, however, that the 4,5-diphenyl-1-toluene-*p*-sulfonamido-1,2,3-triazole is available by way of the Bamford and Stevens method.

(13) See H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1962, p 424.

(14) C. E. Johnson, Jr. and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).



12

The fact that most of **9** undergoes reaction to form **10** and **11**, whereas no detectable amount of similar products could be found in the case of **7**, is strongly reminiscent of the contrasting chemistry of dialkyl- and diarylcarbenes.[15] Dialkycarbenes usually react by intramolecular routes of insertion, hydrogen migration, and rearrangement, whereas intermolecular reactions, such as abstraction, are common for diarylcarbene intermediates.[16] Therefore, it appears tempting to rationalize the present case tentatively on the basis that

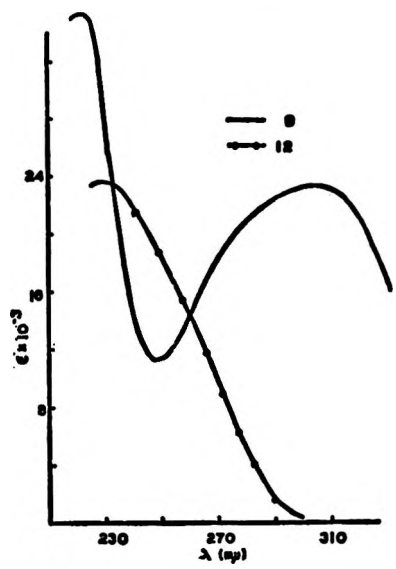


Figure 3.—Comparison of the ultraviolet absorption curves for the sodium salts of benzil ditosylhydrazone and 4,5-diphenyl-1-toluene-*p*-sulfonamido-1,2,3-triazole.

the photodecomposition of **12** results in the generation of a triplet-state intermediate, whereas in the case of **8** product is formed by way of a singlet-state intermediate. Additional experimentation designed to elucidate the details of the photodecompositions of the triazole anions **8** and **12** is presently underway.

In summary, the photodecomposition of **7**, the ditosylhydrazone dianion of a representative aliphatic 1,2-diketone, has been shown to give 2-butyne as the sole volatile reaction product. This product arises, nevertheless, *via* the intermediate formation of **8** rather than by way of a bis elimination process involving the loss of two toluenesulfinate anions and two molecules of nitrogen. The direct photochemical generation of an alkyne from the ditosylhydrazone of a 1,2-diketone represents a potentially useful synthetic route to

(15) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapters 3 and 5.

(16) A somewhat analogous case to that presently under consideration is found in the photodecomposition of 1,4-bis(α-diazobenzyl)benzene, which has been shown to yield a triplet-state dicarbenoid intermediate: R. Murray and A. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961); A. Trozzolo, R. Murray, G. Smolinsky, W. Yager, and E. Wasserman, *J. Amer. Chem. Soc.*, **85**, 2526 (1963).

alkynes, eliminating the necessity of preparing the triazole intermediate in a separate step. Dianion **9** exhibits the same general behavior undergoing photocyclization to **12**, but the subsequent photodecomposition of **12** differs significantly from that of **8**, in that it leads to an incorporation of a molecule of solvent, producing methoxystilbenes as the major product fraction.

Experimental Section

All melting and boiling points were uncorrected. Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, Max Planck Institut fur Kohlenforschung, Mülheim (Ruhr), Germany, or Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Spectral absorptions are reported in wavenumbers (cm^{-1}) and are subject to the following general reading errors: $\Delta\nu$ >3000, 10 cm^{-1}; 2200–3000, 5–9 cm^{-1}; 1200–2200, 2–4 cm^{-1}. The intensities of the absorption bands are denoted by the code s (strong), m (medium), and w (weak). Nmr spectra were measured on a Varian Associates A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal standard. Vapor phase chromatographic analyses were performed on an Aerograph A-90-P gas chromatograph equipped with a thermal conductivity detector. Two columns were employed: column A, a 15 ft × 0.25 in. aluminum column containing 15% Carbowax 20M on 70–80 Anakrom A-S; column B, a 7.5 ft × 0.25 in. aluminum column containing 10% Carbowax 20M on 70–80 Chromosorb G. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrometer.

Biacetyl Di-p-tosylhydrazone.—p-Tosylhydrazine[17] (50.0 g, 0.259 mol) was dissolved in 135 ml of methanol contained in a 500-ml three-necked flask equipped with a dropping funnel, mechanical stirrer, and a thermometer. The solution was maintained at 45–50° while a solution of 11.6 g (0.135 mol) of freshly distilled biacetyl [bp 87° (690 mm)] in 85 ml of methanol was added with stirring over a period of 2.5 hr. After addition was complete, stirring was continued at the same temperature for three additional hours. The solid was removed by filtration, washed with methanol, and air dried. The yield of biacetyl di-p-tosylhydrazone was 48.4 g (85%), mp 190° dec (lit.[5] mp 204° from acetic acid). The infrared spectrum (Nujol mull) of this material showed absorptions at 3295 m (N–H), 1595 with shoulder at 1585 w (overlap of aromatic C=C with C=N) 1490 w, 1336 s (SO_2–N, asymmetric), 1293 m, 1184 m, 1166 s (SO_2–N, symmetric), 1096 w, 1068 m, 1017 w, 936 m, 811 m, and 708 cm^{-1} w.

Anal. Calcd for $C_{18}H_{22}O_4N_4S_2$: C, 51.17; H, 5.25. Found: C, 51.30; H, 5.25.

In variations of procedure in which the reagents were mixed all at once in methanol or aqueous N-hydrochloric acid,[5] the product was contaminated with monotosylhydrazone (infrared, weak conjugated carbonyl absorption at 1690 cm^{-1}).

Benzil Di-p-tosylhydrazone.—The procedure of Bamford and Stevens[5] was used employing 22.4 g (0.108 mol) of benzil, 40.1 g (0.216 mol) of p-tosylhydrazine, and 250 ml of 1% ethanolic hydrochloric acid. The yield of benzil di-p-tosylhydrazone was 43.5 g (74%). Recrystallization of the crude product from aqueous acetonitrile gave material melting at 176–178° dec (lit.[3] mp 184° dec from isoamyl alcohol); the infrared spectrum (Nujol mull) showed absorption bands at 3225 m (N–H), 1593 m (aromatic C=C), 1493 m, 1353 s, 1341 s (SO_2–N, asymmetric), 1300 m, 1253 w, 1184 s, 1162 s (SO_2–N, symmetric), 1118 m, 1090 s, 1064 s, 1035 m, 1009 s with shoulder 1018 m, 998 w, 981 w, 955 w, 914 m, 850 w, 835 w, 811 s with shoulder 815 m, 779 w, 766 m, 745 s, and 688 cm^{-1} s.

Irradiations.—Irradiations were conducted in a specially designed immersion reactor (capacity, 200 and 425 ml) which consisted of an interchangeable three-necked cylindrical Pyrex flask; within its standard taper 60/50 center neck was a water-jacketed quartz probe housing a Hanovia 450-W Type L high pressure mercury arc lamp. Vycor and Corex filters were used as specified. All irradiations were carried out in anhydrous methanol prepared by distillation from magnesium metal turnings.[18] Sodium methoxide solutions were prepared by the dissolution of freshly cut sodium metal in anhydrous methanol.

Irradiation of the Dianion of Biacetyl Di-p-tosylhydrazone.—Biacetyl di-p-tosylhydrazone (42.0 g, 0.100 mol) was dissolved in a sodium methoxide–methanol solution (425 ml) prepared using 4.8 g (0.21 g-atom) of sodium metal. The solution was placed in the immersion reactor (see above) provided with an outlet through a Dry Ice–isopropyl alcohol cold trap to a wet test meter. Irradiation through Vycor for 9 hr resulted in the evolution of 75% of the theoretical volume of gas. The cold trap contained a liquid (0.5 g) whose nmr spectrum displayed signals due to methanol and a sharp singlet at τ 8.28, which corresponded exactly with the methyl singlet in the spectrum of an authentic sample of 2-butyne. Vpc analysis on column A at 35° revealed the presence of only one product component; its retention time was the same as that of authentic 2-butyne. Additional 2-butyne (0.64 g) was recovered from the reaction mixture as a 25% solution in methanol by warming under a stream of nitrogen directed to a cold trap. Vpc analysis of the reaction mixture employing pentane as an internal standard revealed the presence of 1.26 g of residual 2-butyne. The over-all yield of 2-butyne was 2.00 g (50% based on starting material decomposed) which represents a lower limit for the actual amount of this elusive hydrocarbon formed in the reaction. The reaction mixture was diluted with four volumes of water and extracted with three 300-ml portions of ether which after drying and concentration left a liquid residue. Vpc analysis (column A at 70°) showed the presence of toluene, ether, and methanol but no other aliphatic products.

Incomplete Photodecomposition of the Dianion of Biacetyl Di-p-tosylhydrazone. Isolation of 4,5-Dimethyl-1-toluene-p-sulfonamido-1,2,3-triazole.—Biacetyl di-p-tosylhydrazone (22.75 g, 0.0539 mol) was dissolved in a solution of methanolic sodium methoxide (200 ml) prepared using 2.5 g (0.108 g-atom) of sodium metal. The solution was irradiated in the manner described previously except that irradiation was discontinued after 1.08 hr (29% of the theoretical volume of gas). The reaction mixture was treated with 52 ml of 2 *N* hydrochloric acid and the precipitated solid removed by filtration. The dry solid was identified as starting material (2.63 g, 12%) by a comparison of infrared spectra. Concentration of the filtrate by use of a rotary evaporator left an aqueous residue containing a separated yellow oil. The oil was taken up in ether (two extractions). Removal of the ether gave back the oil which was dissolved in chloroform and placed on a chromatographic column containing 120 g of acidic alumina (pH 4) previously moistened with 7.2 ml of water to achieve a Brockman activity grade of III. The column was successively eluted with the following solvents and solvent mixtures, with the eluent collected in 50-ml fractions: chloroform, four fractions; 25% ethyl acetate–75% chloroform, three fractions; ethyl acetate, three fractions; 25% methanol–75% ethyl acetate, four fractions; and 50% methanol–ethyl acetate, three fractions. Residues, either oils or solids, remained on evaporation of solvent from all of the collected fractions. The solid obtained from fraction 10 (mp 137.5–142.0°) did not depress the melting point of authentic 4,5-dimethyl-1-toluene-p-sulfonamido-1,2,3-triazole[5] in a mixture melting point determination; infrared spectra of the two materials were virtually identical. The quantity of the triazole obtained from fractions 6–13 was 1.49 g 12% based on unrecovered starting material).

Irradiation of the Dianion of Biacetyl Di-p-tosylhydrazone Using a Corex Filter.—The initial procedure was the same as described above, employing 20.0 g (0.0474 mol) of ditosylhydrazone, 2.3 g (0.10 g-atom) of sodium metal, and 200 ml of methanol. The solution was irradiated through Corex for 2 hr during which period nitrogen evolution was very slow (total volume of liberated gas, 175 ml). The reaction mixture was diluted with four volumes of water and treated with 50 ml of 2 *N* hydrochloric acid. The precipitated solid was removed by filtration and dried giving 8.20 g of material melting 150–170°. On standing, the filtrate deposited two crops of white crystals (4.02 g) which did not depress the melting point of authentic 4,5-dimethyl-1-toluene-p-sulfonamido-1,2,3-triazole. The solid which initially precipitated on acidification of the reaction mixture was stirred with 150 ml of methanol. Insoluble material was removed by filtration and shown to be starting material by comparison of infrared spectra (3.38 g). Concentration of the filtrate gave an oil which

(17) L. Friedman, R. Little, and W. Reichle, *Org. Syn.*, **40**, 63 (1960).

(18) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 289.

yielded a yellowish solid (4.47 g) on trituration with water. The infrared spectrum of this material was virtually identical with that of authentic triazole. The combined yield of the triazole was 8.49 g (80.7% based on unrecovered starting material).

Irradiation of the Dianion of Benzil Di-*p*-tosylhydrazone.—Benzil di-*p*-tosylhydrazone (34.9 g, 0.0639 mol) was stirred into a solution of methanolic sodium methoxide prepared using 4.4 g (0.191 g-atom) of sodium metal and 4.25 ml of methanol. The resulting suspension of the salt[19] was irradiated through Vycor until gas evolution retarded (*ca.* 5.5 hr, 72% of the theoretical quantity of gas). The final red-orange solution was diluted with three volumes of water and extracted with four 150-ml portions of petroleum ether (bp 30–60°). Removal of petroleum ether using a steam bath left a residual oil (11.6 g) whose nmr spectrum showed absorption bands due to aromatic hydrogens, a pair of olefinic hydrogens (τ 3.92 and 4.20), and a pair of methoxyl resonances (τ 6.26 and 6.42). After removal of an additional quantity of petroleum ether (2.63 g) by distillation at atmospheric pressure, the residual liquid was distilled under reduced pressure giving the following fractions: 90.5–94.0° (0.02–0.03 mm), 0.68 g; 94.0–97.5° (0.02–0.03 mm), 2.49 g; and 93–96° (0.04 mm), 2.94 g, leaving a residue (1.50 g). The nmr spectra of the fractions showed the features of the undistilled material. Vpc analysis (column B at 200–220°) showed two major peaks of varying area ratio. Material corresponding to the two peaks, here designated as isomer 1 and isomer 2 in order of increasing vpc retention time, were subsequently identified as *cis*- and *trans*-α-methoxystilbene, respectively, on the basis of the spectral and chemical evidence presented below.

Analysis of Isomer 1, *cis*-α-Methoxystilbene.—Samples of this isomer obtained by vpc were always contaminated with the *trans* isomer (10–20%) and another impurity (35–50%) with retention time identical with the *cis* isomer, but exhibiting only aromatic hydrogens; the impurity is identified as diphenylacetylene. The following spectra were obtained: infrared ($CDCl_3$) 3090 s, 2945 m, 2820 w, 1870 w, 1800 w, 1747 w, 1642 s (C=C conjugated with aromatic ring), 1600 s, 1573 m (C=C aromatic, indicative of conjugation with olefinic bond), 1497 s, 1460 m, 1440 s, 1375 m, 1307 w, 1282 w, 1237, 1200 s (either band assignable to =COC, asymmetric), 1188 w, 1156 w, 1121 s (=COC, symmetric), 1073 m, 1038 m, 1000 w, 960 m, 876 m, 842 w, 814 m, and 776 cm^{-1} s. The four bands which are assigned above with the exception of the band at 1573 cm^{-1} are completely absent from the spectrum of diphenylacetylene in $CDCl_3$. The band at 1573 cm^{-1} has only a weak counterpart in the latter spectrum. The nmr spectrum ($CDCl_3$) showed signals at τ 2.30–3.10 (multiplet, aromatic, 20.5 H) 4.20 (singlet, olefinic, 1.0 H), 6.26 (singlet, OCH_3, 3.0 H) and 6.42 (singlet, OCH_3 due to the *trans* isomer, 0.6 H). The spectrum is consistent with a mixture of 10% *trans*-α-methoxystilbene, 49% *cis*-α-methoxystilbene, and 41% diphenylacetylene. The ultraviolet spectrum (methanol) showed considerable fine structure in the form of four rather sharp maxima at 264 mμ (ϵ ~19,000), 278.5 (~27,000) with a shoulder at 272.5 (~21,000), 287 (~20,000), and 295.5 (~23,000). The values for the extinction coefficients, which are uncorrected for the presence of impurities, are included in order to give a rough measure of absorption intensity.

Analysis of Isomer 2, *trans*-α-Methoxystilbene.—A sample of this compound obtained by vpc was a solid melting 45–50°, containing less than 8% *cis* isomer. The infrared spectrum showed absorption bands at 3030 s, 2935 m, 2825 m, 1950 w, 1875 w, 1800 w, 1720 w, 1635 s (C=C conjugated with aromatic ring), 1600 s (C=C, aromatic), 1570 m (C=C aromatic, indicative of conjugation with olefinic bond), 1492 s (C=C, aromatic), 1445 s, 1340 s, 1280 m, 1255 m, 1200 s (=COC, asymmetric) 1178 w, 1153 w, 1120 w, 1062 s (=COC, symmetric), 1026 s, 1000 m, 980 s, 856 m, and 770 cm^{-1} s. The nmr spectrum displayed signals at τ 2.12–3.06 (multiplet, aromatic, 10.0 H), 3.92 (singlet, olefinic, 0.9 H), and 6.42 (singlet, OCH_3, 2.9 H). The ultraviolet spectrum (methanol) showed structureless maxima at 220 mμ (ϵ 12,250) and 292 (21,000).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.50; H, 6.85.

The yield of products was *ca.* 8.0 g (93% based on a 72% conversion of starting material). The product mixture was composed of approximately 80% isomeric α-methoxystilbenes (62% *trans* and 38% *cis*) calculated on the basis of nmr.

Hydrolysis of *cis*- and *trans*-α-Methoxystilbene to Deoxybenzoin.—A sample (0.5–1 g) containing approximately equal amounts of the two isomers was added to 50 ml of aqueous 6 *N* sulfuric acid containing dioxane to increase the solubility of the organic material. The mixture was heated for 4 hr on a steam bath and then extracted with three portions of chloroform. The combined extracts were washed with three portions of water and with 10% sodium bicarbonate solution. The chloroform was removed by distillation using a steam bath leaving a residual oil. Vpc showed the absence of peaks due to the two isomeric α-methoxystilbenes and in their place a new peak. The material corresponding to the new peak, separated by vpc, was a solid melting at 54.8–55.8°. Its infrared spectrum was essentially identical with one of an authentic sample of desoxybenzoin.

Irradiation of the Dianion of Benzil Di-*p*-tosylhydrazone Using a Corex Filter.—The initial procedure was the same as that described above, employing 17.0 g (0.0311 mol) of benzil di-*p*-tosylhydrazone, 1.55 g (0.0674 g-atom) of sodium metal and 200 ml of methanol. The intensely yellow solution of the ditosylhydrazone dianion was irradiated through Corex for a period of 55 min, during which period 670 ml of gas was evolved (39% of the theoretical volume). The reaction mixture was diluted with two volumes of water and extracted with four 80-ml portions of cyclohexane. The extracted reaction mixture was treated with 34 ml of 2 *N* hydrochloric acid and the yellowish precipitate was removed by filtration and dried giving 8.43 g. The solid was stirred with 150 ml of absolute ethanol and the insoluble material collected by filtration (6.22 g). The ethanol was evaporated leaving 1.94 g of solid residue which was recrystallized from aqueous ethanol which afforded 0.22 g of purified material. The material was identified as 4,5-diphenyl-1-toluene-*p*-sulfonamido-1,2,3-triazole. The infrared spectrum (Nujol mull) showed absorptions at 1597 w, 1302 w, 1288 w, 1272 w, 1260 w, 1184 w, 1167 s, (SO_2–N, symmetric), 1155 m, 1140 w, 1087 w, 1040 w, 1019 w, 981 w, 925 w, 865 w, 831 w, 814 m, 779 w, 761 m, 730 w, and 693 cm^{-1} m. This spectrum was identical with one of a material melting at 226° dec obtained in larger amounts (3.18 g) when a 20.0-g quantity of crude ditosylhydrazone in 250 ml of sodium methoxide solution in methanol was irradiated in a 500-ml quartz flask, using a Vycor filter. The maximum yield of the triazole based on 1.94 g of crude material and 10.78 g of unrecovered starting material is 25%.

Anal. Calcd for $C_{21}H_{18}N_4O_2S$: C, 64.60; H, 4.65. Found: C, 64.43; H, 4.65.

The combined cyclohexane extracts (above) after drying were stripped of solvent by distillation employing a steam bath yielding 5.11 g of residual liquid. An nmr spectrum of this material indicated the presence of the isomeric methoxystilbenes, only in the ratio 62:38 *cis*:*trans*.

Irradiation of Diphenylacetylene in Methanol.—Diphenylacetylene (8.95 g, 0.0503 mol) was dissolved in 200 ml of methanolic sodium methoxide solution prepared using 1.5 g (0.0652 g-atom) of sodium metal. The solution was irradiated for 3.75 hr. Work-up in the usual manner employing petroleum ether (bp 30–60°) as extracting solvent afforded a green oil from which crystals readily deposited. An nmr spectrum of the mother liquor revealed the absence of both olefinic and methoxyl hydrogens as did a spectrum of the crystalline solid which showed only aromatic hydrogens. The identity of the solid was confirmed as starting material by a mixture melting point determination. The recovery of diphenylacetylene was 8.26 g (92%).

Registry No.—**7**, 19185-60-5; **8**, 19185-61-6; **9**, 19185-62-7; **10**, 19202-54-1; **11**, 19191-03-8; **12**, 19185-63-8.

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(19) The concentration of excess sodium methoxide (*ca.* 0.14 *M*) is sufficient to cause precipitation of the salt in this instance.

The Photodecomposition of the Dianion of Tetramethylcyclobutane-1,3-dione Di-*p*-tosylhydrazone

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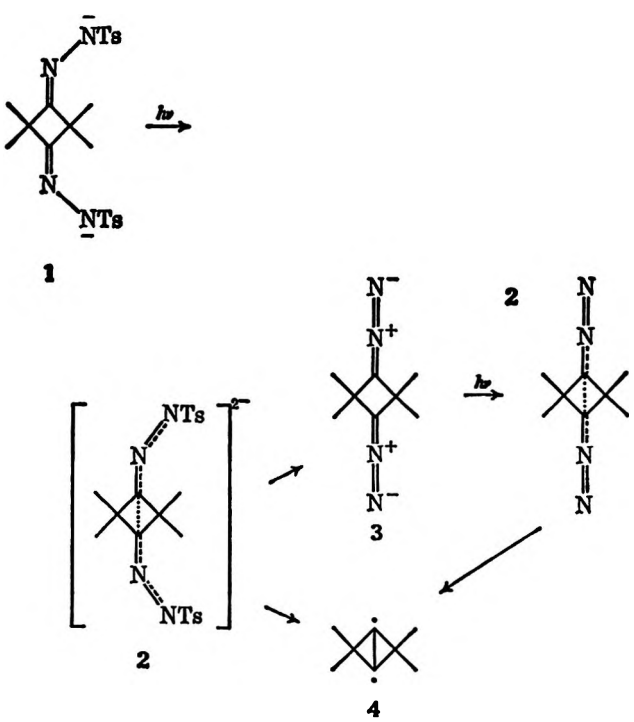
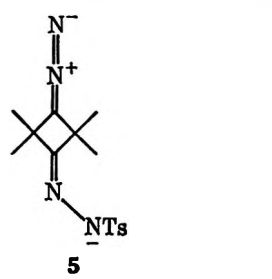
Irradiation of the disodium salt of the di-*p*-tosylhydrazone of tetramethylcyclobutane-1,3-dione in methanol generates 2,2,4-trimethylpent-3-enal dimethyl acetal and 2,2,4-trimethylpent-3-enal, accompanied by methyl 2,2,4-trimethylpent-3-enoate, which was subsequently found to be due to an impurity of the mono-*p*-tosylhydrazone of tetramethylcyclobutane-1,3-dione in the starting material. The mechanism of decomposition is discussed.

A study of the photodecomposition of the disodium salt of the ditosylhydrazone of tetramethylcyclobutane-1,3-dione (1) was undertaken concurrently with our investigation of the photodecomposition of the dianions of the ditosylhydrazones of biacetyl and benzil,[2] prompted by the thought that, if transannular conjugation is assumed, molecular orbital theory predicts that excitation of 1 to the first excited state should result in decreasing the bond order at the S–N and N–C linkages, while increasing the C-1–C-3 transannular bond order.[2] If these bond-order changes are chemically significant, the excited state (2) might undergo a bis elimination, shedding two molecules of nitrogen and two *p*-toluenesulfinate anions to yield an intermediate with bicyclobutane character (4). Alternatively, excited state 2 might lose just two *p*-toluenesulfinate anions to generate the didiazo compound 3. Here, again, a consideration of the nodes in the highest occupied molecular orbital (ψ_4) and lowest unoccupied molecular orbital (ψ_5), assuming transannular conjugation, suggests that excitation of 3 might also proceed by a bis elimination process to generate a bicyclobutane intermediate 4[2] (Scheme I).

SCHEME I



The geometry of the ditosylhydrazone salt 1 is advantageous for testing for a bis elimination process, when compared with the analogous salts of the ditosylhydrazones of biacetyl and benzyl, since the linear arrangement of functional groups in probable intermediates 3 and 5 would be expected to prevent cyclization in a fashion analogous to that of the salts of the ditosylhydrazones of 1,2-diketones (reaction 1).



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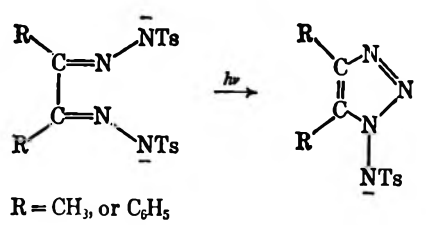
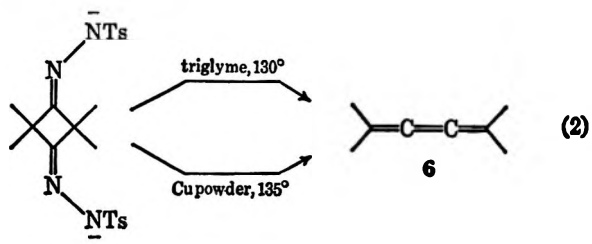


(1)

R = CH_3, or C_6H_5

Although, here, we are benefiting to some extent from hindsight, since this study and the one reported in the previous paper[2] were carried out concurrently.

While this investigation was in progress, two closely related studies of the thermal decomposition of 1 were reported by Bond and Bradway[3] and by Maier.[4] The major product found in both studies was tetramethylbutatriene (6) (eq 2). The nature of the product does not allow a choice to be made between a 1,3-dicarbenacyclobutane intermediate, favored by Maier,[4] and a process in which the bivalent carbon centers are



(2)

1

(1) To whom correspondence should be addressed: Department of Chemistry, Oregon State University, Corvallis, Ore.

(2) P. K. Freeman and R. C. Johnson, *J. Org. Chem.*, **34**, 1746 (1969).

(3) F. T. Bond and D. E. Bradway, *J. Amer. Chem. Soc.*, **87**, 4977 (1965).

(4) G. Maier, *Tetrahedron Lett.*, 3603 (1965).

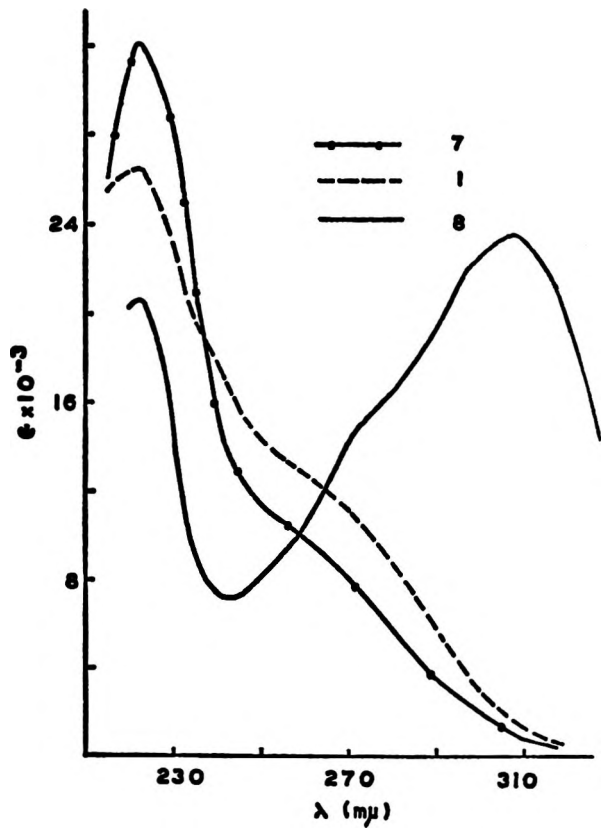


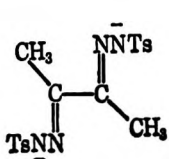
Figure 1.—Comparison of the uv absorption curves for the sodium salts of tetramethylcyclobutanedione ditosylhydrazone, tetramethylcyclobutanone tosylhydrazone (2ε), and biacetyl ditosylhydrazone.

generated in consecutive steps, favored by Bond and Bradway, although the latter alternative would seem to be the more reasonable one.

Results and Discussion

Appropriate models for examination of transannular conjugation in 1 appeared to be the anion of tetramethylcyclobutanone tosylhydrazone (7) and the dianion of biacetyl ditosylhydrazone (8). The spectra of 1, 7, and 8 are shown in Figure 1. The curve for 1

7



8

is seen to be a definite compromise between the curves for 7 and 8. In the region of <235 mμ, the dominant characteristic is the presence of maxima which are found at approximately the same wavelength for all three anions. The intensity of the absorption bands, however, varies and it is especially notable that ε for 1 falls between ε for 7 and 8. In the region of >235 mμ, the spectrum of 8 shows a high-intensity, long-wavelength maximum at 307 mμ (ε 23,600). The spectra of 1 and 7 show only shoulders in this region. However, the curve for 1 distinctly shows a hyperchromic effect relative to that for 7.

In a second comparison, we found it worthwhile to consider the ultraviolet (uv) spectra of the anion of

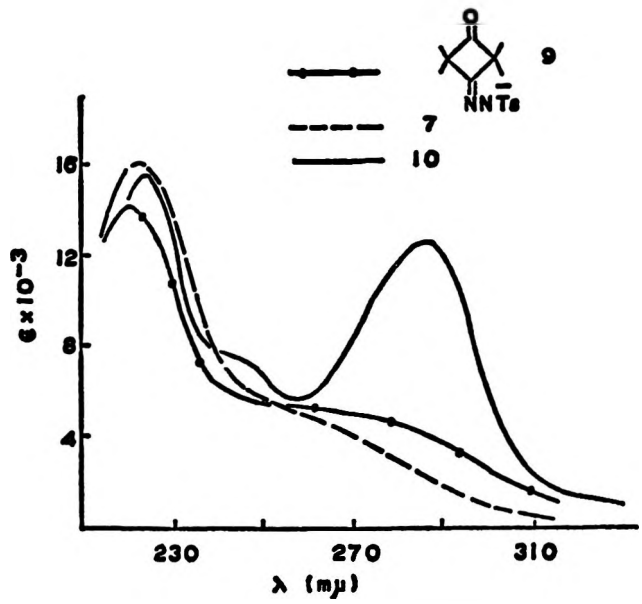
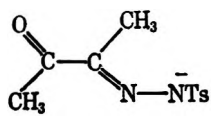


Figure 2.—Comparison of the uv absorption curves for the sodium salts of the monotosylhydrazones of biacetyl, tetramethylcyclobutanone, and tetramethylcyclobutanedione.

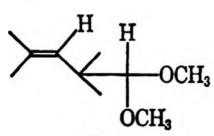
tetramethylcyclobutane-1,3-dione monotosylhydrazone (9) and the spectra of appropriate model compounds 7 and 10 (Figure 2). The curve for 10 shows a long-



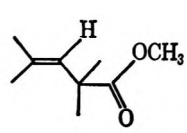
10

wavelength, high-intensity maximum [287 mμ (ε 12,200)] similar to the one observed in the curve for 8. The maximum is associated with increasing the length of conjugation of a tosylhydrazone chromophore by the addition of two p orbitals. The short-wavelength maxima for 7, 9, and 10 are closely grouped but, in the region of >235 mμ, the shoulder in the curve for 9 clearly appears shifted to longer wavelengths and enhanced over that for 7. Although the effect is not large for either 9 or 1, it does not appear unreasonable to ascribe the enhancement of the shoulders in the region of >235 mμ to transannular conjugation and to look for further evidence in the photochemistry of ditosylhydrazone dianions 1 and 9.

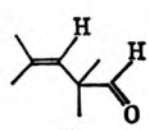
Irradiation of 1 in methanolic sodium methoxide solution resulted in a smooth decomposition producing a nearly quantitative evolution of nitrogen. A mixture of volatile products separated from the reaction medium was shown to consist of two major components (A and B, 49 and 17%, respectively) and a multiplicity of minor components by vapor phase chromatography (vpc). Components A and B and one of the minor components (C, 5%) were subsequently identified as 2,2,4-trimethylpent-3-enal dimethyl acetal (11), methyl 2,2,4-trimethylpent-3-enoate (12), and 2,2,4-trimethylpent-3-enal (13), respectively. The remaining



11



12

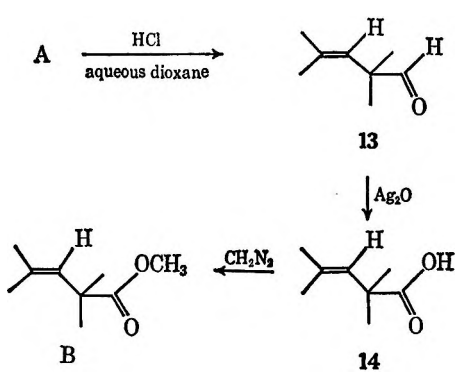


13

minor components were quite difficult to separate by vpc[5] and no individual structural assignments were made. Spectral analysis of various fractions of the mixture separated by vpc indicated the presence of unsaturated materials. One fraction apparently contained a compound or compounds having an allenic structure as indicated by the characteristic doublet at 2010 and 1995 cm^{-1}.[6]

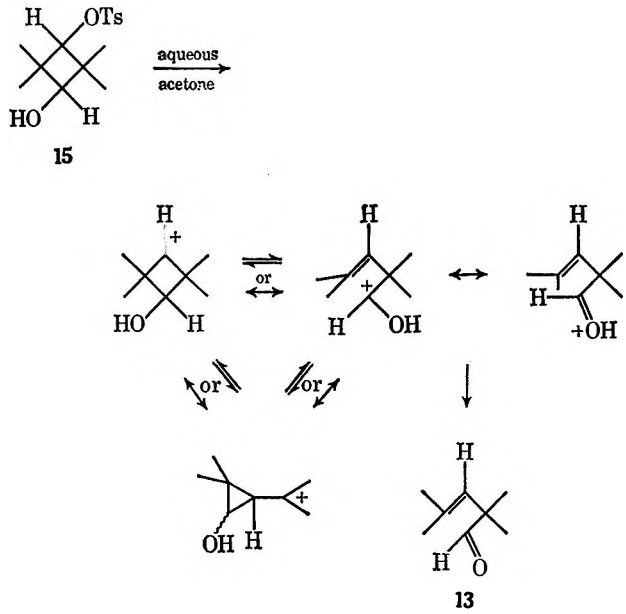
Component C was identified as the aldehyde **13** by comparison of its infrared (ir) spectrum with that of an authentic sample.[7] The structural assignments for A and B follow by virtue of the similarities of their ir and nmr spectra with the corresponding spectra of C. Both A and B show ir absorptions due to a trisubstituted carbon–carbon double bond (A, 1663 and 825 cm^{-1}; B, 1666 and 820 cm^{-1}) and nmr signals attributable to a single vinyl hydrogen and two allylic methyl groups [A, τ 4.88 (multiplet) and 8.32 (broadened singlet) in the ratio 1:6; B, τ 4.88 (multiplet), 8.32, and 8.48 (broadened singlets) in the ratio 1:3:3]. The ir spectrum of B showed an ester carbonyl absorption at 1735 cm^{-1} and the nmr spectrum of A showed a one-proton singlet whose chemical shift (τ 6.18) is appropriate for an acetal hydrogen.[8] Ultimate confirmation of the structures of A and B was achieved through the chemical transformations, outlined in Scheme II, which establish relationships between these compounds and the known aldehyde **13**. Component A was shown to be acetal **11** by its ready hydrolysis to **13**. Oxidation of **13** with silver oxide afforded acid **14** which yielded B on treatment with diazomethane.

SCHEME II



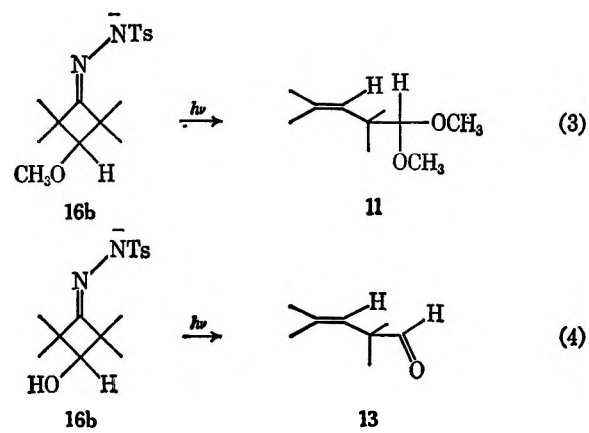
The structure of products **11–13** suggests that the photodecomposition of **1** in methanol occurs by way of a carbonium-ion mechanism. Thus Hasek, *et al.*,[9] discovered that treatment of *trans*-tetramethylcyclobutane-1,3-diol with hot dilute sulfuric acid yields **13**. In related work, Wilcox and Nealy[10] solvolyzed the monotosylate of this diol (**15**) obtaining again **13**. The formation of **13** from **15** was explained in terms of a cyclobutyl–allylcarbinyl rearrangement (Scheme III).

SCHEME III



Since the thermal decomposition of the anions of monotosylhydrazones has been shown to occur largely *via* a cationic process in solvents of high "protonicity,"[11] the mechanism proposed in Scheme IV views the formation of **13** and closely related **11** from **1** by the sum of two processes (a and b), each similar to that of Scheme III. The operation of this mechanism is supported by the isolation of 3-methoxytetramethylcyclobutanone tosylhydrazone from a reaction in which **1** was incompletely decomposed. In addition, irradiation of the anion **16b**, under the conditions used for **1**, produced **11** (eq 3). Similarly, irradiation of **16a** gave **13** (eq 4). Although the irradiation of **1** was carried out under anhydrous conditions, the source of hydroxide ion giving rise to **16a** may be traced to a small amount of hydroxide formed on the surface of freshly cut sodium on brief exposure to air.

A clue to the source of **12** was disclosed on examination of the ir spectrum of tetramethylcyclobutane-1,3-dione monotosylhydrazone, which exhibited a carbonyl absorption whose intensity is only moderate relative to the strong carbonyl absorption observed in



(5) One fraction representing 12% of the total chromatogram area due to products was separated into two components: an apparently pure compound whose identity still remains unknown and toluene.

(6) The presence of a compound having an allenic structure suggests that a small fraction of **1** decomposes by way of a carbenoid process.[3,4]

(7) The ir spectrum of 2,2,4-trimethylpent-3-enal was kindly provided by Dr. Edward Elam of the Tennessee Eastman Co., Kingsport, Tenn.

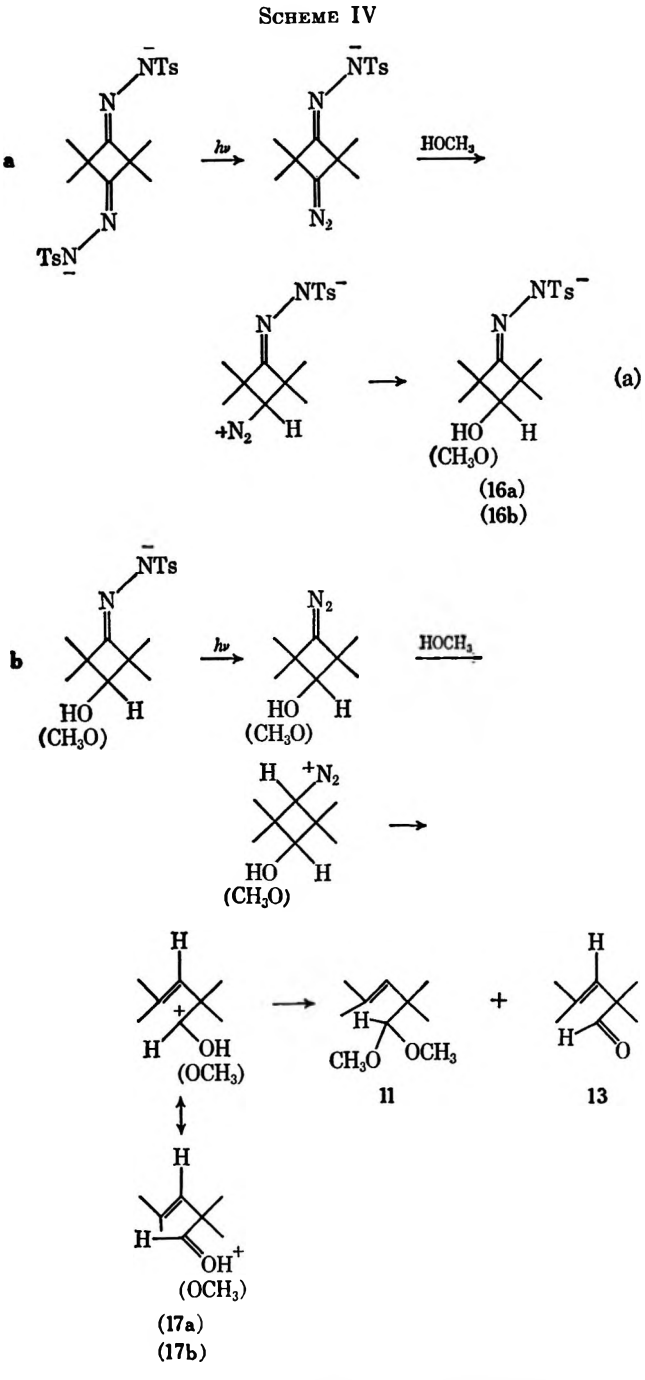
(8) H. U. Hostettler, *Helv. Chim. Acta*, **49**, 2417 (1966).

(9) R. H. Hasek, R. D. Clark, and J. H. Chaudet, *J. Org. Chem.*, **26**, 3130 (1961).

(10) C. F. Wilcox, Jr., and D. L. Nealy, *ibid.*, **28**, 3450 (1963).

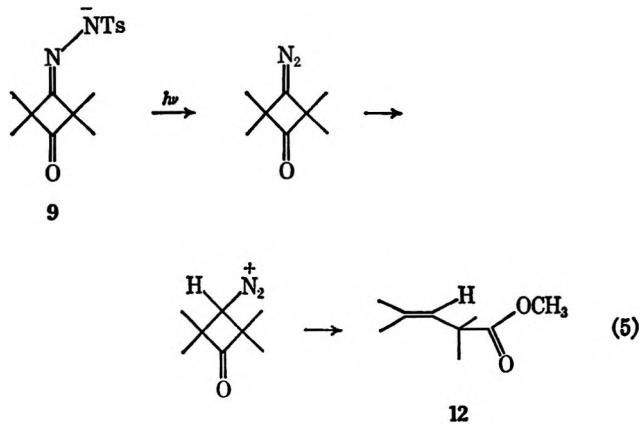
(11) (a) J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Amer. Chem. Soc.*, **90**, 531 (1968). (b) J. A. Smith, H. Shechter, J. Bayless and L. Friedman, *ibid.*, **87**, 659 (1965). (c) L. Friedman and H. Shechter, *ibid.*, **81**, 5512 (1959). (d) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

SCHEME IV

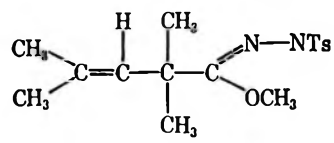


the spectra of most ketones. Consequently, the quantity of monotosylhydrazone contaminating the ditosylhydrazone as determined from the ir spectrum of the latter was always underestimated. Indeed, examination of the crude ditosylhydrazone by nmr revealed that the amount of contaminant was about 15 mol % which made monotosylhydrazone a ready suspect as the parent of **12**. This was reinforced by the fact that irradiation of a sample of **1**, in which the amount of contaminant was reduced to 5% by an intensive purification procedure, gave a product mixture containing a higher ratio of **11** to **12** (62:8 instead of 49:17). Finally, irradiation of anion **9** under the same conditions used for **1** gave **12** (eq 5).

The substitution pattern found for the carbonium-ion intermediates generated in the photodecomposition of **1** whether the ions are delocalized in a nonclassical sense or not, would be expected to be dictated by the substituents on the carbon skeletons of the particular



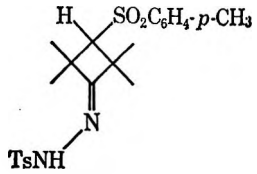
intermediates involved.[12] Thus in process b (Scheme IV), the production of end products **11** and **13** is most likely due to the stabilization of the allylcarbinyl form, relative to the cyclopropylcarbinyl and cyclobutyl forms, by electron delocalization by α-methoxyl[13] and hydroxyl.[10] In process a, the cyclobutyl form should be more stable than the cyclopropylcarbinyl form owing to the energy increase imposed by the trigonal carbon atom in the cyclopropane ring. The relative stability of the cyclobutyl over the allylcarbinyl form, however, is not clear and one might consider an alternate pathway between **1** and **11** in which the allylcarbinyl structure **18** is formed in the first step by a process analogous to



18

that for the transformation of **9** to **12**. While it is conceivable that this mechanism is competitive with that of process a (Scheme IV), we have no evidence which supports it, while we do have evidence supporting reaction *via* **16a** and **16b**.

The extent to which mechanisms competitive with process a (Scheme IV) are possible, may be judged by the fact that, when the irradiation of **1** was carried out employing a Vycor filter, the acid form of **16b** accounted for 43% of the methanol-soluble intermediates formed in the reaction.[14] A second tosylhydrazone (**19**) was



19

isolated in addition to the conjugate acid of **16b**; however, the amount of this material was minor, constituting only 4% of the methanol-soluble substances.[15]

(12) *Cf.* R. Breslow in "Molecular Rearrangements," P. de Mayo, ed, John Wiley & Sons, Inc., New York, N. Y., p 266 and references therein.

(13) R. H. Martin and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 1353 (1966); B. G. Ramsey and R. W. Taft, *ibid.*, **88**, 3058 (1966).

(14) Tetramethylcyclobutane-1,3-dione ditosylhydrazone is insoluble in methanol in contrast with the solubility of most monotosylhydrazones, so that extraction of recovered solid material with methanol was a convenient means of isolating substances such as the conjugate acid of **16b**.

(15) Sulfones have been isolated in other tosylhydrazone photolyses. See D. M. Lemal and A. J. Fry, *J. Org. Chem.*, **29**, 1673 (1964).

The remaining solid components were present as a complex mixture which resisted further attempts at separation. A second and clearer view of the composition of methanol-soluble materials was obtained from a similar reaction in which 1 was irradiated through Corex. The conjugate acid of **16b** and tosylhydrazone **19** were obtained in approximately equal amounts, accounting for 70% of the extracted material. Only minor amounts of other substances were present.

Thus, in summary, we find that in spite of the spectral data supporting possible transannular conjugation and the favorable geometry of this system, which should allow the observation of a bis elimination process, there is no evidence which suggests or requires a bicyclobutane-type intermediate such as **4**. Instead the experimental results are rationalized most simply in terms of a stepwise carbonium-ion process.

Experimental Section

In addition to the general comments made earlier,[2] the following apply.

Vapor phase chromatographic analyses and analytical separations were made using an Aerograph A-90 P chromatograph equipped with a thermal conductivity detector or an F & M Model 609 flame ionization chromatograph. A 5 ft by 0.25 in. column of aluminum (column C) containing 15% Carbowax 20M on 60–80 Gas-Chrom P was employed along with columns A and B specified earlier.[2] Product ratios and percentage yields calculated from chromatographic data were made on the basis of relative peak area and are uncorrected for variations of thermoconductivity with molecular weight.

Ultraviolet Spectral Analyses.—Ultraviolet spectra were obtained using a Cary Model 14 recording spectrometer. The samples used were, except for tetramethylcyclobutane-1,3-dione ditosylhydrazone, analytically pure. Tetramethylcyclobutanedione ditosylhydrazone was purified by precipitation from a solution of its dianion in methanol by the addition of methanolic hydrochloric acid.[16] The ditosylhydrazone contained the monotosylhydrazone as a contaminant after repeated precipitation and recrystallization from both aqueous and methanolic dimethylformamide. The spectral data reported for **1** are corrected for an estimated 5% monotosylhydrazone (ir).

The uv spectra, run either in 10^{-3} *N* sodium hydroxide solution or Spectrograde methanol, were reproducible with minor deviations in two separate trials.

Preparation of the Tosylhydrazones.—Tosylhydrazine was prepared according to "Organic Syntheses."[17] Unless obtained in relatively pure state (mp >100°), the product was recrystallized from 50% aqueous methanol, which gave purified material melting generally in the range 105–108°. The recrystallized tosylhydrazine was then subsequently used in the preparation of the tosylhydrazones. An analytical grade sample was obtained after three recrystallizations from 50% aqueous methanol (mp 107.8–109.8°).

Tetramethylcyclobutane-1,3-dione Ditosylhydrazone.—A modification of the method of Bamford and Stevens was used.[18] Tetramethylcyclobutane-1,3-dione (15.1 g, 0.108 mol) was placed with 125 ml of absolute ethanol in a 1-l. round-bottom flask. The dione was brought into solution by heating on a steam bath and a solution of 40.0 g (0.215 mol) of tosylhydrazine in 250 ml of absolute ethanol was added. The flask was fitted with a water condenser and the mixture was heated to gentle reflux, then allowed to cool slightly, whereupon 7 ml of concentrated hydrochloric acid was added in portions. Reflux was resumed and after 5 to 10 min, the solution became cloudy. At the end of 2.5 hr, the product was collected by filtration of the hot reaction mixture, washed with hot absolute ethanol, and air dried. The yield of crude product [mp 270° dec (lit.[4] mp 268°)] was 34.7 g (68%). The crude product contained monotosylhydrazone as an impurity (ir 1798 cm^{-1}). The nmr spectrum of this material exhibited aromatic methyl absorptions due to mono- and ditosylhydrazone in the area ratio 3:44 and ring methyl signals in the ratio 8:50 corresponding to an approximate composition of 13% mono- and 87% ditosylhydrazone. The quantity of monotosylhydrazone could be reduced but not removed by repeated recrystallization from aqueous or methanolic dimethylformamide or by repeated precipitation from a stirred solution of the dianion in methanol (0.3 *M*) at 0° by the slow dropwise addition of methanolic hydrochloric acid (2 ml of concentrated acid to 20 ml of methanol). The ir spectrum (Nujol mull) of the purified material (containing *ca.* 5% monotosylhydrazone) exhibited ν_{max} 3270 (m, NH), 1798 (w, C=O, monotosylhydrazone), 1595 (w, C=C, aromatic), 1397 (m), 1338 (s, SO_2N, asymmetric), 1188 (m), 1157 (s, SO_2N, symmetric), 1120 (w), 1097 (w), 1080 (w), 1020 (m), 927 (w), 827 (m), 819 (m), and 780 cm^{-1} (w). The nmr spectrum (D_2O containing 1 drop of concentrated aqueous sodium hydroxide solution)[19] displayed signals at τ 2.32, 2.45, 2.71, and 2.85 (A_2B_2 quartet, aromatic, 8.0 H), 7.76 (singlet, $ArCH_3$, 6.65 H), and 8.78 (singlet, ring CH_3, 12.3 H).

Anal. Calcd for $C_{22}H_{28}N_4O_4S$: C, 55.43; H, 5.92. Found: C, 55.63; H, 5.94. The calculated percentages for a mixture of 13% mono- and 87% ditosylhydrazone are C, 55.70; H, 5.85.

In variations of procedure in which a solution (100 ml) of the dione (0.0280 mol) was added dropwise to a stirred refluxing solution (250 ml) of tosylhydrazine (0.0591 mol) containing concentrated hydrochloric acid (1.7 ml) or in which a solution (100 ml) of the dione (0.00860 mol), tosylhydrazine (0.0258 mol), and concentrated hydrochloric acid (0.7 ml) was allowed to stand overnight always resulted in product contaminated with >10% monotosylhydrazone.

Tetramethylcyclobutane-1,3-dione Monotosylhydrazone.—A solution of the dione (17.4 g, 0.124 mol) and tosylhydrazine (23.06 g, 0.124 mol) in ethanol (450 ml) was heated at near reflux on a steam bath for 30 min and then poured over ice. After the mixture was allowed to come to room temperature, the product was separated by filtration and recrystallized from absolute ethanol. The yield of tetramethylcyclobutane-1,3-dione monotosylhydrazone (mp 178–180.5°) was 24.2 g (63.5%). The ir spectrum (Nujol mull) displayed ν_{max} 3270 (m-w, NH), 1798 (m-w, C=O), 1675 (w, C=N), 1596 (w, C=C, aromatic), 1399 (w), 1343 (s, SO_2N, asymmetric), 1273 (w), 1188 (w), 1162 (s, SO_2N, symmetric), 1070 (w), 1036 (w), 987 (w), 897 (w), and 820 cm^{-1} (m). Signals were observed in the nmr spectrum ($CDCl_3$–CCl_4) at τ 2.06, 2.18, 2.59, and 2.71 (A_2B_2 quartet, aromatic), 7.53 (singlet, $ArCH_3$), and 8.67 and 8.75 (singlets, ring CH_3).

Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.41; H, 6.53. Found: C, 58.27; H, 6.70.

Tetramethylcyclobutanone Tosylhydrazone.—Tetramethylcyclobutane-1,3-dione was reduced to tetramethylcyclobutanone in 5% over-all yield by the Wolff–Kishner method described by Herzog and Buchman.[20] Tetramethylcyclobutanone was converted into the tosylhydrazone in 63% yield by the procedure outlined by Meinwald.[21] Infrared and nmr spectral data for the tosylhydrazone were in accord with those reported.[21]

Biacetyl Monotosylhydrazone.—The procedure of Meinwald, *et al.*,[21] was employed omitting the use of hydrochloric acid. After several hours, the product was induced to crystallize by seeding. After 12 hr, the solid was removed by filtration, washed with chilled methanol, and air dried giving material melting at 134.0–134.5°. A second crop (mp 133–134°) was obtained by diluting the mother liquor with water. The over-all yield was 85%. One recrystallization of the crude product from aqueous ethanol afforded an analytical sample melting at 135° dec. The ir spectrum (Nujol mull) of this material showed absorptions at 3240 (m, NH), 1693 (s, C=O, conjugated), 1587 (m, C=C, aromatic), 1488 (w), 1342 (s, SO_2N, asymmetric), 1300 (m), 1290 (m), 1186 (s), 1172 (s, SO_2N, symmetric), 1123 (w), 1102 (m), 1086 (s), 908 (m), 812 (s), and 741 cm^{-1} (s). The nmr spectrum ($CDCl_3$) showed signals at τ 2.08, 2.21, 2.60, and 2.75 (A_2B_2 quartet, aromatic, 4.0 H), 7.43 (singlet, $ArCH_3$, 3.0 H), 7.55 (singlet, CH_3C=O, 2.7 H), and 7.98 (singlet, CH_3C=N, 3.2 H).

(16) This method was kindly suggested to us by Dr. F. T. Bond.

(17) L. Friedman, R. Little and W. Reichle, *Org. Syn.*, **40**, 93 (1960).

(18) W. R. Bamford and R. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(19) Methanol was used as an internal reference assigning the position of the $-OCH_3$ signal a value of τ 6.66 relative to tetramethylsilane.

(20) H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

(21) J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu, *ibid.*, **30**, 1038 (1965).

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55. Found: C, 51.95; H, 5.52.

Irradiations.—Irradiations were conducted in the same manner described previously.[2] Volatile products were isolated by diluting the reaction mixture with an equal volume of water followed by extraction with four–five portions of pentane. The combined extracts were washed with three portions of water and the pentane was removed by distillation. A Vycor filter was employed unless otherwise stated. Gas evolution was measured using either a wet test meter or an inverted cylinder.

Irradiation of the Dianion of Tetramethylcyclobutane-1,3-dione Ditosylhydrazone.—Tetramethylcyclobutane-1,3-dione ditosylhydrazone (23.3 g containing *ca.* 13% monotosylhydrazone and thus 0.0445 mol of ditosylhydrazone) was dissolved in methanolic sodium methoxide solution prepared by dissolving 7.92 g (0.146 mol) of commercial sodium methoxide in 192 ml of methanol. The resulting slightly yellow solution was irradiated without filter[22] until gas evolution retarded (4 hr, 90% of theoretical volume). The lemon-yellow, pleasant-smelling reaction mixture was processed giving 6.61 g of residual liquid after removal of pentane. Vapor phase chromatography (column A at 60–120°, column C at 50–60°) indicated that the residual liquid was a complex mixture consisting of at least 13 components. Three components (A, B, and C in the ratio 49:17:5) were separable from the remainder of the products. Component C was identified as 2,2,4-trimethylpent-3-enal by a comparison of its ir spectrum with one of an authentic sample.[7]

Component A (2,2,4-trimethylpent-3-enal dimethyl acetal) exhibited the following absorptions in the ir (neat): 2990–2915 (unresolved, s, CH), 2832 (s, OCH_3), 2700 (w), 2635 (w), 1663 (w, C=C, trisubstituted), 1445 and shoulder 1465 (s, CH), 1389 and 1360 (s, doublet, *gem*-dimethyl), 1375 (s, CH_3), 1343 (s), 1190, 1140, 1113, 1080, and 1023 (s, acetal), 1008 (s), 983 (s), 966 (s), 927 (m), 841 (m), and 825 cm^{-1} (m, C=CH, trisubstituted). The nmr showed absorption bands at τ 4.88 (multiplet, nonconjugated olefinic, 1.0 H), 6.18 (singlet, acetal, 1.0 H), 6.62 (singlet, OCH_3, 6.0 H), 8.32 (broadened singlet, CH_3C=C, 5.7 H), and 8.97 (singlet, saturated CH_3, 6.1 H).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.91; H, 11.50.

The structures of components A and C were related by the following experiment. A sample (0.50 g) of the crude product mixture obtained by processing the photolysate was placed in a 5-ml flask along with 0.60 g of 4% aqueous hydrochloric acid and 1.20 g of purified dioxane. The reaction mixture was heated at reflux for 45 min,[23] cooled, and extracted twice with pentane. A sample of the first extract was analyzed by vpc (column C at 61°). The essential feature was that no peak corresponding to component A was present, but the peak due to component C had increased by an equal proportion. The combined pentane extracts were washed with three portions of water and the pentane was removed by distillation leaving a residual liquid. Material corresponding to the new peak having retention time equal to that of component C was separated by vpc and identified as 2,2,4-trimethylpent-3-enal by a comparison of ir spectra.

Component B (methyl 2,2,4-trimethylpent-3-enoate) exhibited the following peaks in the ir (neat): 2990–2930 (s, CH), 2710 (w), 1735 (s, C=O, ester), 1666 (w, C=C, trisubstituted), 1468 (s), 1440 (s), 1389 (s) and 1362 (m, doublet *gem*-dimethyl), 1377 (s), 1268 (s, COC, asymmetric), 1228 (s), 1206 (s), 1195 (s), 1145 (s, COC, symmetric), 1077 (m), 1020 (m), 996 (m), 947 (w), 901 (m), 820 (s, C=CH, trisubstituted), and 773 cm^{-1} (m). The nmr spectrum gave absorptions at τ 4.88 (multiplet, nonconjugated olefinic, 0.8 H), 6.38 (singlet, OCH_3, 2.5 H), 8.32 and 8.48 (broadened singlets of equal area, CH_3C=C, 6.0 H), and 8.75 (singlet, saturated CH_3, 5.9 H).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.32; H, 10.47.

The structures of components B and C were related by the following procedure. A sample of 2,2,4-trimethylpent-3-enal dimethyl acetal (2.50 g) isolated in 98% purity by spinning-band distillation of the processed photolysate was hydrolyzed to 2,2,4-trimethylpent-3-enal by the above-described procedure. Analysis of the product by vpc indicated complete conversion into the aldehyde. The initial steps in the procedure described by Clark, *et al.*,[24] were followed in converting the aldehyde into 2,2,4-trimethylpent-3-enoic acid. After stirring for 3 hr, the reaction mixture was extracted with pentane. The extract showed no traces of the aldehyde by vpc. The reaction mixture was acidified with dilute sulfuric acid and extracted with several portions of ether. The combined extracts were dried over anhydrous magnesium sulfate and the ether was removed by distillation leaving a yellow oil. The ir spectrum of the oil indicated the presence of an acid (broad absorption 3700–2400, carbonyl at 1707, and an OH out-of-plane bending absorption at 920 cm^{-1}). The oil was cooled in an ice bath and treated with an excess of ethereal diazomethane prepared according to the method of DeBoer and Backer.[25] The mixture was allowed to stand at ice-bath temperature until nitrogen evolution had ceased. Excess diazomethane was destroyed by the dropwise addition of acetic acid. Ether was removed by distillation leaving a yellow oil. Analysis of the oil by vpc indicated the presence of a component with retention time equal to that of component B under the same column conditions. An ir spectrum of a sample of this component separated by vpc was superimposable on a spectrum of component B.

Incomplete Photodecomposition of the Dianion of Tetramethylcyclobutane-1,3-dione Ditosylhydrazone. Isolation of 3-Methoxytetramethylcyclobutanone Tosylhydrazone.—The dianion was prepared from the ditosylhydrazone (23.3 g, 0.0445 mol) according to the standard method. Irradiation was interrupted after 53 min. After volatile reaction products had been removed in the usual manner, the reaction mixture was acidified with 80 ml of 2 *N* hydrochloric acid. The precipitate was collected by filtration and dried. The dry solid (16.19 g) was extracted with methanol in a Soxhlet apparatus for a period of 24 hr. Removal of methanol using a rotary evaporator left a solid residue (3.35 g). The residue was dissolved in chloroform and placed on a column prepared using 80 g of Camag alumina (pH 4.5) previously moistened with 3.2 ml of water. The column was eluted with 420 ml of 10% ethyl acetate–chloroform and the eluate was collected in 40-ml fractions. Solid residues remained on evaporation of solvent from all of the fractions. The nmr spectra of the residues from fraction 3 (1.65 g) and fraction 4 (0.72 g) were similar in gross features to a spectrum of 3-methoxytetramethylcyclobutanone tosylhydrazone prepared by the procedures described below. The nmr spectra of residues from the other fractions were dissimilar. Recrystallization of the residue from reaction 3 gave a purified material whose ir and nmr spectra were essentially identical with corresponding spectra of 3-methoxytetramethylcyclobutanone tosylhydrazone. The yield of this tosylhydrazone based on the nmr spectra of residues 3 and 4 was 1.43 g (43% of the methanol-soluble solids isolated by extraction).

Irradiation of the Dianion of Tetramethylcyclobutanedione Ditosylhydrazone Using a Corex Filter.—The standard method was used employing 23.0 g (0.0439 mol) of the ditosylhydrazone, 2.22 g (0.0965 g-atom) of sodium metal, and 200 ml of methanol. Irradiation for 1.58 hr through Corex resulted in the evolution of 48% of the theoretical volume of gas. After processing in the usual manner, the reaction mixture was acidified with 51 ml of 2 *N* hydrochloric acid. The precipitate was collected by filtration and dried. The dry solid (13.5 g) was stirred with 300 ml of methanol for 30 min and the undissolved solid was separated by filtration and dried giving 9.35 g. The filtrate was concentrated by removal of solvent using a rotary evaporator giving a solution from which white crystals were deposited on cooling in an ice bath. The crystals were removed by filtration and dried affording 1.56 g. The solid behaved peculiarly on heating, appearing first to melt (<100°) and then to solidify once more (100–160°) melting finally at >170°. The solid was tentatively identified as 3-toluenesulfonyltetramethylcyclobutanone tosylhydrazone. The ir spectrum (Nujol mull) showed absorptions at 3700 (w), 3530 (w), 3250 (shoulder, w, NH), 1675 (w, C=N), 1607 (w), 1598 (C=C, aromatic), 1322 (s, SO_2N, asymmetric), 1282 (s, SO_2, asymmetric), 1186 (m), 1162 (s, SO_2N, symmetric), 1142 (s, SO_2, symmetric), 1091 (m), 1019 (m), 888 (w), 848 (w),

(22) The results of this experiment were the same regardless of whether uv radiation was unfiltered or filtered through Vycor, also whether sodium methoxide solutions were prepared using commercial sodium methoxide or freshly cut sodium metal.

(23) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," Fourth Ed., John Wiley & Sons, Inc., New York, N. Y., and London, 1956, p 195.

(24) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(25) T. J. DeBoer and H. J. Backer, *Rec. Trav. Chim.*, **73**, 229 (1954).

817 (s), 738 (m), and 708 cm^{-1} (m). The nmr spectrum (CD_3COCD_3) showed signals at τ 2.06, 2.20, 2.44, and 2.58 and 2.15, 2.31, 2.54, and 2.68 (two overlapping A_2B_2 quartets, aromatic, 8 H), 6.38 (singlet, ring H, 1 H), 7.54 and 7.56 (two overlapping broadened singlets, $ArCH_3$, 6 H), 8.36, 8.55, 8.71, and 8.92 (singlets of equal area, ring CH_3, 12 H). The uv spectrum (10^{-3} *N* aqueous sodium hydroxide solution) showed a maximum at 228 mμ (ϵ 29,000) and a shoulder extending from 245 mμ (ϵ 8600) to greater than 320 mμ. The intensity of the maximum is in accord with the presence of a *p*-tolylsulfonyl group (ϵ *ca.* 12,000) and a tosylhydrazone group (ϵ *ca.* 16,000).

Anal. Calcd for $C_{22}H_{28}N_2O_4S_2$: C, 58.90; H, 6.29. Found: C, 58.80; H, 6.49.

The filtrate obtained upon separation of the above-described sulfone was evaporated to dryness leaving 2.21 g of residue whose nmr spectrum showed the features of the spectrum of 3-methoxytetramethylcyclobutanone tosylhydrazone. The amount of this tosylhydrazone contained in the residue was estimated to be 1.5 g (*ca.* 36% of the methanol-soluble materials separated by extraction).

Irradiation of Purified Tetramethylcyclobutanedione Ditosylhydrazone Dianion.—The ditosylhydrazone containing 5% monotosylhydrazone (30.0 g, 0.0606 mol) was dissolved in 470 ml of sodium methoxide solution prepared with 4.50 g (0.195 g-atom) of sodium metal. The solution was placed in a quartz vessel and irradiated for 22 hr in a Rayonet photochemical reactor employing medium-pressure mercury arc lamps. In the course of this time, 90% of the theoretical volume of gas was liberated. The reaction mixture was processed in the usual manner giving 17.9 g of liquid residue. Analysis by vpc revealed that the composition of the residue was essentially the same as before except that the ratio of areas of peaks due to components A and B (A:B) was 62:8. Spinning-band distillation of the lower boiling components left 2,2,4-trimethylpent-3-enal dimethyl acetal as a residue (6.64 g, 72% based on a 90% conversion of starting material). Results similar to these were obtained when the irradiation was carried out in the immersion reactor.

Irradiation of the Anion of 3-Methoxytetramethylcyclobutanone Tosylhydrazone.—3-Methoxytetramethylcyclobutanone tosylhydrazone (10.0 g, 0.0308 mol) was dissolved in 200 ml of methanolic sodium methoxide solution and the irradiation, carried out according to the standard method for 1.6 hr, produced 93% of the theoretical volume of gas. Processing of the reaction mixture gave 11.81 g of residual liquid. Analysis of the liquid by vpc (column B) indicated the presence of a major component (54% of the chromatogram area due to products) and other minor materials. An ir spectrum of a sample of the major component separated by vpc was identical with a spectrum of 2,2,4-trimethylpent-3-enal dimethyl acetal obtained by photodecomposition of **1**.

Irradiation of the Anion of 3-Hydroxytetramethylcyclobutanone Tosylhydrazone.—3-Hydroxytetramethylcyclobutanone tosylhydrazone (13.05 g, 0.0420 mol) was dissolved in 180 ml of methanolic sodium methoxide solution prepared using 1.50 g (0.0625 g-atom) of sodium metal. Irradiation according to the standard method for 2.6 hr was accompanied by the evolution of 85% of the theoretical volume of gas. Processing of the reaction mixture gave 5.67 g of residual liquid. Analysis of the liquid by vpc (column C) showed the presence of a major component (60%) and minor materials. Additional pentane (1.05 g) was removed by distillation at atmospheric pressure. Under reduced pressure (10 mm) lower boiling components (0.88 g) slowly distilled followed by the major component (0.20 g), leaving a residue (1.99 g), composed predominantly of the major component. An ir spectrum of a sample of the major component purified by vpc was identical with a spectrum of 2,2,4-trimethylpent-3-enal. The yield of the aldehyde was estimated to be 2.0 g by vpc (44% based on an 85% conversion of starting material).

Irradiation of the Anion of Tetramethylcyclobutane-1,3-dione Monotosylhydrazone.—Tetramethylcyclobutane-1,3-dione monotosylhydrazone (14.9 g, 0.0485 mol) was dissolved in 185 ml of methanolic sodium methoxide solution prepared using 1.65 g (0.0717 g-atom) of sodium metal. Irradiation according to the standard method resulted in a quantitative evolution of gas in 1.3 hr. Processing of the nearly colorless reaction mixture gave 8.4 g of yellowish liquid residue. Analysis of the liquid by vpc (column C at 73°) indicated the presence of a major component (82%) with the same retention time as that of methyl 2,2,4-trimethylpent-3-enoate under identical column conditions. Distillation of the residue under reduced pressure (23–18 mm) gave 4.63 g (bp 57–59°) of material (>95% major component by vpc) leaving a residue (0.56 g) with the same degree of purity. A sample of the major component purified by vpc furnished an ir spectrum superimposable on one of methyl 2,2,4-trimethylpent-3-enoate. The yield of ester based on vpc analyses of the collected fractions and the residue was 5.19 g (65%).

3-Hydroxytetramethylcyclobutanone Tosylhydrazone.—In a 500-ml, three-necked flask equipped with a water condenser, mechanical stirrer, and dropping funnel was placed 5.78 g (0.152 mol) of lithium aluminum hydride and 250 ml of dry tetrahydrofuran. A solution of 22.3 g (0.075 mol) of tetramethylcyclobutane-1,3-dione monotosylhydrazone in 175 ml of dry tetrahydrofuran was added dropwise with stirring. When addition was complete, the reaction was heated at reflux for 5 hr and allowed to cool, and excess hydride was destroyed by the dropwise addition of water. Sulfuric acid (10%) was added to dissolve the solids and the organic phase was separated. The aqueous phase was extracted with four portions of ether and the extracts were combined with the organic phase. After the mixture was dried, over anhydrous magnesium sulfate, ether was removed using a rotary evaporator yielding 18.80 g (84%) of crude product melting at 118–126°. Reduction using sodium borohydride gave material of higher purity only in a lower yield. A sample of this material recrystallized satisfactorily from aqueous ethanol yielding tosylhydrazone with mp 125–127° (lit.[26] mp 132–133°). The ir spectrum (Nujol mull) showed absorptions at 3432 (m, OH), 3285 (m, NH), 1670 (w, C=N), 1599 (w, C=C, aromatic), 1495 (m), 1399 (m), 1342 (s, SO_2N, asymmetric), 1295 (m), 1174 (s, SO_2N, symmetric), 1115 (m), 1095 (m), 1073 (m), 1000 (s–m), 933 (w), 875 (w), 838 (w), 821 (m), 813 (m), and 748 cm^{-1} (m). Signals were observed in the nmr spectrum (D_2O containing 1 drop of 40% aqueous sodium hydroxide solution) at τ 2.18, 2.33, 2.52, and 2.66 (A_2B_2 quartet, aromatic 4.0 H), 6.28 (singlet, ring H, 0.7 H), 7.58 (broad singlet, $ArCH_3$, 3.0 H), and 8.67, 8.75, 8.85, and 8.92 (singlets of equal area, ring CH_3, 9.2 H). The nmr sample seemed unstable evolving gas slowly which perhaps accounts for the lower than theoretical ratio of ring hydrogens to aromatic hydrogens.

Tetramethylcyclobutane-1,3-diol.—This procedure is based on one reported by Roberts and Sauer.[27] Lithium aluminum hydride (16.9 g, 0.423 mol) and anhydrous ether (750 ml) were placed in a 2-l. three-necked flask equipped with a water condenser, dropping funnel, and mechanical stirrer. A solution of tetramethylcyclobutane-1,3-dione (101.5 g, 0.725 mol) in a mixture of anhydrous tetrahydrofuran (450 ml) and anhydrous ether (300 ml) was added dropwise with stirring over a period of 2.5 hr. The reaction was exothermic. Stirring was maintained for 7.25 hr after addition was complete. Excess hydride was destroyed by the careful dropwise addition of water. Sulfuric acid (10%) was added to dissolve the solids. The reaction mixture was diluted with 500 ml of saturated sodium chloride solution and the organic phase was separated, dried over anhydrous magnesium sulfate, and stripped of solvent, using a rotary evaporator, yielding 69.1 g of crude product. An additional 15.6 g of product, obtained from an ether extraction of the aqueous phase, was combined with the main product giving 84.7 g (81%) of tetramethylcyclobutane-1,3-diol melting at 125.5–128.0° (lit.[28] mp 125–135°). The nmr spectrum displayed signals at τ 4.60 (singlet, OH, 2.2 H), 6.20 and 6.41 (singlets, ring H due to the *cis* and *trans* isomers respectively, 1.9 H), and 8.70, 8.83, and 8.78 (singlets, ring CH_3 due to *cis* and *trans* isomers respectively, 12.0 H). The ratio of areas of the ring-methyl absorptions in the two isomers was 0.775, indicating that the mixture consisted of 43.7% *cis*- and 56.3% *trans*-diols. In another reaction where stirring was less efficient, the ratio of *trans* to *cis* isomer formed was 4:1.

3-Methoxytetramethylcyclobutanol.—Sodium hydride dispersion (60.1%) in mineral oil (14.3 g, 0.358 mol) was washed with four portions of anhydrous ether. The mineral oil free reagent was transferred with the aid of 250 ml of anhydrous ether to a 1-l. three-necked flask provided with a water condenser and dropping funnel. A solution of tetramethylcyclobutane-1,3-diols (43.7% *cis* and 56.3% *trans*, 48.6 g, 0.338 mol) in anhydrous tetrahydrofuran (250 ml) was added with magnetic stirring over a period

(26) J. R. Chapman, *Tetrahedron Lett.*, 113 (1966).

(27) J. D. Roberts and C. W. Sauer, *J. Amer. Chem. Soc.*, **71**, 3925 (1949)

(28) Tetramethyl-1,3-cyclobutanedione, "Properties. . .Reactions," Eastman Chemical Products, Inc., Kingsport, Tenn., May 1960.

of 0.5 hr. The reaction mixture was stirred while being heated at reflux for 18.5 hr. Heating was discontinued and the reaction mixture was allowed to cool to room temperature. Subsequently, methyl iodide (25 ml, 0.402 mol) was added dropwise, with stirring, to the light gray alcoholate slurry over a period of 1 hr. The reaction was exothermic. After addition was complete, the reaction mixture was heated at reflux for 2.5 hr. An additional 15 ml of methyl iodide was added and heating was continued at reflux for 6 hr more. The reaction mixture was diluted with saturated sodium chloride solution and the organic phase was separated. The aqueous phase was extracted with three portions of ether which were combined with the organic phase. After the mixture was dried over anhydrous magnesium sulfate, solvent was removed by distillation through a short Vigreux column leaving a residue (51.2 g) consisting of a liquid with suspended crystalline solid. Distillation under reduced pressure gave the following fractions: (I) 31–45° (155–73 mm) (0.30 g); (II) 66–77° (40 mm) (1.59 g); (III) 75–79° (40 mm) (4.74 g); (IV) 76–77° (33–35 mm); (V) 65–71° (20 mm) (5.51 g); (VI) 71–80° (20 mm) (3.54 g); (VII) 80–85° (20 mm) (1.17 g); (VIII) 85–91° (20 mm) (8.18 g); (IX) 89–91° (20 mm) (5.53 g); and a solid residue (15.40 g). Fractions VIII and IX showed a major peak (95 and 88%, respectively) by vpc (column C at 102°) which was subsequently shown to correspond to a mixture of *cis*- and *trans*-3-methoxytetramethylcyclobutanols. A sample of this isomeric mixture isolated from fraction IX by vpc furnished the following spectra: ir (CCl_4) 3490 (s, OH), 2970–2850 (s, CH), 1465 (s, CH), 1379 and 1368 (s, doublet, *gem*-dimethyl), 1310 (m), 1255 (m), 1204 (s), 1127 (s, COC, symmetric), 1073 (s, CO, alcohol), 1010–983 (s), 950 (m), and 860 cm^{-1} (m); nmr τ 6.60 (singlet, ring H in *trans* isomer, 0.8 H), 6.76 (singlet, OCH_3, 3.0 H), 6.99 (ring H in *trans* isomer, 0.7 H), 7.16 (singlet, ring H in *cis* isomer, 0.3 H), 8.28 (singlet, OH?, 1.0 H), 8.87 (singlet, axial ring CH_3 in *cis* isomer, 2.4 H), 8.99 (singlet, axial and equatorial ring CH_3 in *trans* isomer, 8.15 H), and 9.05 (singlet, equatorial ring CH_3 in *cis* isomer, 1.6 H). The ring hydrogen in the *cis* isomer, counterpart to the ring hydrogen in the *trans* isomer at τ 7.16, seems to overlap with the methoxyl hydrogen signal. The mole ratio of the two isomers (*cis*/*trans*) was calculated to be 32:68 on the basis of the areas of the ring-methyl signals.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.38; H, 11.32.

3-Methoxytetramethylcyclobutanol formed a brosylate as a mixture of *cis* and *trans* isomers melting at 65–75°. The *trans* isomer obtained by recrystallization melted at 60.5–62.5°.

Anal. Calcd for $C_{15}H_{21}O_4SBr$: C, 47.75; H, 5.61. Found: C, 47.65; H, 5.76.

Fractions I–VI showed two important peaks by vpc (column C at 65°) in varying area ratio. The peaks were subsequently shown to correspond to *trans*- and *cis*-1,3-dimethoxytetramethylcyclobutanes in order of increasing retention time.

trans-1,3-Dimethoxytetramethylcyclobutane furnished the following spectra: ir (CCl_4) 2995–2860 (s, CH), 2830 (s, OCH_3), 1463 (s, CH), 1386 and 1373 (s, doublet, *gem*-dimethyl), 1353 (s), 1204 (s), 1174 (m), 1151 (m), 1105 (s, COC, asymmetric), 1032 (m), 1005 (m), 994 (s), 982 (s), 950 (w), 875 (w), and 860 cm^{-1} (w); nmr τ 6.82 (singlet, OCH_3, 6.0 H), 7.12 (singlet, ring H, 2.2 H), and 9.03 (singlet, ring CH_3, 11.8 H).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.69; H, 11.72.

cis-1,3-Dimethoxytetramethylcyclobutane furnished the following spectra: ir (CCl_4) 2940–2875 (s, CH), 1458 (s, CH), 1388 and 1371 (s, doublet, *gem*-dimethyl), 1345 (s), 1235 (m), 1205 (s), 1191 (s), 1152 (m), 1135 (s), 1100 (s, COC, asymmetric), 1021 (s), 990 (m), and 972 cm^{-1} (s); nmr τ 6.76, (singlet, OCH_3, 6.0 H), 7.22 (singlet, ring H, 2.0 H), and 8.85 and 9.04 (singlets of equal area, axial and equatorial ring CH_3 respectively, 12.0 H).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.75; H, 11.84.

The residue consisted of a mixture of 3-methoxytetramethylcyclobutanol and starting material as indicated by its nmr spectrum which was superimposable on one of an isomeric mixture of tetramethylcyclobutanediols except for a signal at τ 6.76 due to the former compound. The composition of the residue calculated from the ratio of areas corresponding to ring methyl and methoxyl hydrogens was 87% tetramethylcyclobutane-1,3-diols (a mixture of 33% *cis* and 67% *trans*) and 13% 3-methoxytetramethylcyclobutanol. A sample of the residue injected as a solution in acetone on column C (128°) gave a peak with the same retention time as that of the starting material under identical column conditions. Analysis of the residue by nmr showed the following products and yields calculated from vapor phase chromatograms of the various fractions: 1,3-dimethoxytetramethylcyclobutanes, 8.96 g of *trans* (15.4%) and 12.9 g of *cis* (22.0%), and 3-methoxytetramethylcyclobutanols (a mixture of *ca.* 32% *cis* and 68% *trans*), 14.9 g (27.9%). The amount of starting material recovered was 13.4 g (27.5%).

3-Methoxytetramethylcyclobutanone.—This compound was prepared according to a procedure described by Holum[29] using an isomeric mixture of 3-methoxytetramethylcyclobutanols (16.4 g, 0.104 mol). Samples were withdrawn at 12-hr intervals, diluted with water, and extracted with ether, and the extract was subjected to vpc analysis after removal of ether. Following the reaction in this manner, the starting material was observed to decrease concomitant with the appearance of a product having a lower retention time on the column employed (column B at 150°). The reaction rate decreased after 2 days and the reaction was discontinued finally after 3 days when 84% of the starting material had disappeared. Distillation under reduced pressure through a short Vigreux column gave three fractions. The major fraction boiling at 84–88° (40 mm) (7.15 g) was 97% product and 3% starting alcohol by vpc. The ir spectrum (CCl_4) showed absorption bands at 2990, 2950, 2890 (s, CH), 2840 (s, OCH_3), 1773 (s, strained C=O), 1460 (s, CH), 1383 and 1361 (s, doublet, *gem*-dimethyl), 1272 (s), 1211 (m), 1200 (s), 1178 (m), 1149 (m), 1120 (s, COC, asymmetric), 1080 (m), 1012 (s), 993 (s), 954 (w), and 902 cm^{-1} (w). The nmr spectrum showed signals at τ 6.73 (singlet, OCH_3, ring H superimposed, 3.86 H), and 8.88 and 8.93 (singlets of equal area, ring CH_3, 12.0 H). An analytical sample was prepared by vpc separation on column B. The yield of 3-methoxytetramethylcyclobutanone based on vpc analysis of the collected fractions and residue was 10.5 g (61%).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.03; H, 10.29.

3-Methoxytetramethylcyclobutanone Tosylhydrazone.—This tosylhydrazone was obtained from 3-methoxytetramethylcyclobutanone (9.25 g, 0.0570 mol based on 97% purity) and tosylhydrazine (11.0 g, 0.0591 mol) as a succession of crystalline crops totaling 15.08 g (81.5%) employing the method of Meinwald.[21] A sample recrystallized from aqueous methanol had mp 132.5–133.5°. The nmr spectrum (CD_3COCD_3) of this material showed signals at τ 2.46, 2.59, 2.84, and 2.88 (A_2B_2 quartet, aromatic, 4.0 H), 6.85 (singlet, OCH_3, 3.0 H), 6.93 (singlet, ring H, 1.0 H), 7.73 (singlet, $ArCH_3$, 3.0 H), and 8.78, 8.89, 8.95, and 9.05 (singlets of equal area, ring CH_3, 12.0 H). The ir spectrum ($CDCl_3$) displayed absorption bands at 3290 (m, NH), 2973 (s), 2942 (s), 2913 (m), 2978 (m, CH), 2837 (m, OCH_3), 1678 (w, C=N), 1600 (m, C=C, aromatic), 1497 (m), 1397 and 1373 (s, doublet, *gem*-dimethyl), 1340 (s, SO_2N, asymmetric), 1308 (w), 1293 (w), 1223 (w), 1206 (w), 1188 (m), 1170 (s, SO_2N, symmetric), 1127 (m), 1097 (w), 1076 (w), 1022 (s), 1012 (s), 987 (s), and 816 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{24}N_2O_3S$: C, 59.23; H, 7.46. Found: C, 59.39; H, 7.60.

Registry No.—**1**, 19203-14-6; **7**, 19203-15-7; **8**, 19185-60-5; **9**, 19203-17-9; **10**, 19203-18-0; tetramethylcyclobutane-1,3-dione ditosylhydrazone, 5530-15-4; tetramethylcyclobutane-1,3-dione monotosylhydrazone, 4930-35-2; biacetyl monotosylhydrazone, 19203-21-5; component A, 19203-22-6; component B, 19203-23-7; 3-toluenesulfonyltetramethylcyclobutanone tosylhydrazone, 19203-24-8; 3-hydroxytetramethylcyclobutanone tosylhydrazone, 1156-43-0; *cis*-3-methoxytetramethylcyclobutanol, 19206-06-5; *trans*-3-methoxytetramethylcyclobutanol, 19206-07-6; *cis*-3-methoxytetramethylcyclobutanol brosylate, 19206-08-7; *trans*-3-methoxytetramethylcyclobutanol brosylate, 19206-09-8; *trans*-1,3-dimethoxytetramethylcyclobutane, 19206-10-1; *cis*-1,3-dimethoxy-

(29) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

tetramethylcyclobutane, 19206-11-2; 3-methoxytetramethylcyclobutanone, 19203-26-0; 3-methoxytetramethylcyclobutanone tosylhydrazone, 19203-27-1.

Acknowledgments.—The authors wish to thank the Air Force Office of Scientific Research (Grant AF-AFOSR-34-65) and the National Institute of General Medical Sciences Division of the National Institutes of Health (predoctoral fellowship to R. C. J., 1-F1-GM-33,506-01) for their generous support of this work. We also express our appreciation to Dr. Richard A. Porter for numerous helpful discussions.

Kinetic Studies on the Autoxidation of Phenylhydrazones[1]

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Detailed kinetic studies were carried out on the thermally initiated autoxidation of cyclohexanone phenylhydrazone (CHPH) and cyclopentanone phenylhydrazone (CPPH) to their corresponding phenylazoalkane hydroperoxides. The rate of oxidation was measured over the range of 0–35° in four different solvents, *i.e.*, benzene, *n*-heptane, acetone, and methanol. In all solvents, CHPH was oxidized more rapidly than CPPH, reflecting the sterochemistry of the cyclohexane and cyclopentane ring systems at the carbon–nitrogen linkage during the allylic rearrangement of the intermediate free radical which takes place in the autoxidation process. The rate of oxidation of both CHPH and CPPH is more rapid in nonpolar solvents than in polar solvents. A compensation effect was observed with CPPH; it has oxidized more rapidly in benzene than in acetone, but the observed activation energy was less (11.5 *vs.* 7.3 kcal/mol). These results suggest that solvent–phenylhydrazone interaction is greater than solvent–radical interaction.

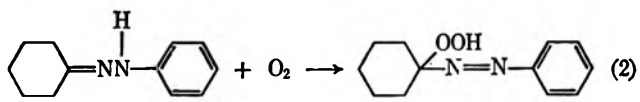
In recent years, studies in these laboratories have been concerned with the oxidation of thiols under a variety of conditions.[2] These studies aroused our interest in an "*in situ*" peroxidation technique for thiols. Phenylhydrazones looked attractive for this purpose since it has been reported that they are readily autoxidized to hydroperoxides.[3–5] A careful examination of the literature disclosed that there is a paucity of data on the mechanism of this reaction. Most studies have been qualitative in nature and have employed either unsubstituted or substituted benzaldehyde phenylhydrazones. Spectroscopic studies have established that the initial oxidation products are unstable phenylazoalkane hydroperoxides.[6–8] In view of this situation, we undertook a detailed study of the kinetics of the thermally initiated autoxidation of both cyclohexanone phenylhydroazone (CHPH) and cyclopentanone phenylhydarzone (CPPH).[9]

Results

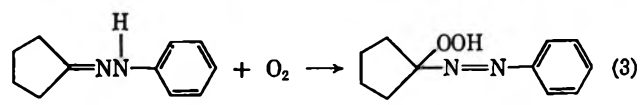
In preliminary experiments the reaction stoichiometry shown below (eq 1) was confirmed by a comparison of

$$PH + O_2 \rightarrow POOH \quad (1)$$

oxygen consumption and phenylhydrazone (PH) disappearance by glpc for a number of runs. Direct evidence for hydroperoxide formation was obtained from the 60-MHz proton spectra of freshly oxidized Ia and IIa in benzene (eq 2 and 3). Both products



Ia Ib (2)



IIa IIb (3)

exhibited a diagnostic singlet resonance band at *ca.* τ 0.1 which is ascribed to the proton of the hydroperoxide group. Similar results were obtained by Bellamy and Guthrie.[6] Accordingly, proton spectroscopy afforded a complementary method for monitoring the formation of hydroperoxide formed from Ia and IIa.

An examination of the rates of oxidation of CPPH and CHPH indicated that the reaction was initially autocatalytic with the rate increasing exponentially with time.[9] As pointed out by Semenov, such initial autoacceleration is typical of many thermal (*i.e.*, noncatalyzed) hydrocarbon oxidations.[10] Initial reaction rates in terms of the moles of PH oxidized per liter per second were obtained from semilogarithmic plots of rate *vs.* time by extrapolating the linear portion of these curves to zero reaction time. The rate of oxidation at "lined-out" conditions was also obtained; however, a comparison of "lined-out" rates and initial rates indicated that both sets of data produced the same directional effects. Initial rates were employed to obtain kinetic parameters because such values can be directly associated with a given phenylhydrazone and oxygen concentration. A study was first made of the effect of phenylhydrazone concentration and oxygen

(1) This work was carried out under U. S. Army Contract No. DA18-035-AMC-330(A) and was monitored by the Chemical Research Laboratory, Edgewood Arsenal, Md.

(2) For recent studies, see (a) T. J. Wallace, and A. Schriesheim, *Tetrahedron*, **21**, 2271 (1965); (b) T. J. Wallace, *J. Org. Chem.*, **31**, 3071 (1966); (c) T. J. Wallace, and A. Schriesheim, *J. Appl. Chem.*, **14**, 48 (1967).

(3) M. Busch, and N. Dietz, *Ber.*, **47**, 3281 (1914).

(4) K. H. Pausacker, *J. Chem. Soc.*, 3478 (1950).

(5) R. Criegee, and G. Lohaus, *Ber.*, **314**, 219 (1951).

(6) A. J. Bellamy, and R. D. Guthrie, *J. Chem. Soc.*, 2788 (1965).

(7) G. J. Karabatsos, and R. A. Taller, *J. Amer. Chem. Soc.*, **85**, 3627 (1963).

(8) H. C. Yao, and P. Resnick, *J. Org. Chem.*, **30**, 2832 (1965).

(9) For a preliminary account of part of this work, see W. F. Taylor, H. A. Weiss, and T. J. Wallace, *Chem. Ind.* (London), 1226 (1968).

(10) N. N. Semenov, "Some Problems in Chemical Kinetics and Reactivity," Vol. 2, Princeton University Press, 1959, Chapter 12.

TABLE I

EFFECT OF PHENYLHYDRAZONE CONCENTRATION AND OXYGEN PARTIAL PRESSURE ON THE INITIAL RATE OF OXIDATION

Phenylhydrazone	Initial concn, mol/l.	Initial oxygen pressure, Torr	Relative initial rate at 0° in acetone[a]
CHPH	0.025	830	0.45
	0.050	830	1.00
	0.100	830	2.06
	0.050	660	0.76
	0.050	830	1.00
	0.050	939	1.09
CPPH	0.025	830	0.47
	0.05	830	1.00
	0.10	830	1.94
	0.050	660	0.80
	0.050	830	1.00
	0.050	939	1.10

[a] Initial rate at given conditions relative to the initial rate at the standard conditions (0.05 mol/l., 830-Torr O_2) for the given phenylhydrazone; the relative rate values cannot be used by themselves to compare the oxidation rates of CHPH and CPPH.

partial pressure on the rate of oxidation. This study was made at 0° in acetone. The CHPH and CPPH concentration was varied from 0.025 to 0.100 mol/l. at a fixed oxygen partial pressure of 830 Torr and the oxygen partial pressure was varied from 660 to 939 torr at a fixed PH concentration of 0.050 mol/l. The results of this study are shown in Table I. An examinination of the data indicates that the initial rate is first order in phenylhydrazone and approximately first order in oxygen partial pressure, although the oxygen dependency appears to be decreasing with increasing oxygen

Figure 1

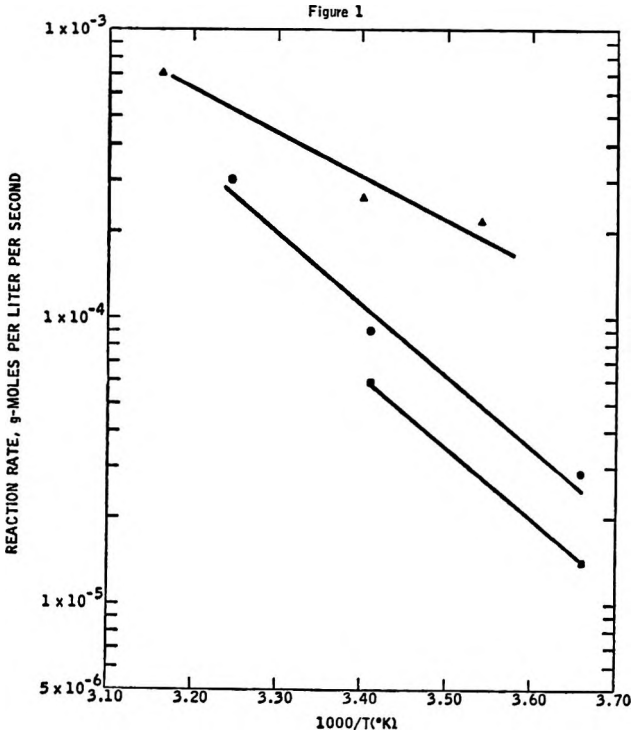


Figure 1.—The temperature dependence of the initial rate of oxidation at an initial concentration of 0.05 mol phenylhydrazone/l. at 830-Torr O_2 partial pressure: ▲, cyclohexanone phenylhydrazone in benzene; ●, cyclohexanone phenylhydrazone in acetone; ■, cyclopentanone phenylhydrazone in acetone.

TABLE II

EFFECT OF SOLVENT TYPE ON THE RATE OF PHENYLHYDRAZONE OXIDATION

Solvent	Initial rate, mol/l./sec × 10⁶[a] CHPH	CPPH
Methanol	5.5	2.6
Acetone	11.2	6.1
n-heptane	51.0	22.5
benzene	31.8	18.9

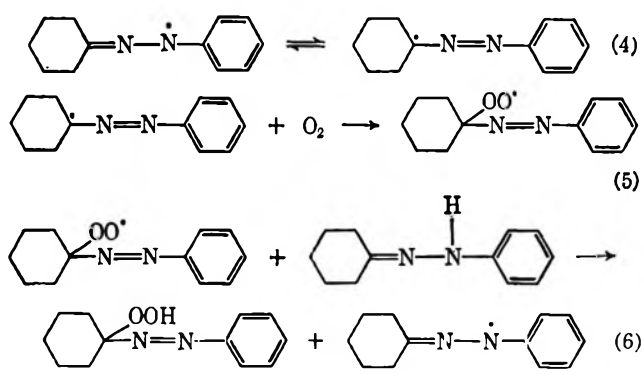
[a] Conditions: 21°, 830-Torr O_2 partial pressure, initial phenylhydrazone concentration 0.05 mol/l.

partial pressure, which is typical of many autoxidation reaction processes. The effect of temperature on the initial rate of oxidation was investigated for CHPH and CPPH in acetone and CHPH in benzene at the same PH concentration and oxygen partial pressure. An Arrhenius plot of these initial rates is shown in Figure 1. The temperature dependence of the initial rate of oxidation of CHPH and CPPH in acetone was the same; however, CHPH in benzene exhibited a lower temperature dependence than that observed in acetone. At a given temperature in acetone CHPH was oxidized more rapidly than CPPH. The observed activation energy obtained from the slope of the Arrhenius plots was 11.5 kcal/mol for the oxidation of CHPH and CPPH in acetone and 7.3 kcal/mol for CHPH in benzene.

The effect of solvent type on the initial rate of phenylhydrazone oxidation was investigated at 21° using a phenylhydrazone concentration of 0.05 mol/l. and 830-Torr oxygen partial pressure. Four solvents were employed, *i.e.*, acetone, methanol, *n*-heptane, and benzene. Results are shown in Table II. As shown previously in the acetone solvent system, the initial rate of oxidation of CHPH is faster than that of CPPH in all of the other solvents investigated. Also, the initial rate of oxidation of both CHPH znd CPPH in hydrocarbon media such as heptane and benzene is greater than that observed in the polar solvents (acetone and methanol).

Discussion

The phenylazoalkane hydroperoxide product (Ib and IIb) observed for the thermal autoxidation of CHPH and CPPH is in agreement with the results obtained by other workers who oxidized various benzaldehyde phenylhydrazones.[4-8] In explaining their results it was assumed that a chain reaction occurred involving radical attack on the N–H bond, followed by allylic shift of the odd electron system as shown in eq 4–6.



As pointed out by Walling,[11] a similar free-radical rearrangement occurs in the autoxidation of tetrahydrocarbazole.

The initial rate of oxidation was much higher in nonpolar solvents than in polar solvents for both CHPH and CPPH. A similar effect of solvent type was observed in semiquantitative studies by Pausacher of the oxidation of benzaldehyde phenylhydrazone[4] and by Bellamy and Guthrie in studies of the oxidation of cyclohexanone phenylhydrazone.[6] In the present work, it can be seen that the solvent affects more than just the rate at a given temperature alone. It exerts an influence on both the rate at a fixed temperature and the activation energy such that a compensation effect results. If one compares the benzene and acetone solvent effects, it can be seen that the highest rate and lowest activation energy occurs in the same solvent. In contrast, as discussed by Huyser,[12] in studies of the effect of solvent on the autoxidation of styrene, cyclohexane, and cumene, the most polar solvents produced the fastest rates of oxidation. Huyzer[12] indicated that complexation of the chain-carrying peroxy radicals by the solvent is probably responsible for the observed solvent effect on rate in these studies. Huyser[13] also discusses the effect of solvent type on a radical-forming reaction. In the decomposition of phenylazotriphenylmethane, the highest rate and lowest activation energy was observed in nonpolar solvents; a compensation effect identical with that observed in the present study. Huyser[13] attributed this effect to the fact that the ground-state azo compound is more strongly solvated by the more polar solvents relative to the nonpolar solvents and that the transition state is not solvated in any of the solvents. These results suggest that the effect of solvent on the present autoxidation reaction system reflects the effect of solvation on the phenylhydrazone itself, rather than on the intermediate phenylazoalkyl peroxy radical.

CHPH was oxidized more rapidly than CPPH in all solvents studied. This effect reflects the stereochemistry of the cyclohexane and cyclopentane ring systems.[14] In both the CHPH and CPPH systems, autoxidation produces a free radical which rearranges and changes the hybridization at the carbon–nitrogen linkage from sp^2 (planar) to sp^3 (tetrahedral). In the cyclopentane system, sp^2 hybridzation at the carbon–nitrogen linkage is favored over sp^3, since it reduces the amount of nonbonded interaction and internal strain in the five-membered ring. By contrast to the cyclopentane system, in the cyclohexane system, nonbonded interaction and internal ring strain are decreased when hybridization at the carbon–nitrogen linkage changes from sp^2 to sp^3.

(11) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 416.

(12) E. S. Huyser, in "Advances In Free Radical Chemistry," Vol. I, Academic Press, 1965, p 119 ff.

(13) Reference 12, p 129 ff.

(14) For a specific discussion, see (a) H. D. Orloff, *Chem. Rev.*, **54**, 347 (1954); (b) V. Prelog, *J. Chem. Soc.*, 420 (1950).

Experimental

Reagents.—Cyclohexanone phenylhydrazone and cyclopentanone phenylhydrazone were prepared by conventional methods in a nitrogen drybox and recrystallized twice from degassed ethanol–water solutions. Melting points were in agreement with published values. The phenylhydrazones were stored under nitrogen prior to use. Stock solutions of the phenylhydrazones were prepared in the nitrogen drybox from degassed spectroquality and chromatoquality grade solvents and were used immediately after preparation.

Oxidation Apparatus and Procedure.—The oxidation system consisted of a reaction vessel connected to a Hg manometer. The reaction vessel was a 500-ml round-bottomed flask equipped with a paddle stirrer, thermometer, and serum cap. Oxygen uptake was monitored by use of the Hg manometer. A 100-ml round-bottomed flask was used in series to serve as a ballast flask. A stopcock manifold allowed the introduction of oxygen and vacuum. In a typical run, the solvent was placed in the reaction flask, evacuated, and flushed with oxygen three times. Oxygen was added to the desired pressure. A stock solution (0.5 *M*) of the phenylhydrazone in the same solvent was prepared in a nitrogen drybox. An aliquot was withdrawn and transferred to the reaction flask to give a 0.05 *M* phenylhydrazone solution. Oxygen consumption was measured by the Hg manometer. The reaction vessel was surrounded by a constant-temperature bath. Stirring rates were maintained well above those for diffusion controlled conditions. The reaction mixture was sampled by inserting a Hamilton microliter syringe through the serum cap and withdrawing liquid with the syringe. This was immediately analyzed by glpc.

Analytical Instruments and Procedures.—Phenylhydrazone disappearance was followed by glpc using an F & M Model 609 chromatograph equipped with a recorder and a 2-ft 10% silicone rubber on Chromosorb P column, operated at 125° using helium as the carrier gas. N-Hexadecane was used as an internal standard. Peak areas were corrected by relative response factors.

Nmr Analyses.—Samples for nmr studies were prepared as concentrated solutions in a N_2 drybox using degassed benzene. The phenylhydrazones were oxidized by bubbling oxygen through the solutions and analyzed immediately. Spectra were recorded on a Varian A-60 spectrometer at ambient temperature. Tetramethylsilane was used as an internal standard.

Registry No.—CHPH, 946-82-7; CPPH, 1132-58-7.

Acknowledgment.—The authors are indebted to Dr. S. J. Brois for his interpretation of the nmr spectra. Helpful discussions with Mr. Jerome Goldenson are gratefully acknowledged.

Bridged Polycyclic Compounds. LIV. Rearrangements Attending the Radical-Anion Reduction of Dehydronorbornyl and Nortricyclyl Chlorides[1]

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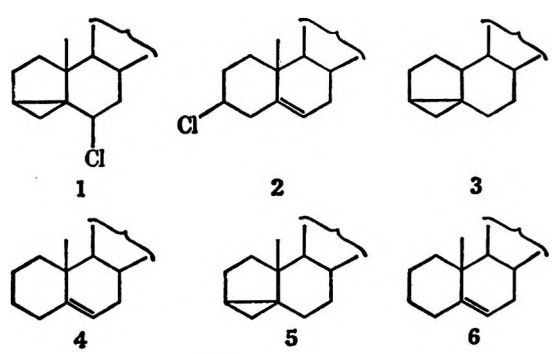
exo-Dehydronorbornyl chloride (**7** Cl), its *endo* epimer (**9** Cl) and nortricyclyl chloride (**8** Cl) were reduced by sodium biphenyl radical anion to mixtures of norbornene (**7**, Y = H) and nortricyclene (**8**, Y = H). At room temperature, all three chlorides gave identical mixtures containing about two-thirds nortricyclene. However, at −58° the unsaturated chlorides gave mixtures substantially richer in norbornene (*ca.* one-third nortricyclene), and the tricyclic chloride gave mixtures richer in nortricyclene (*ca.* 87% **8**, Y = H). Rapid carbonation of the reaction mixture from the *exo* chloride resulted in the formation of 3-nortricyclenecarboxylic acid (**12**) in very low yield. The results are rationalized in terms of an initial reduction to classical radicals and competition between rearrangement of these radicals to each other and capture by reduction to carbanions.

For some time we have been interested in homoallylic free-radical systems and in their interconversions with the corresponding cyclopropylcarbinyl systems. All of the work which we and others have done indicates that cyclopropylcarbinyl and homoallyl free radicals are not significantly stabilized by electron delocalization; that is, they have the properties of classical free radicals.[2]

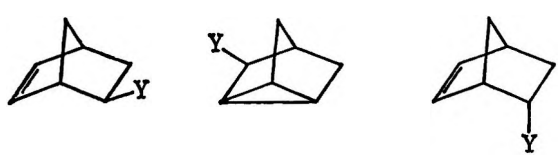
The reduction of 3,5-cyclocholestan-6-yl chloride (**1**) and of cholesteryl chloride (**2**) with sodium biphenyl radical anion in glyme (1,2-dimethoxyethane) has recently been described.[2] In that work, it was shown that each of these chlorides reacts by electron transfer and loss of halide ion to give the related classical radical (**1** → **3** and **2** → **4**), and that, given sufficient lifetime, the cyclopropylcarbinyl radical **3** rearranges to the homoallyl radical **4**. Capture of the radical **3** by another biphenyl radical anion with electron transfer to give the carbanion related to **3** competes effectively with rearrangement. That carbanion is neutralized by proton transfer from glyme faster than rearrangement. The net result was that the ratio of the hydrocarbons **5** to **6** from **1** was related to the concentration of radical anion. Put another way, larger concentrations of radical anion led to an increasing amount of capture of **3** rather than rearrangement to **4**, and thus led to larger amounts of **5** compared with **6**. Radical **4** appeared to be thermodynamically more stable than **3**, so that **2** gave only **6** as product.



1 **2** **3**

4 **5** **6**

It seemed worthwhile to extend these experiments to the dehydronorbornyl–nortricyclyl system, a system in which extensive studies of homoallyl–cyclopropylcarbinyl rearrangements have been carried out.[2,3] In the first reported study of the relationship of dehydronorbornyl and 3-nortricyclyl free radicals in which the free radicals were generated from both dehydronorbornyl and 3-nortricyclyl derivatives, Warner, Strunk, and Kuivila[4] investigated the tri-*n*-butyltin hydride and the triphenyltin hydride reductions of dehydronorbornyl (**7** and **9**) and 3-nortricyclyl (**8**) chlorides and bromides. With tri-*n*-butyltin hydride, dehydronorbornyl and nortricyclyl halides were reduced to the same mixture of norbornene (**7**, Y = H) and nortricyclene (**8**, Y = H). However, the reductions of **8** Br with triphenyltin hydride produced product mixtures the compositions of which were dependent upon the concentration of the reducing agent, with more nortricyclene (**8**, Y = H) produced at higher hydride concentration. These data are consistent with a pair of classical radicals, rather than with a nonclassical intermediate.



7 **8** **9**

Procedure and Results

The three isomeric chlorides, *exo*-dehydronorbornyl (**7**), *endo*-dehydronorbornyl (**9**), and nortricyclyl (**8**), were reduced with sodium biphenyl radical anion using two different experimental procedures and two different temperatures. In the first procedure, a solution of the chloride in pentane or 1,2-dimethoxyethane (glyme) was added under nitrogen to an excess of a stirred solution of sodium biphenyl in glyme. In Table I, this mode of addition is designated "normal." The second procedure involved the addition, under nitrogen, of an excess of sodium biphenyl in glyme to a stirred solution of the chloride in pentane or glyme. In Table I, this mode of addition is designed "inverse."

The reaction of the chlorides with sodium biphenyl was very rapid at room temperature and complete in a few minutes even at the lower temperature. After completion of the reaction, excess sodium biphenyl was

(1) Previous paper in series: S. J. Cristol and G. W. Nachtigall, *J. Amer. Chem. Soc.*, **90**, 7133 (1968).

(2) For leading references, see S. J. Cristol and R. V. Barbour, *ibid.*, **90**, 2832 (1968).

(3) A review of such rearrangements may be found in an article by D. I. Davies and S. J. Cristol, *Advan. Free-Radical Chem.*, **I**, 155 (1966).

(4) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966).

TABLE I

REDUCTION OF *exo*-DEHYDRONORBORNYL (7), *endo*-DEHYDRONORBORNYL (9), AND 3-NORTRICYCLYL (8) CHLORIDES WITH SODIUM BIPHENYL RADICAL ANION

Chloride	Addition mode	Temp, °C	Mixture composition % 7 (Y = H)[a]	% 8 (Y = H)[a]
7	Normal	25	38	62
7	Inverse	25	33	67
7	Inverse	−58	64	36
9	Normal	25	35[b]	65[b]
9	Inverse	25	37[b]	63[b]
9	Inverse	−58	73[b]	27[b]
8	Normal	25	35	65
8	Inverse	25	32	68
8	Inverse	−58	13	87

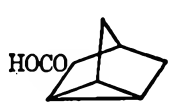
[a] Average of from two to five runs. The extreme values deviated from the average no more than 5% and were usually within 3%. [b] One run only.

destroyed with water, and the mixture was extracted with pentane. After gross distillation, the product mixture was analyzed for norbornene (**7**, Y = H) and nortricyclene (**8**, Y = H) using vapor phase chromatography (vpc). The results are tabulated in Table I.

The data in Table I show that, at room temperature, essentially the same mixture of norbornene and nortricyclene is formed regardless of the chloride used as a reactant, and that, at room temperature, the product distribution is insensitive to the concentration of radical anion in the reaction mixture. These results could be accommodated by postulating a single nonclassical radical as an intermediate common to all three reaction systems or by proposing that, under the conditions of the experiments, rearrangement between the classical radicals **10** and **11** occurs more rapidly than capture of either by electron transfer from biphenyl radical anion. That the second alternative is the correct one seems inescapable considering the low temperature reduction and results listed in Table I. Reductions at −58° (the freezing point of glyme) clearly result in different product mixtures depending upon the reactant chloride, even though the reactions were run under "inverse" conditions. Thus the reduction of nortricyclyl chloride at −58° yields mostly nortricyclene, and the reduction of either *exo*- or *endo*-dehydronorbornyl chloride yields mostly norbornene. It is apparent that with **8** Cl the initially formed nortricyclyl radical (**11**) is reduced to the nortricyclyl anion[2] before it can rearrange completely to its equilibrium mixture with the dehydronorbornyl free radical **10**. At −58°, a similar situation obtains with *exo*- and *endo*-dehydronorbornyl chlorides. (The slight difference in composition with **7** Cl and **9** Cl listed in Table I is probably within the limits of experimental uncertainties.) The data then leave little doubt that classical radicals intervene in these reactions.[2,3,4]

10

11



12

Just as in the rearrangement of cyclocholestanyl radical **3** to cholesteryl radical **4** and the competitive electron transfers, rearrangement is favored by higher temperatures. Put another way, the Arrhenius activation energy is greater for the rearrangement of **10** to **11** or *vice versa* than for the electron-transfer reduction of these radicals to carbanions by biphenyl radical anion.

To demonstrate the intermediacy of carbanions in the sodium biphenyl reduction of alkyl halides, *exo*-dehydronorbornyl chloride (**7** Cl) was treated with an excess of sodium biphenyl radical anion in glyme and immediately quenched with solid carbon dioxide. After a series of extraction procedures, a mixture of acidic materials was obtained from the reaction mixture. From this mixture, 3-nortricyclenecarboxylic acid (**12**) was isolated in low yield. The structure of this material was confirmed by its melting point and a mixture melting point with an authentic sample. In addition, its infrared (ir) spectrum and that of an authentic sample were identical. Since we know of no case in which a free radical has been carbonated, this substantiates the postulate[2,5,6] that in radical-anion reductions of alkyl halides, the free radical is converted (at least in part) into a carbanion by a second mole of radical anion and the carbanion then forms products by abstracting a proton from solvent.

Experimental Section

Materials.—Sodium biphenyl (1 *M*) in glyme was prepared according to the method of Liggett,[7] and a mixture (75:25) of nortricyclyl chloride (**8** Cl) and *exo*-dehydronorbornyl chloride, (**7** Cl) was prepared according to the procedure of Schmerling.[8] The isomers were separated using preparative vpc on a 20 ft × ⅜ in. column packed with 30% QF-1-0065 on 70–80 mesh Anakrom SD. The nortricyclyl and dehydronorbornyl chlorides separated in this fashion were determined to be 98.5 and 98% pure, respectively. The data in Table I have not been corrected to account for these small deviations from 100% purity. *endo*-Dehydronorbornyl chloride (**9** Cl) was prepared according to the procedure of Roberts[9] and purified by a combination of chromatography on a 4.3 × 95 cm alumina column and fractional distillation. The material used was determined by analytical vpc on a 20 ft × 0.25 in. stainless steel column packed with 20% QF-1-0065 on 70–80 mesh Anakrom ABS to contain 80% *endo*-dehydronorbornyl chloride (**9** Cl), 9% *exo*-dehydronorbornyl chloride (**7** Cl), and 11% nortricyclyl chloride (**8** Cl). The data in Table I have been corrected to account for this composition.

Procedure.—In a typical procedure, a 100-ml three-necked flask was fitted with a pressure-equalizing dropping funnel, the top of which was fitted with a Claisen adapter. One arm of the adapter served as a nitrogen inlet and the other was sealed with a rubber serum cap. The second neck of the flask was sealed with a serum cap and the system was exhausted through the third neck which was connected to a mercury trap. After the system had been swept with nitrogen for 1 hr, 20 ml of a 1 *M* solution of sodium biphenyl in glyme was injected into the reaction flask using a hypodermic syringe. The dropping funnel was then charged using a syringe with a solution of 1.0 g of the chloride in 5 ml of glyme, and the reaction flask was immersed in a bath at the appropriate temperature. The chloride solution was added dropwise over a period of 0.6 hr to the rapidly stirred solution of sodium biphenyl. After the addition was complete, the reaction mixture was poured into 100 ml of cold water. The resulting mixture was extracted with four 50-ml portions of pentane. The pentane extracts were combined and extracted with five 10-ml portions of water to remove most of the glyme.

(5) J. F. Garst, P. W. Ayers, and R. C. Lamb, *J. Amer. Chem. Soc.*, **88**, 4260 (1966).

(6) S. J. Cristol and R. V. Barbour, *ibid.*, **88**, 4262 (1966).

(7) L. M. Liggett, *Anal. Chem.*, **26**, 748 (1954).

(8) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **78**, 2821 (1956).

(9) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

After the pentane solution had been dried over magnesium sulfate it was concentrated by distilling the pentane through a semimicro column (30 × 1 cm) packed with glass helices. After most of the pentane had been distilled, 2 ml of chlorobenzene was added to the distillation flask. The distillation was continued and the portion boiling from 70 to 120° was collected. This material was analyzed by vpc at 98° on a 20 ft × ⅜ in. column packed with 30% SE-30 on Chromosorb 60–80 mesh.

Isolation of 3-Nortricyclenecarboxylic Acid.—A 60-ml separatory funnel was attached at its stem to a piece of glass capillary tubing (i.d. 1.0 mm). A second 60-ml separatory funnel was attached to a piece of capillary tubing (i.d. 1.7 mm). The smaller capillary tubing was joined to the larger one and the larger tubing was cut off 2 cm below the junction. By trial and error, conditions were found under which equivalent amounts of sodium biphenyl (1 *M*) in glyme and a mixture of dehydronorbornyl chloride and nortricyclyl chloride (*ca.* 80:20) would pass through the capillary tubes and meet at the junction. The funnel attached to the larger capillary was charged with 60 ml of 1 *M* sodium biphenyl in glyme and in the other funnel was placed 2.5 g of the chloride mixture. A slight pressure of nitrogen was applied to the funnel containing the chloride mixture and the stopcocks on the two funnels were opened simultaneously. As the reaction mixture issued from the capillary tubing, it dropped into an excess of vigorously stirred crushed Dry Ice. After the reaction was complete, the Dry Ice was allowed to sublime. The yellow liquid residue was treated with 50 ml of water and extracted with one 100-ml and two 50-ml portions of ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with three 40-ml portions of ether. The combined ether extracts were washed with 10 ml of saturated sodium chloride solution and then dried over magnesium sulfate. After removal of the magnesium sulfate by filtration and concentration of the ether in a rotary evaporator, there remained approximately 1.5 g of a viscous yellow oil. Thin layer chromatography on silica gel indicated the presence of at least five components. Chromatography of 0.75 g of the oil on a 1 × 45 cm column and elution with 2% ether in Skelly-B resulted in the isolation of 237 mg of a foul-smelling amber oil. Thick layer chromatography of this material on silica gel and developing with 5% methyl alcohol in ether resulted in the isolation of 103 mg of a yellow-brown oil. Trituration of this oil with pentane followed by evaporation of the solvent left 80 mg of amber oil. Vapor phase chromatography of this oil (on a 7 m × 0.25 in. stainless steel column packed with 20% QF-1-0065 on 70–80 mesh Anakrom ABS) indicated the presence of three components. A minor component had the same retention time as biphenyl and the major component (probably 80% of the mixture assuming equal detector response) had the same retention time as authentic 3-nortricyclenecarboxylic acid. By collecting the major component of a portion of the mixture by gas chromatography on a 20 ft × ⅜ in. column packed with 30% QF-1-0065 on Anakrom SD 70–80 mesh, 14 mg of 3-nortricyclenecarboxylic acid was obtained. After one recrystallization from pentane, it had mp 49.5–51.6° (lit.[9] mp 49–50°) and a mixture melting point with an authentic sample was not depressed. The ir spectra of the major component of the oil and of authentic 3-nortricyclenecarboxylic acid were identical. Whether or not 5-norbornene-2-carboxylic acid was present was not determined.

Registry No.—**7** Cl (*exo*), 3721-19-5; **8** Cl, 3509-46-4; **9** Cl (*endo*), 3721-18-4.

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The Addition of Trichloromethyl Radicals to Alkenylsilanes[1]

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Dibenzoyl peroxide catalyzed addition of bromotrichloromethane to various types of vinyl- and ω-alkenylsilanes have been investigated. Six new addition compounds have been prepared and characterized. It has been found that the reactivity of the double bond in the series of $R(CH_3)_2SiCH{=}CH_2$, where R = Me, Et, *i*-Pr, and *t*-Bu, toward addition of the trichloromethyl radical is governed by the Taft steric factor, E_s, of R, while the reactivity in the series of $Cl_n(CH_3)_{3-n}SiCH{=}CH_2$ is approximately related to the inductive effect. In the series of $(CH_3)_3Si(CH_2)_nCH{=}CH_2$, where n = 0–4, the reactivity reaches a maximum when n = 1. Factors influencing the reactivity have been discussed.

The addition of reagents across the double bond of vinyl- and alkenylsilanes is one of the most useful reactions in preparing carbon-functional organosilicon compounds.[2] These reagents can involve electrophilic and nucleophilic ones, as well as free-radical, or carbene intermediates and the influence of the silicon atom upon the reactivities has been one of the fascinating problems in organosilicon chemistry.

Bromotrichloromethane has been known to undergo the reaction resulting in the formation of a carbon–carbon bond *via* the free-radical mechanism.[3a] A useful tabular survey[3b] has been compiled by Walling and Huyser.

For vinylsilanes, some examples of addition products with bromotrichloromethane by the free-radical mechanism have been reported; thus, dibenzoyl peroxide catalyzed[4] and light-induced[5] addition to (trichloro)vinylsilane, light-induced addition to (methyldichloro)vinylsilane,[4] and dibenzoyl peroxide catalyzed addition to (triphenyl)vinylsilane[6] are known. However, no systematic study on the reactivity of vinyl- and alkenyl-substituted silanes toward free radicals has been undertaken.

During the course of studies on the structure and reactivity in the homolytic process, we have been interested in the reactivities of these compounds toward the trichloromethyl radical and have found an interesting effect of rate enhancement of trimethylsilylmethyl group in the free-radical addition reaction of bromotrichloromethane to substituted ethylenes.

(1) Presented in part at the 7th Symposium on Free-Radical Reactions, Osaka, Japan, Nov 30, 1966; Preprint, p 17.

(2) (a) C. Eaborn, "Organosilicon Compounds," Butterworth and Co. (Publishers) Ltd., London, 1960, Chapter 14; (b) V. Bažant, V. Chvalovský, and J. Rathousky, "Organosilicon Compounds," Publishing House of the Czechoslovak Academy of Sciences, Prague, 1965, p 292.

(3) (a) M. S. Kharasch, W. Nudenberg, and E. Simon, *J. Org. Chem.*, **18**, 328 (1953); (b) C. Walling and E. S. Huyser, *Org. Reactions*, **13**, 91 (1963).

(4) Midland Silicones Ltd., British Patent 769,499 (1957); *Chem. Abstr.*, **51**, 13903 (1957).

(5) A. M. Geyer, R. N. Haszeldine, K. Leedham, and R. J. Marklow, *J. Chem. Soc.*, 4472 (1957).

(6) R. K. Freidlina, G. T. Martirosyan, and A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR*, **137**, 1129 (1961); *Chem. Abstr.* **55**, 19842 (1961).

TABLE I
BOILING POINTS AND CH_2 WAGGING FREQUENCIES OF VINYL- AND ALKENYLSILANES[a]

Compound	Bp, °C	CH_2 wag, cm^{-1}
$Me_3SiCH=CH_2$	55	950
$EtMe_2SiCH=CH_2$	88–89	950
i-$PrMe_2SiCH=CH_2$	110	951
t-$BuMe_2SiCH=CH_2$	127	951
$ClMe_2SiCH=CH_2$	82.5–83	962
$Cl_2MeSiCH=CH_2$	91	971
$Cl_3SiCH=CH_2$	90	979
$Me_3SiCH_2CH=CH_2$	85–86.5	893
$Me_3Si(CH_2)_2CH=CH_2$	113–115	903
$Me_3Si(CH_2)_3CH=CH_2$	127–128	912
$Me_3Si(CH_2)_4CH=CH_2$	155–156	910
$Me_3SiSiMe_2CH=CH_2$	131–132	944
$Me_3SiSiMe_2CH_2CH=CH_2$	154	893

[a] Source and other physical properties are described in the Experimental Section.

In this paper, we describe the preparation of some adducts of bromotrichloromethane to vinyl- and alkenylsilanes and discuss factors influential on the relative reactivities.

Results and Discussion

Vinylsilanes were prepared conveniently from vinylmagnesium chloride with the corresponding chlorosilanes in tetrahydrofuran (THF) (eq 1). It seems

$$RMe_2SiCl + CH_2=CHMgCl \xrightarrow{THF} RMe_2SiCH=CH_2 \quad (1)$$

noteworthy that isopropyldimethylchlorosilane can be prepared more simply by the reaction of isopropylmagnesium chloride with dimethyldichlorosilane in THF[7] than by the previous method[8] involving an intramolecular rearrangement of (α-chloroethyl)trimethylsilane. However, isopropylmagnesium bromide gave less satisfactory results.

(ω-Alkenyl)trimethylsilanes were prepared according to the known procedures. Physical properties of these compounds agreed very closely with those reported. Table I lists boiling points and $=CH_2$ deformation frequencies of these compounds, other physical constants being described in the Experimental Section.

Since vinylsilanes have no or very little tendency to homopolymerize with free-radical initiators,[9] the formation of 1:1 adducts may be obtained almost quantitatively. However, because of the relatively unstable nature of the adducts, the final yields after purification are not necessarily high. Some of new addition compounds so prepared are shown in Table II.

Addition products from allyltrimethylsilane and allylpentamethyldisilane could not be isolated. It has been established that (β-bromoalkyl)trialkylsilanes are extremely unstable with respect to β eliminations; consequently, from both allylsilanes, 4,4,4-trichlorobutene-1 and the corresponding bromosilanes were obtained (eq 2 and 3). Alternatively, it seemed also possible that the intermediate radical itself would decompose into the silyl radicals and the olefin. This

(7) H. Sakurai, N. Hayashi, and M. Kumada, unpublished materials.
(8) L. H. Sommer, D. L. Bailey, J. R. Gould, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **76**, 801 (1954).
(9) H. Sakurai, K. Tominaga, and M. Kumada, *Bull. Chem. Soc. Jap.*, **39**, 1279 (1966).

TABLE II
PROPERTIES OF ADDITION PRODUCTS FROM VINYL- AND ALKENYL-SUBSTITUTED SILANES WITH BROMOTRICHLOROMETHANE

Compound	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$	d^{20}_4	MR, deg		Anal., % C		Anal., % H	
						Calcd	Found	Calcd	Found	Calcd	Found
$Me_3SiCHBrCH_2CCl_3$	19185-53-6	88.5	121–122 (27)	1.5024	1.4339	61.70	61.48	24.14	24.67	4.05	4.09
$EtMe_2SiCHBrCH_2CCl_3$	19185-54-7	88.8	140–143 (25)	1.5081	1.4119	66.35	66.00	26.90	26.99	4.52	4.62
i-$PrMe_2SiCHBrCH_2CCl_3$	19185-55-8	65.5	137–139 (19)	1.5069	1.3725	71.00	70.80	29.42	29.72	4.94	4.96
t-$BuMe_2SiCHBrCH_2CCl_3$	19185-56-9	64.7	145–146 (20)	1.5093	1.3490	75.65	75.43	31.74	32.04	5.33	5.51
$Me_2SiMe_2SiCHBrCH_2CCl_3$	19185-57-0	80.2	120–122 (2)	1.5139	1.3026	82.69	82.42	26.94	27.12	5.09	5.24
$Me_2(SiCH_2)_2CHBrCH_2CCl_3$	19185-58-1	49.1	137–142 (20)	1.4940	1.3409	71.00	70.90	29.42	29.81	4.94	5.03

$$Me_3SiCH_2CH{=}CH_2 + BrCCl_3 \longrightarrow [Me_3SiCH_2CHBrCH_2CCl_3] \longrightarrow Me_3SiBr + CH_2{=}CHCH_2CCl_3 \quad (2)$$

$$Me_3SiSiMe_2CH_2CH{=}CH_2 + BrCCl_3 \longrightarrow [Me_3SiSiMe_2CH_2CHBrCH_2CCl_3] \longrightarrow Me_3SiSiMe_2Br + CH_2{=}CHCH_2CCl_3 \quad (3)$$

may be regarded as the reverse process of the free-radical addition of the silyl radical to olefin (eq 4).

$$Me_3SiCH_2\dot{C}HCH_2CCl_3 \longrightarrow Me_3Si\cdot + CH_2{=}CHCH_2CCl_3 \quad (4)$$

However, the following facts may exclude this possibility. Thus, Topchiev, *et al.*,[10] have reported that dibenzoyl peroxide catalyzed reaction of trichlorosilane and methyl(diphenyl)allylsilane effected smooth addition (eq 5).

$$HSiCl_3 + CH_2{=}CHCH_2SiMePh_2 \xrightarrow{(PhCOO)_2} Cl_3SiCH_2CH_2CH_2SiMePh_2 \quad (5)$$

We have also observed that thiophenol added to trimethylallylsilane with peroxide to give (3-phenylthiopropyl)trimethylsilane in good yield (eq 6). These

$$PhSH + CH_2{=}CHCH_2SiMe_3 \xrightarrow{(PhCOO)_2} PhSCH_2CH_2CH_2SiMe_3 \quad (6)$$

facts support that the intermediate free radicals from allylsilanes are stable enough not to decompose. Even if the intermediate free radicals decompose partly, still addition of the trichloromethyl radicals should be rate controlling, since the trichloromethyl radicals may be regenerated very rapidly from bromotrichloromethane by bromine abstraction with silyl radicals.

In Table III are listed the data of relative reactivities for alkenyltrimethylsilanes toward the addition of trichloromethyl radical measured by the disappearance of the olefin in competitive reaction conditions. Vinyltrimethylsilane was taken as the reference standard.

The addition of the trichloromethyl radical to carbon–carbon double bond is an example of well-analyzed free-radical reactions.[11] For aliphatic 1 olefins (reaction 7), the excellent linear correlation of the rate data by the Hammett–Taft equation[12] has been observed.

$$X(CH_2)_nCH{=}CH_2 + CCl_3\cdot \longrightarrow X(CH_2)_n\dot{C}HCH_2CCl_3 \quad (7)$$

Since steric effects are considered to be constant for the compounds studied by Martin and Gleicher, the rate constant of the reaction 7 would be governed only by the inductive polar effects of the substituent.

In a series of vinylsilanes of the $R_3SiCH{=}CH_2$ type, Eisch and Trainor[13] have pointed out that there exists a good correlation between the position of the CH_2 deformation frequency (CH_2 wag) and the electronic effect of R as measured by σ_{para}. In the series of vinylsilanes, $RMe_2SiCH{=}CH_2$, where R = Me, Et, *i*-Pr, and *t*-Bu, CH_2 wag frequencies are in the same position as seen in Table I, indicative of virtually constant electronic effect of silyl groups, RMe_2Si–, toward the carbon–carbon double bond regardless of the nature of an alkyl group. Therefore, the governing factor in the rates of the series of $R(CH_3)_2SiCH{=}CH_2$ seems to be only steric effects, where the relative rates are correlated with Taft steric factors,[12] E_s, of R as shown in Figure 1 above.

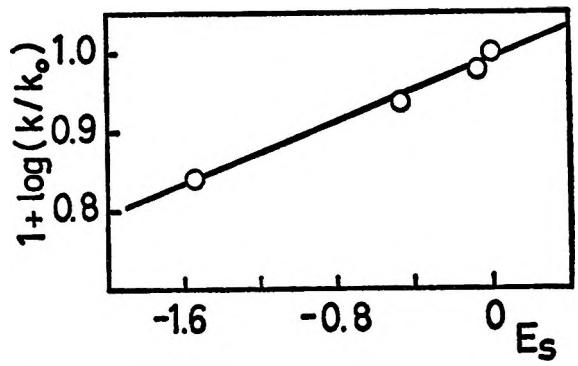

Figure 1.—Correlation of $1 + \log (k/k_0)$ and E_s of R for the addition of the trichloromethyl radical to $R(CH_3)_2SiCH{=}CH_2$ at 80.0°.

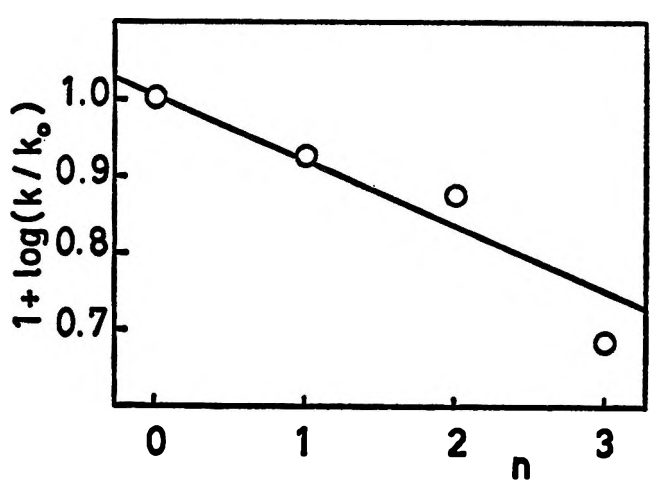

Figure 2.—Correlation of $1 + \log (k/k_0)$ and the number of the chlorine atom in $Cl_n(CH_3)_{3-n}SiCH{=}CH_2$ for the addition of the trichloromethyl radical at 80.0°.

TABLE III

RELATIVE REACTIVITIES OF ALKENYLSILANES TOWARD TRICHLOROMETHYL RADICAL AT 80.0° IN CHLOROBENZENE

Compound	Relative rate, k/k_0[a]
$RMe_2SiCH{=}CH_2$	
$Me_3SiCH{=}CH_2$[b]	1.00
$EtMe_2SiCH{=}CH_2$	0.945 ± 0.005
i-$PrMe_2SiCH{=}CH_2$	0.867 ± 0.005
t-$BuMe_2SiCH{=}CH_2$	0.694 ± 0.000
$Cl_nMe_{3-n}SiCH{=}CH_2$	
$Me_3SiCH{=}CH_2$[b]	1.00
$ClMe_2SiCH{=}CH_2$	0.851 ± 0.05
$Cl_2MeSiCH{=}CH_2$	0.753 ± 0.002
$Cl_3SiCH{=}CH_2$	0.476 ± 0.068
$Me_3Si(CH_2)_nCH{=}CH_2$	
$Me_3SiCH{=}CH_2$[b]	1.00
$Me_3SiCH_2CH{=}CH_2$	8.34 ± 0.84
$Me_3Si(CH_2)_2CH{=}CH_2$	1.60 ± 0.40
$Me_3Si(CH_2)_3CH{=}CH_2$	1.09 ± 0.00
$Me_3Si(CH_2)_4CH{=}CH_2$	0.94
1-Heptene	1.05 ± 0.01

[a] Deviations listed for two runs. [b] Vinyltrimethylsilane was taken as the reference standard.

(10) A. V. Topchiev, N. S. Nametkin, T. I. Chernysheva, and S. G. Drgaryan, *Dokl. Akad. Nauk SSSR*, **110**, 97 (1956); *Chem. Abstr.*, **51**, 4979 (1957).

(11) M. M. Martin and G. J. Gleicher, *J. Amer. Chem. Soc.*, **86**, 233, 238, 242 (1964), and references cited therein.

(12) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 13.

(13) J. J. Eisch and J. T. Trainor, *J. Org. Chem.*, **28**, 487 (1963).

In the series of vinylsilanes of the $(CH_3)_nCl_{3-n}SiCH=CH_2$ type, situations are more complicated than those of peralkylvinylsilanes, since, when the silicon atom binds electronegative atoms or groups capable of the $(p \rightarrow d)_\pi$ interactions between them, the orignal $(p \rightarrow d)_\pi$ bond between silicon and vinyl group may be influenced in a way.[14] Therefore, a simple summation of electron-releasing and -withdrawing inductive effect of methyl and chloro group, respectively, does not account fully for the reactivity; however, as shown in Figure 2, a general trend may be explained in this way.

The most striking feature seen in Table III is an enhancement of rate in allyltrimethylsilane compared with that in other ω-alkenyltrimethylsilanes.

The relative reactivities of silyl-substituted olefins toward carbethoxycarbene[15] and dichlorocarbene[16,17] have also been found to show enhanced reactivities of allylsilanes compared with those of vinylsilanes. For example, Culdín and Chvalovský[16b] have recorded the relative rates of the following olefins to addition of the dichlorocarbene as generated by the reaction of chloroform with potassium *t*-butoxide at −30°: $Me_3SiCH_2CH=CH_2$ (4.97) > $Me_3SiCH_2CH_2CH=CH_2$ (1.20) > 1-heptene (1.00, standard) ≫ $Me_3SiCH=CH_2$ (0.0474).

Since these carbenes as well as the trichloromethyl radical are electron seeking in nature, the relative reactivities toward these species decrease with decreasing nucleophilic character of the olefin. The marked inertness of vinylsilanes toward the dichlorocarbene has been ascribed to a decrease in the nucleophilicity of the carbon–carbon double bond in the vinylsilane due to the overlap of olefinic π bond with vacant d_π orbitals of silicon atom.[14,16,18] However very recently, Seyferth and Dertouzos have pointed out the importance of steric hindrance to attack of the dichlorocarbene in addition to the still important $(p \rightarrow d)_\pi$ bonding effect.[17] Such steric factors seem quite relevant in view of the somewhat crowded structures in the transition state proposed for carbene addition.[19] On the other hand, the relatively high reactivity of allytrimethylsilane was rationalized in terms of an electron-releasing inductive effect of the trimethylsilyl group.[17] In this case, the trimethylsilyl group is separated from the carbon–carbon double bond by a methylene group; therefore, no decreasing effect on the nucleophilicity of the double bond by $(p \rightarrow d)_\pi$ bonding nor steric hindrance can be operated.

The relative reactivities toward the trichloromethyl radical in the present study show that vinyltrimethylsilane is no more unreactive than 1-heptene. Therefore, addition of the radical may lead to less crowded transition state; yet bulkiness of alkyl groups on silicon can be the controlling factor as evidenced in Figure 1. Obviously, the electron-releasing inductive effect of trimethylsilyl group should be responsible for the enhanced reactivity of allyltrimethylsilane. If inductive effect is the sole factor, however, the relative rate of allyltrimethylsilane to 3-butenyltrimethylsilane may be estimated on the following basis. Since the ρ^* value of the reaction 7 has been known to be −0.42 with σ^* values of $X(CH_2)_n$ groups, where n = 1, 2, and 3,[11] the relative rate of allytrimethylsilane to (3-butenyl)trimethylsilane can be calculated approximately as 1.2 from the reported σ^* value for trimethylsilylmethyl group.[20] Therefore, rate enhancement in allyltrimethylsilane appears too great to be expected if other factors would be equal. Since the extra steric effect of trimethylsilylmethyl group, if any, should decrease the reactivity, the enhancement in the reactivity of allyltrimethylsilane must arise from an extra resonance effect in the intermediate free radical.

Recent investigations of homolytic arylation to substituted benzene by Simamura and coworkers[21] have elegantly shown that the influence of a substituent can be divided into resonance and inductive effects. For *meta* substitution, only the latter term was predominant, while, for *para* substitution, partial rate factors were expressed as eq 8 where τ_{para} is the term of additional

$$\log (k/k_0) = \rho\sigma_{para} + \tau_{para} \qquad (8)$$

stabilization correlated with the difference of the extra resonance energy between the substrate and the substituted cyclohexadienyl radical.

Therefore, an enhanced reactivity observed for allyltrimethylsilane in the present case would also be ascribed to an extra resonance effect in the intermediate radical. We propose the homoconjugation shown in eq 9 of an odd electron with the 3d orbitals of silicon as a sort of an extra resonance effect.

$$(CH_3)_3SiCH_2\dot{C}HCH_2CCl_3 \longrightarrow (CH_3)_3Si \cdots CHCH_2CCl_3 \qquad (9)$$
$$\diagdown\ \diagup$$
$$CH_2$$
$$\mathbf{1}$$

Price and Yukuta[22] have currently reported a greater reactivity of allylsilanes ($Q \simeq 0.06$) compared with that of vinylsilanes ($Q \simeq 0.03$) in the free-radical colpolymerization and suggested that such enhanced reactivity of allylsilanes could arise either from the homoconjugation like **1** or hyperconjugation such as **2** (eq 10). The latter conjugation involves the carbon–

$$\sim\dot{C}H—CH_2—SiR_3 \longleftrightarrow \sim CH=CH_2\cdot SiR_3 \qquad (10)$$
$$\mathbf{2}$$

silicon-bonding electrons, and, hence, may resemble to the concept of σ–π conjugation proposed by Russian workers[23] to explain the high reactivity of allylsilanes compared with that of vinylsilanes toward rhodanation. However, the fact that *e* value for allytrimethylsilane

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(20) Only σ^* for trimethylsilylmethyl group is known to be −0.26,[13] but it has been established that the interposition of a methylene group decreases σ^* values by a factor of 2.3 to 3.3. For pertinent reviews of this topic, see (a) S. Ehrenson, *Progr. Phys. Org. Chem.*, **2**, 195 (1964); (b) C. D. Ritchie and W. F. Sager, *ibid.*, **2**, 323 (1964).

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($e = 0.01$) is more positive than that of vinyltrimethylsilane ($e = -0.14$) could be the evidence in favor of the homoconjugation process at least in the free-radical intermediates, since the positive e value suggests that the silyl group is accepting electrons.[22]

This sort of a silyl-bridged radical has also been suggested as a possible intermediate for *trans* addition of trichlorosilane to 1-methylcyclohexene[24] in an analogous way to bromine-bridged[25] radicals.

Now these supporting evidences indicate such a homoconjugation to be a likely process and therefore it is concluded that an enhanced reactivity of allytrimethylsilane toward the trichloromethyl radical is due to the homoconjugation effect as well as to the inductive effect.

Experimental Section

All preparations were carried out under an atmosphere of dry nitrogen. Trimethylchlorosilane, dimethyldichlorosilane, (methyldichloro)vinylsilane, and vinyltrichlorosilane were commercial samples. Bromotrichloromethane, solvents, and other reagents were of reagent grade, and used after distillation through a 35-cm column packed with glass helicoils.

Vinylsilanes.—Trimethylvinylsilane was prepared by methylation of vinyltrichlorosilane with methylmagnesium chloride in dibutyl ether. The following were prepared according to known procedures: (ethyldimethyl)vinylsilane, bp 88–89°, n^{20}D 1.4097, d^{20}_4 0.7243 [lit.[26] bp 88° (737 mm), n^{20}D 1.4089, d^{20}_4 0.7242], MR 39.07 (calcd 39.01); (isopropyldimethyl)vinylsilane,[8] bp 110–110.5°, n^{20}D 1.4198, d^{20}_4 0.7412, MR 43.78 (calcd 43.66); (*t*-butyldimethyl)vinylsilane,[8] bp 127°, n^{20}D 1.4277, d^{20}_4 0.7497, MR 48.80 (calcd 48.31); and (dimethylchloro)vinylsilane, bp 82.5° (lit.[27] bp 82–82.5°). Vinylpentamethyldisilane[9] and allylpentamethyldisilane[23b] were also prepared by the published procedure.

Allyltrimethylsilane.—From allylmagnesium chloride and trimethylchlorosilane was prepared allyltrimethylsilane, bp 85–86.5°, n^{20}D 1.4072, d^{20}_4 0.7150 [lit.[28] bp 84.9° (737 mm), n^{20}n 1.4074, d^{20}_4 0.7193], MR 39.36 (calcd 39.01).

(3-Butenyl)trimethylsilane.[29]—This compound was prepared from trimethylsilylmethylmagnesium chloride and allyl chloride: bp 113–115°, n^{20}D 1.4141, d^{20}_4 0.7425 [lit.[30] bp 110.5° (752 mm), n^{20}D 1.4149, d^{20}_4 0.7372], MR 43.19 (calcd 43.46).

(4-Pentenyl)trimethylsilane.—4-Penten-1-ol was prepared from tetrahydrofurfuryl chloride with sodium in ether and was converted into 5-bromopentene-1 with phosphorus tribromide in pyridine. A Grignard reagent from 5-bromopentene-1 in ether was allowed to react with trimethylchlorosilane; after work-up, a mixture consisting of (4-pentenyl)trimethylsilane and other isomers (not identified) was obtained. (4-Pentenyl)-trimethylsilane was then separated from the mixture by preparative glpc on a 3-m silicone DC 550 column: bp 127–128° (as a mixture), n^{20}D 1.4232, d^{20}_4 0.7449 [lit.[31] 31–32° (14 mm), n^{20}D 1.4208, d^{20}_4 0.754], MR 48.67 (calcd 48.31).

(5-Hexenyl)trimethylsilane.[29]—From a Grignard reagent of 3-(trimethylsilyl)propyl bromide and allyl chloride was prepared (5-hexenyl)trimethylsilane, bp 155–156°, n^{20}D 1.4268, d^{20}_4 0.7673 [lit.[32] bp 158–159° (750 mm), n^{20}D 1.4246, d^{20}_4 0.7566], MR 52.29 (calcd 52.65).

Dibenzoyl Peroxide Catalyzed Addition of Bromotrichloromethane to Trimethylvinylsilane.—The next procedure may serve as a typical example for preparation of the adducts. In a glass tube, 14.87 g (0.075 mol) of bromotrichloromethane, 6.12 g (0.061 mol) of trimethylvinylsilane, and 0.10 g of benzoyl peroxide were placed. After repeated freezing and melting under vacuum, the tube was sealed and immersed in a constant-temperature bath kept at 80° for 10 hr. The reaction mixture was then fractionated; after recovering a small amount of the starting materials, 3,3,3-trichloro-1-bromopropyltrimethylsilane was obtained. Physical constants and yields together with those of other adducts are listed in Table II.

Reaction of Allyltrimethylsilane with Bromotrichloromethane.—From 4.22 g (0.037 mol) of allyltrimethylsilane, 7.32 g (0.037 mol) of bromotrichloromethane, and 30 mg of dibenzoyl peroxide, 3.76 g (0.025 mol, 66.7% yield) of trimethylbromosilane, bp 78°, and 3.02 g (0.019 mol, 51.5% yield) of 4,4,4-trichlorobutene-1, bp 120–125°, n^{20}D 1.4693, d^{20}_4 1.2852, MR 34.57 (calcd 34.67) (lit.[33] bp 128–129°, n^{20}D 1.4678) were obtained. The nmr spectrum (CCl_4) of this compound exhibited a typical allylic pattern; two methylene protons occurred as a doublet (J = 7 cps) with further splitting into a doublet (J = *ca.* 1 cps) at τ 6.64, two terminal vinylic protons as a pair of doublets with further complicated splittings at 4.66 and 4.73, and an olefinic proton as a diffused multiplet at 3.7–4.4.

Dibenzoyl Peroxide Catalyzed Addition of Thiophenol to Allyltrimethylsilane.—By essentially the same procedure as addition of bromotrichloromethane to vinyltrimethylsilane, 5.10 g (0.045 mol) of allyltrimethylsilane, 10.94 g (0.099 mol) of thiophenol, and 0.128 g (0.53 mmol) of dibenzoyl peroxide were subjected to reaction and, after fractional distillation through a 35-cm column packed with glass helices, 6.0 g (0.027 mol, 60.5 % yield) of pure 3-trimethylsilylpropyl phenyl sulfide was obtained: bp 140° (14 mm), n^{20}D 1.5287, d^{20}_4 0.9559, MR 72.38 (calcd 71.81). The nmr ($CDCl_3$) spectrum exhibited a sharp singlet at τ 9.97 (9 H, trimethylsilyl group), a multiplet at 9.15–9.5 (2 H, α-methylene to silicon), a multiplet at 7.95–8.6 (2 H, central methylene), a triplet (J = 7.5 cps) at 7.02, and an aromatic multiplet at 2.7.

Anal. Calcd for $C_{12}H_{20}SSi$: C, 64.22; H, 8.98. Found: C, 64.29; H, 9.21.

Procedure for Kinetic Runs.—Samples of olefin (A), trimethylvinylsilane (B, standard olefin), and carbon tetrachloride (internal standard) were accurately weighed into a flask, to which 5 ml of bromotrichloromethane and 10 ml of chlorobenzene containing dibenzoyl peroxide were added. A reactant ratio of bromotrichloromethane/trimethylvinylsilane/olefin/carbon tetrachloride/dibenzoyl peroxide of 4:1:1:0.75:0.012 was employed. In a glass tube the reaction mixture was then placed and degassed by repeated freezing and melting under vacuum. The tube was then sealed under vacuum and immersed in a constant-temperature bath kept at 80° for 0.5–1 hr. The extent of total olefin consumption varied from 30 to 60%. The mixtures were analyzed by glpc on a column packed with polyethylene glycol 20M or Apiezon L using helium as a carrier gas. In each run, the amount of chloroform was negligibly small, mostly not detectable, indicative of the absence of hydrogen abstraction by the trichloromethyl radical as a side reaction. The ratio of rate constants for addition was calculated by the usual expression shown in eq 11.

$$(k_A/k_B) = \frac{\log (\text{initial moles of A/final moles of A})}{\log (\text{initial moles of B/final moles of B})} \quad (11)$$

Registry No.—3-Trimethylsilylpropyl phenyl sulfide, 19185-59-2.

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Oxidation of Silanes. III. The Reaction of Aryldimethylsilanes with Mercuric Acetate and Thallium Triacetate[1,2]

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The reaction of aryldimethylsilanes with mercuric acetate and thallium triacetate in acetic acid at 25° has been studied by competitive techniques. The reactions are first order in the silane. Hammett correlations with σ of the ring substituents have been established with $\rho = -0.96$ and -1.15 for mercuric acetate and thallium triacetate, respectively. The reactions are postulated to involve electrophilic attack of the metal acetate on the silicon–hydrogen bond to produce an unstable silicon–metal bond which solvolytically decomposes to yield the observed products, aryldimethylsilyl acetates.

Nucleophilic substitution at a silicon atom is a characteristic reaction of organosilicon compounds and has been investigated extensively.[5] The high reactivity of silicon derivatives as compared to their carbon analogs has been interpreted in terms of the ability of silicon to increase its coordination number above four by utilizing d orbitals. The basic stereochemical features of displacement at silicon have been elucidated by Sommer.[6]

While interest in electrophilic displacement at a saturated carbon atom is receiving increased attention, little note has been made of the possibilities for similar reactions at a silicon atom. Considering the propensity for nucleophilic displacement at silicon it might be assumed that electrophilic attack would be even less likely to occur at silicon than at carbon. However, it is not clear whether the two modes of attack are directly comparable. Experimentally it might be difficult to observe electrophilic attack on silicon in the absence of competitive nucleophilic attack.

A search of the literature revealed several reactions which might proceed by attack of an electrophile at a silicon–hydrogen bond. These are (a) the formation of silyl perchlorates by treatment of silanes with silver perchlorate,[7] (b) the reaction of triethylsilane with mercuric acetate to yield triethylsilylacetate[8] and (c) the reaction of triethylsilane with ozone to produce triethylsilanol.[9]

Eaborn[7] studied the reaction of trisubstituted silanes and silver perchlorate in toluene in detail. The approximate material balance is represented by general eq 1.

$$2R_3SiH + 2AgClO_4 \longrightarrow 2R_3SiClO_4 + 2Ag + H_2 \qquad (1)$$

However, deviations of as much as 20% in the yields of silver and hydrogen are common. Eaborn postulated an electrophilic attack of silver ion on the hydrogen bound to silicon to yield silver hydride which then could decompose and initiate a chain process. The reaction exhibits a marked steric deceleration of rate and, therefore, a nucleophilic attack of perchlorate ion on silicon also was postulated. Therefore, the question of electrophilic substitution is still an open one.

The aryldimethylsilanes were shown to be ideal substrates for an examination of the electronic factors controlling the conversion into silanol by the action of ozone.[1] However, the difficulty of controlling the reaction variables for the low-temperature reaction involving a two-phase system limits the extension of studies of the ozone reaction.

Although the reaction of mercuric acetate with triethylsilane has been reported,[8] the generality of the

$$(C_2H_5)_3SiH + Hg(OAc)_2 \longrightarrow (C_2H_5)_3SiOAc + Hg + HOAc \qquad (2)$$

reaction has not been demonstrated. While mercuric acetate reacts as an electrophile with a variety of compounds having electron-rich centers, the effect of electronic and steric factors of its reaction with silanes are not known. Mercuric acetate is known to cleave aryl–silicon bonds in aryltrimethylsilanes to produce arylmercuric acetates and oxygenated silicon derivatives.[10] Therefore, a study of the reaction of mercuric acetate with the silicon–hydrogen bond of arylsilanes could entail experimental difficulties with a competing desilylation reaction. However, mercuric acetate can be handled with greater facility than ozone and is a well-known electrophile toward centers such as π bonds.[11] Our recent work with this reagent in the cleavage of cyclopropane bonds by mercuric acetate[12] has provided a point of reference for comparison of the reaction of silanes under identical reaction conditions. Furthermore the thallium triacetate[13] oxidative cleavage of cyclopropanes also has been studied and a quantitative comparison of the electrophilicities of the two metal acetates has been obtained. A study of the reaction of mercuric acetate and thallium triacetate with silanes should provide a criterion for the proposed electrophilic attack on silicon–hydrogen bonds.

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Results

The aryldimethylsilanes where the ring substituents are *p*-MeO, *p*-Me, *p*-Cl, *m*-Cl and *p*-CF_3 in addition to the parent unsubstituted compound all react almost instantaneously with mercuric acetate at 30° to quantitatively yield mercury. At 25° the aryl–silicon bond cleavage by mercuric acetate has a half-life of over 1 hr for phenyltrimethylsilane. Since the reaction of mercuric acetate with the silicon–hydrogen bond is much faster than the cleavage of the carbon–silicon bond, the latter reaction may be neglected.

The initial products of the reactions are the aryldimethylsilyl acetates as shown by an nmr analysis. The acetates are quite prone to hydrolysis and an aqueous work-up produces a mixture of silanols and siloxanes. When equimolar amounts of *p*-methoxyphenyldimethylsilane and mercuric acetate react in acetic acid in the absence of water, a 95% yield (nmr) of *p*-methoxyphenyldimethylsilyl acetate is obtained. Analysis by vpc indicated the absence of any other volatile products.

The initial concentrations of various mixtures of silanes and mercuric acetate were gravimetrically established. Since the reaction is quantitative, the remaining quantities of each silane in a competitive reaction can be mathematically determined without the use of an internal standard for vpc analysis of reactions in which equimolar quantities of mercuric acetate were not employed. The total amount of silane remaining at the conclusion of the reaction are related in eq 3 where [X] and [Y] represent the molar concentrations of individual silanes and $[X]_0$ and $[Y]_0$ are the initial concentrations. The molar ratio of the silanes remaining, [X]/[Y], is available from corrected integrated peak areas obtained from vpc analysis. The peak areas were corrected for molecular weights and differences in thermal conductivity. Using eq 3 and the ratio [X]/[Y] the individual concentrations of [X] and [Y] can be calculated. The kinetic order is first power with respect to the silane. The initial and final concentrations of the silanes are related by eq 4.

$$[X] + [Y] = [X]_0 + [Y]_0 - [HgOAc_2]_0 \quad (3)$$

$$\log ([X]/[X]_0) = k_X/k_Y \log ([Y]/[Y]_0) \quad (4)$$

The ratios of the rate constants given in Table I as calculated from eq 4 are identical within experimental error and confirm the kinetic order. The relative rates of the *p*-methoxy, *p*-methyl, *p*-chloro, *m*-chloro and *p*-trifluoromethyl derivatives relative to the phenyl compound are listed in Table II. From a plot (Figure 1) of $\log k_X/k_H$ *vs.* σ, $\rho = -0.96$ is obtained with a correlation coefficient $r = 0.995$.

Phenyldiisopropylsilane reacts 8.2 times slower than *m*-chlorophenyldimethylsilane. Therefore the calculated rate of phenyldiisopropylsilane relative to phenyldimethylsilane is 0.056.

Thallium triacetate reacts with aryldimethylsilanes in acetate acid at 30° quite rapidly. However, in order to ensure completion of the reaction, it was necessary to allow sufficient time for all of the $Tl(TlOAc_4)$ formed to dissociate (eq 6) and react.[13]

Table I
Kinetic Order Determination

$[p\text{-}CH_3OC_6H_4Si(CH_3)_2H]_0$, *M*	$[p\text{-}ClC_6H_4Si(CH_3)_2H]_0$, *M*	$[HgOAc_2]_0$, *M*	$k_{p\text{-}CH_3O}/k_{p\text{-}Cl}$
0.0390	0.0417	0.0280	3.07
0.0404	0.0404	0.0400	3.15
0.0202	0.0202	0.0202	3.20
0.0605	0.0238	0.0400	3.04

Table II
Relative Reaction Rates of Aryldimethylsilanes with Mercuric Acetate and Thallium Triacetate

Substituent	k_X/k_H $HgOAc_2$	k_X/k_H $TlOAc_3$
p-Methoxyl	1.89 ± 0.07	2.07 ± 0.06
p-Methyl	1.61 ± 0.06	1.65 ± 0.05
p-Chloro	0.60 ± 0.02	0.57 ± 0.02
m-Chloro	0.46 ± 0.02	0.38 ± 0.01
p-Trifluoromethyl	0.36 ± 0.01	

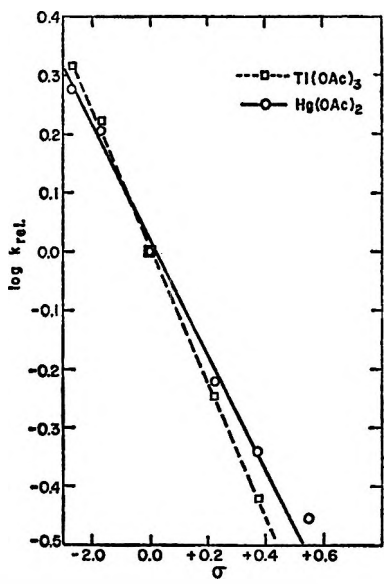


Figure 1.—Hammett correlation of rates of oxidation by mercuric acetate and thallium triacetate.

$$ArSiH(CH_3)_2 + Tl(OAc)_3 \longrightarrow ArSiOAc(CH_3)_2 + TlOAc + HOAc \quad (5)$$

$$Tl(OAc)_3 + TlOAc \rightleftarrows TlTl(OAc)_4 \quad (6)$$

Analysis by nmr confirmed that the silicon-containing products of the thallium triacetate oxidation are identical with those of the mercuric acetate oxidation reaction.

After 1 hr the reactions were analyzed in the same manner as for the reaction with mercuric acetate. The relative rate constants for the thallium triacetate reaction are given in Table II. From a plot (Figure 1) of $\log k_X/k_H$ *vs.* σ, $\rho = -1.15$ is obtained with a correlation coefficient $r = 0.993$.

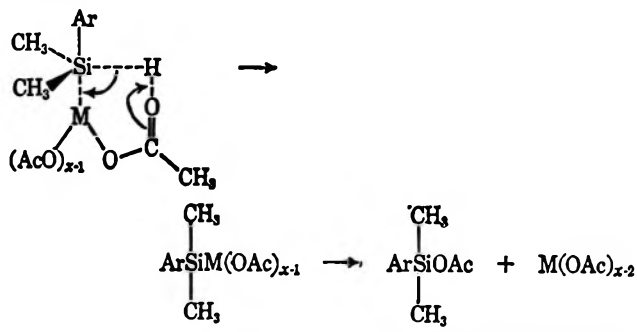
Discussion

The negative ρ values for both the reactions of mercuric acetate and of thallium triacetate with aryldimethylsilanes indicate that some positive charge is generated on silicon in progressing to the transition state. Attack of electrophilic reagents such as mercuric acetate and thallium triacetate might be expected to lead to a σ^+ correlation. These reagents give rise to $\rho^+ = -3.3$ and -4.2 for the cleavage of arylcyclopropane by mercuric acetate[12] and thallium triacetate,[13] respectively. However, the data for the oxidation of silanes clearly eliminate any contribution of σ^+ of the

substituent. Since both the σ and σ^+ scales are based on carbon centers, it is not obvious what function these values serve in organosilicon compounds. A positive charge on silicon in a pentacovalent siliconium ion intermediate might be tolerable without substantial resonance contribution of ring substituents.

The difference in magnitudes of the ρ values for the oxidation of silanes is consistent with the difference observed previously in the oxidative cleavage of cyclopropanes which involves electrophilic attack on the ring electrons. However, the level of response of the rate of reaction to changes in ring substituent is substantially lower. The reaction appears to involve an electrophilic substitution in which the positive charge generated at silicon is less than that generated at carbon in the cyclopropane cleavage reaction.

The reaction of the silicon–hydrogen bond may involve a concerted mechanism in which the metal acetate, $M(OAc)_x$, becomes attached to silicon.[14]



Rapid solvolysis of the intermediate compound containing the silicon–metal bond to yield the silyl acetate and a reduced metal species finds analogy in the solvolysis of alkylmercuric acetates.[15]

The decrease in the rate of oxidation when the two methyl groups are replaced by two isopropyl groups is not inconsistent with an S$_E$2 mechanism. In a bipyramidal transition state the isopropyl and phenyl groups would have to be oriented at 90° to each other. Steric hindrance in proceeding to the transition state would be expected on the basis of the necessary alteration in bond angles.

Experimental Section

Aryldimethylsilanes.—The preparation of substituted phenyldimethylsilanes has been described previously.[1]

Phenyldiisopropylsilane.—The method of Harvey, Nebergall, and Peake[16] was used in the preparation of the title compound.

Competition Reaction with Mercuric Acetate.—The procedure for the determination of relative rates of aryldimethylsilanes reacting with mercuric acetate is described for *p*-chlorophenyldimethylsilane and *p*-methoxydimethylsilane. A standard solution of mercuric acetate in acetic acid was prepared from 100 ml of acetic acid and 1.2744 g (4.000×10^{-3} mol) of mercuric acetate. The stoppered flask containing this solution was then placed in a 30.0° constant-temperature bath. A mixture of 0.1635 g (9.86×10^{-4} mol) of *p*-methoxyphenyldimethylsilane and 0.168 g (9.90×10^{-4} mol) of *p*-chlorophenyldimethylsilane contained in a 50-ml round-bottomed flask was also placed in this bath. After sufficient time had elapsed for achieving temperature equilibrium, 25 ml of the mercuric acetate solution was transferred by pipet to the silane mixture. Immediate precipitation of mercury occurred. After remaining in the bath for 15 min, the reaction mixture was filtered and the filtrate diluted with 70 ml of ether. This solution was then washed several times with both water and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and stripped of low-boiling solvent by means of a rotary evaporator. A control experiment was run, in which the same procedure as above was followed, except that pure acetic acid rather than mercuric acetate solution was used. Vpc analysis of the residue indicated no change in weight ratio of silanes took place during work-up. An Aerograph Model A-90 vpc was used to analyze the reaction mixture employing a 25% DC silicon oil 300 on Chromosorb 30/60 column at 90° column temperature. The relative peak areas of the two silanes was determined with a planimeter. All peak areas were corrected for variations in peak intensity due to variance in the thermal conductivities of the silanes.

Competition Reaction with Thallium Triacetate.—The reactions were carried out using the same general procedure as described for the reactions with mercuric acetate. The sole difference was that 1 hr was allowed for the reaction.

***p*-Methoxyphenyldimethylsilyl Acetate.**—To a stirred solution of 0.50 g (3×10^{-3} mol) of *p*-methoxyphenyldimethylphenylsilane in 15 ml of carbon tetrachloride was added 48 g (0.003 mol) of bromine in 15 ml of carbon tetrachloride. A nitrogen atmosphere was maintained in the system throughout the reaction. After the solution had lost all bromine color, 0.42 g (7×10^{-3} mol) of acetic acid in 5 ml of carbon tetrachloride was added to it. The reaction mixture was stirred for 12 hr during which a slow stream of nitrogen was bubbled through the solution. At the end of this process most of the solvent had been driven off and the residue was then analyzed by vpc on a 25% D.C. silicon oil 300 on Chromosorb 30/60 at 140° and by nmr. Vpc analysis indicated one main product in addition to excess acetic acid while nmr analysis (six-proton singlet at τ 9.87, three-proton singlet at 8.28, three-proton singlet at 6.59 and four-proton multiplet at 3.42) confirmed the presence of the desired silyl acetate.

Product Analysis.—*p*-Methoxyphenyldimethylsilane was allowed to react with mercuric acetate in acetic acid in the same manner described for the relative rate determinations with the important exception that the reaction flask was kept under a nitrogen atmosphere and no work-up was attempted due to the inevitable hydrolysis of silyl acetate to silanol and siloxane. Vpc analysis of the reaction mixture under the same conditions as described above for *p*-methoxyphenyldimethylsilyl acetate showed a trace amount of remaining silane, acetic acid and a major peak at the same retention time as the silyl acetate.

In a separate experiment the nmr spectrum of the product in acetic acid was obtained. The six-proton singlet of *p*-methoxyphenyldimethylsilyl acetate was observed in addition to a very low-intensity doublet corresponding to the parent silane. The one-proton septuplet at τ 5.65 of the parent silane could not be detected. The yield of the silyl acetate was determined to be approximately 95% by the use of *t*-butylbenzene as an internal standard.

The yield of mercury in the case of the reaction of *p*-methoxyphenyldimethylsilane was determined as 98%. The analytical method involved dissolution of the mercury in nitric acid followed by a standard thiocyanate–silver ion back-titration.[17]

The products of the reaction of compounds other than *p*-methoxyphenyldimethylsilane were examined only by nmr. The disappearance of the one-proton septuplet at *ca.* τ 5.6 coupled with the appearance of a six-proton singlet at *ca.* τ 9.9 was regarded as sufficient to ensure that the same reaction was occurring for all compounds.

The product analysis procedure for the thallium triacetate reaction was identical with that for mercuric acetate. The yield of *p*-methoxyphenyldimethylsilyl acetate is essentially quantitative (>95% by nmr).

Registry No.—Mercuric acetate, 1600-27-7; thallium triacetate, 2570-63-0; aryldimethylsilane (aryl = *p*-CH_3O), 1432-38-8; aryldimethylsilane (aryl = *p*-CH_3), 1432-39-9; aryldimethylsilane (aryl = *p*-Cl), 1432-31-1; aryldimethylsilane (aryl = *m*-Cl), 2083-13-8; aryldimethylsilane (aryl = *p*-CF_3), 19254-78-5.

(14) A referee suggests that a concerted reaction involving an electrophilic attack of the metal on the hydrogen atom of the silicon–hydrogen bond and nucleophilic attack of the acetate group on silicon also should be considered. Such a process could be consistent with the observed ρ. At the present time there is no physical probe extant which would provide a distinction between these mechanisms. Chemical support of our mechanism must await the isolation of suitable organometallic derivatives of the type proposed herein.

(15) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **83**, 4478 (1961).

(16) M. C. Harvey, W. H. Nebergall, and J. S. Peake, *ibid.*, **76**, 4555 (1954).

(17) R. J. Ouellette and B. G. van Leuwen, *ibid.*, **91**, 7061 (1968).

Hybridization Effects in Fluorocarbons

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Hybridization calculations based on experimental bond-angle data show that the carbon hybrid atomic orbitals in double bonds, carbonyls, and cyclopropyl groups containing a *gem*-difluoro group are not sp^2 hybridized as formerly thought, but are sp^3 hybridized. This is also true of the trifluoromethyl free radical. This new understanding of the hybridization in fluorocarbons makes possible an explanation of the unusual chemical reactivity of perfluoroolefins and perfluorocyclopropanes. While the carbon HAOs used in forming the C—F bonds in these compounds are sp^3 hybridized as in saturated fluorocarbons, with the C—F bonds having approximately the same bond energies, those used in forming the C—C bonds have less p character than in the corresponding hydrocarbons.

The unique chemical reactivity and unusual physical properties of fluorocarbons, due to the high electronegativity of fluorine, places these compounds in a class of their own. A theoretical understanding of some of their behavior is still lacking, however. In this paper a localized molecular orbital (LMO) theory is developed to explain the chemical reactivity of strained fluorocarbon systems containing *gem*-difluoro groups.

Bent has proposed that a rehybridization occurs at carbon centers when a substituent is replaced by one of differing electronegativity, and that more p character tends to be concentrated in carbon orbitals directed toward more highly electronegative groups.[1] On the basis of this theory one would expect that the carbon hybrid atomic orbitals (HAO's) used in forming C—F bonds should have more p character than those used in forming C—H bonds, and that the HAO's used in forming the C—C bonds in fluorocarbons should have more s character. If such hybridization changes are dramatic enough it would be expected that the effects would show up in the chemical reactivity of fluorocarbons.

Hybridization Measurement.—Numerous approaches to the calculation of hybridization at carbon centers have been taken. Perhaps the most straightforward approach to a measure of hybridization is the relationship with bond angles. The states of hybridization of carbon centers with local C_{3v}, C_{2v}, and C_s symmetry can be calculated from known bond angles,[2-4] and these procedures have been used herein. Bond-angle data can also be used to calculate the state of hybridization at trigonally, though not equivalently, hybridized carbon centers, for example, in unsymmetrically substituted olefins.[5]

During the period when good experimental bond-angle data for a multitude of compounds was becoming available from microwave and electron diffraction work it was suggested that the nmr spin–spin coupling constant J^{13}_{C-H} offered a direct measure of the hybridization of the carbon HAOs used in forming the C—H bonds in organic compounds.[6-8] The states of carbon hybridization in halomethanes calculated from J^{13}_{C-H} were found to be greatly different from those calculated from bond-angle data, and on this basis it was largely concluded that bond angles did not serve as a measure of hybridization.[7a] Recent work, however, has shown that electronegative substituents bonded to a carbon center can change the effective nuclear charge at that carbon as seen by a proton also bonded to that center without changing the carbon hybridization.[9-12] Because of this fact, in those cases where heteroatoms are bonded to carbon, as in halomethanes, J^{13}_{C-H} cannot be taken as a measure of the per cent s character in the C—H bond(s). It has also been observed that J^{13}_{C-F} is not a measure of the carbon hybridization in fluorocarbons.[7b]

There is one piece of experimental evidence which does not appear to be consistent with simple bond-angle–hybridization relationships, and that is the fact that in methylene chloride both the H—C—H and Cl—C—Cl bond angles are greater than 109°28′. The Cl—C—Cl bond angle was found by Myers and Gwinn to be 111°47′ while the H—C—H angle is 112°58′.[13] Nuclear quadrupole studies by Flygare and Gwinn showed that the Cl—C—Cl bonds are not bent.[14] For this Cl—C—Cl bond angle the assumption of normalized, orthogonal carbon HAO's requires that the H—C—H bond angle be 107°17′. The data for methylene fluoride fits with theoretical bond angles much better. The experimental values for the F—C—F and H—C—H bond angles are 108°17′ ± 6′ and 111°52′ ± 25′, respectively.[15] For this F—C—F angle the predicted H—C—H angle is 110°42′.

To the extent that the bonding at carbon centers can be described by normalized, orthogonal HAO's formed from linear combinations of atomic orbitals using a limited basis set of carbon 2s, $2p_x$, $2p_y$, and $2p_z$ AO's the bond-angle–hybridization relationship is valid. Since this assumption has served as a very useful and valuable basis for the interpretation of structure and reactivity in organic chemistry, it seemed worthwhile to apply the bond-angle–hybridization relationships to fluorocarbons, keeping in mind possible limitations in the assumption.

Hybridization in Fluorocarbons.—Table I lists the experimentally determined bond angles and the corresponding hybridization states, calculated by afore-

(1) H. A. Bent, *J. Chem. Phys.*, **33**, 1258, 1259, 1260 (1960).
(2) P. Tarkington, *ibid.*, **19**, 528 (1951).
(3) W. H. Flygare, *Science*, **140**, 1179 (1963).
(4) W. A. Bernett, *J. Chem. Educ.*, **44**, 17 (1967).
(5) C. A. Coulson, "Victor Henri Commemoratif Volume," Maison Desoer, Liege, 1947–1948, p 15.
(6) J. Shoolery, *J. Chem. Phys.*, **31**, 1427 (1959).
(7) (a) N. Muller and D. E. Pritchard, *ibid.*, **31**, 768, 1471 (1959); (b) N. Muller and D. T. Carr, *J. Phys. Chem.*, **67**, 112 (1963).
(8) C. Juan and H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2198 (1962).
(9) D. M. Grant and W. M. Litchman, *J. Amer. Chem. Soc.*, **87**, 3994 (1965).
(10) W. J. Considine, *J. Chem. Phys.*, **42**, 1130 (1965).
(11) J. E. Huheey, *ibid.*, **45**, 405 (1966).
(12) A. W. Douglas, *ibid.*, **45**, 3465 (1966).
(13) R. J. Myers and W. D. Gwinn, *ibid.*, **20**, 1420 (1952).
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(15) D. R. Lide, Jr., *J. Amer. Chem. Soc.*, **74**, 3548 (1952).

TABLE I
BOND ANGLES AND CARBON HYBRIDIZATION IN TRIFLUOROMETHYL AND METHYL GROUPS

	∠FCF	C—F, sp	∠HCH	C—H, sp	C—F, Å	Ref
CF_3CH_3	107°18′ ± 1°	3.36			1.335 ± 0.005	*a*
$CF_3C{\equiv}CH$	107°30′ ± 1°	3.33			1.335 ± 0.01	*b*
$CF_3C{\equiv}CCF_3$	107°30′ ± 1°	3.33			1.34 ± 0.02	*c*
$CF_3C{\equiv}CCH_3$	107°32′	3.32	108°44′	3.11	1.340	*d*
CF_3CF_3	108° = 1°30′	3.24			1.330 ± 0.015	*e*
CF_3I	108°24′ ± 1°36′	3.17			1.34 ± 0.02	*f*
CF_3CN	108°30′ ± 1°30′	3.15			1.335	*g*
CF_3Cl	108°36′ ± 24′	3.14			1.328 ± 0.002	*h*
CF_3H	108°48′ ± 45′	3.10		2.72	1.332 ± 0.008	*i*
CF_4	109°28′	3.00			1.323 ± 0.005	*j*
CH_3SiH_3			107°42′ ± 30′	3.29		*k*
CH_3GeH_3			108°25′ ± 30′	3.17		*l*
CH_3CH_3			109°45′	2.96		*m*
CH_3F		3.25	110°0′ ± 3′	2.92	1.3852 ± 0.0005	*n*
CH_3Cl			110°30′ ± 30′	2.86		*o*
CH_3Br			111°12′ ± 30′	2.76		*o*
CH_3I			111°24′ ± 30′	2.74		*o*

[a] W. F. Edgell, G. B. Miller, and J. W. Amy, *J. Amer. Chem., Soc.*, **79**, 2391 (1957). [b] J. N. Shoolery, R. G. Shulman, W. F. Sheehan, V. Schomaker, and D. M. Yost, *J. Chem. Phys.*, **19**, 1364 (1951). [c] W. F. Sheehan, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **74**, 4468 (1952). [d] V. M. Laurie, *J. Chem. Phys.*, **30**, 1101 (1959). [e] J. L. Brandt and R. L. Livingston, *J. Amer. Chem. Soc.*, **76**, 2096 (1954). [f] C. Wong and V. Schomaker, *J. Chem. Phys.*, **28**, 1010 (1958). [g] M. D. Danford and R. L. Livingston, *J. Amer. Chem. Soc.*, **77**, 2944 (1955). [h] L. S. Bartell and L. O. Brockway, *J. Chem. Phys.*, **23**, 1860 (1955). [i] S. N. Ghosh, R. Trambarulo, and W. Gordy, *ibid.*, **20**, 605 (1952). [j] C. G. Thornton, *Dissertation Abstr.*, **14**, 604 (1954). [k] R. W. Kilb and L. Pierce, *J. Chem. Phys.*, **27**, 108 (1957). [l] W. V. Laurie, **30**, 1210 (1959). [m] H. C. Allen, Jr., and E. K. Plylor, *ibid.*, **31**, 1062 (1959). [n] O. R. Gilliam, H. D. Edwards, and W. Gordy, *Phys. Rev.*, **76**, 195 (1949). [o] S. L. Miller, L. C. Aamodt, G. Dousmanis, C. H. Townes, and J. Kraitchman, *J. Chem. Phys.*, **20**, 1112 (1952).

mentioned methods,[2-5] for a number of methyl- and trifluoromethyl-containing compounds. Several interesting features are observed. In the case of trifluoromethyl groups it appears that the carbon HAO's used in forming the C—F bonds do have slightly more p character than those used in forming the C—H bonds in methyl groups, ranging from $sp^{3.00}$ to $sp^{3.36}$. There are, however, several examples where the HAO's used in forming the C—H bonds in methyl groups have a hybridization in this range when a more electropositive silicon or germanium atom is also bonded to the carbon. Second, it is observed that the hybridization of the carbon HAO's used in forming the C—F bonds in the series CF_4, CF_3H, CF_2H_2, and CFH_3 does show increasing p character ($sp^{3.00}$, $sp^{3.10}$, $sp^{3.18}$, and $sp^{3.25}$), as suggested by Bent to explain the increasing C—F bond length in this series. The C—F bond lengths will be influenced by the state of hybridization of the carbon HAO and the fluorine bonding HAO (which need not be the same in each case) and also by nonbonded interactions which will affect the degree bond orbital overlap. In general, although there appears to be slightly more p character in the carbon HAO's used in forming C—F bonds at tetrasubstituted carbons, they appear to be essentially sp^3 hybridized. Symmetry requires that the HAO's of carbon used in forming the C—F bonds in tetrafluoromethane be sp^3 hybridized.

Table II shows the bond angles and hybridization states of a number of methylene- and difluoromethylene-containing compounds. The most striking and significant conclusion to be drawn from this table is that *the carbon HAO's used in forming the C—F bonds in gem-difluoro groups remain essentially sp^3 hybridized even when that carbon center is part of a double bond, carbonyl group, or three-membered ring.* This conclusion is supported by the data on carbonyl fluoride, 1,1-difluoroethylene, tetrafluoroethylene, and difluorodiazirine. It is seen that in the corresponding hydrocarbons the carbon HAO's used in forming the C—H bonds are essentially sp^2 hybridized, as has been traditionally accepted for olefins, carbonyls, and cyclopropanes. It is also observed in the trifluoromethyl free radical that the carbon HAO's used in forming the C—F bonds are nearly sp^3 hybridized, in contrast to the approximately sp^2 hybridization of the HAO's used in forming the C—H bonds in the planar or nearly planar methyl free radical. It is worth pointing out in the case of all of the compounds in Table II containing *gem*-difluoro groups (except CF_2H_2) that within experimental error the C—F bond lengths are the same as in tetrafluoromethane and hexafluoroethane. This, when coupled with carbon sp^3 HAO's in each case, suggests that the C—F bonds in these compounds probably have about the same bond energy.

No firm conclusions can be drawn about the carbon HAO's used in forming the C—F bond at unsaturated centers bearing only a single fluorine substituent (see Table III) other than that the amount of p character is greater than that in sp^2 HAO's, ranging from $sp^{2.5}$ in fluoroethylene and *cis*-1,2-difluoroethylene to $sp^{3.32}$ in CH_3COF and $sp^{3.50}$ in HCOF. It should be pointed out in the case of hexafluorobenzene that symmetry requires the carbon HAO's used in forming the C—F bonds to be sp^2 hybridized or the C—C σ bonds to be bent.

Chemical Reactivity of Perfluoro Olefins.—The chemistry of fluoro olefins shows a number of unusual effects when compared with the behavior of the corresponding protonated olefins. Much of this work has been reviewed by Roberts and Sharts,[16] but a few examples will be cited. Tetrafluoroethylene (TFE) is observed to dimerize thermally to give octafluorocyclo-

(16) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 1 (1962).

TABLE II

BOND ANGLES AND HYBRIDIZATION IN DIFLUOROMETHYLENE AND METHYLENE GROUPS

	∠FCF	C—F, sp	∠HCH	C—H, sp	C—F, Å	Ref
CF_2H_2	108°17′ ± 6′	3.18	111°52′ ± 25′	2.83	1.358 ± 0.001	*a*
CF_2Cl_2	109°30′ ± 3°	3.00			1.33 ± 0.02	*b*
c-C_4F_8	109°30′ ± 3°	3.00			1.33 ± 0.02	*c*
CF_2=O	108°0′ ± 30′	3.24			1.312 ± 0.01	*d*
CF_2=CH_2	109°18′ ± 24′	3.03	121°48′	1.89	1.321 ± 0.005	*e, f*
CF_2=CF_2	110° ± 2°	2.92			1.33 ± 0.02	*g*
CF_3·	111°6′	2.78				*h, i*
c-CF_2N_2	111°50′ ± 31′	2.69			1.315 ± 0.004	*j*
c-C_3H_4			114°42′ ± 10′	2.39		*k*
c-C_3H_6			115°12′ ± 1°	2.35		*l*
c-CH_2N_2			117° ± 2°	2.20		*m*
CH_2=CH_2			117°12′ ± 36′	2.19		*n*
CH_2=C=CH_2			118°12′ ± 12′	2.12		*o*
CH_2=O			119°20′ ± 30′	2.04		*p*
CH_3·			~120°	2.00		*q, r*
CH_2=C=O			121°35′	1.91		*s*

[a] Reference 15. [b] R. L. Livingston and D. H. Lyon, *J. Chem. Phys.*, **24**, 1283 (1956). [c] H. P. Lemaire and R. L. Livingston, *J. Amer. Chem. Soc.*, **74**, 5732 (1952). [d] V. W. Laurie and D. T. Pence, *J. Chem. Phys.*, **37**, 2995 (1962). [e] W. F. Edgell, P. A. Kinsey, and J. W. Amy, *J. Amer. Chem. Soc.*, **79**, 2691 (1957). [f] W. V. Laurie and D. T. Pence, *J. Chem. Phys.*, **38**, 2693 (1963). [g] Reference 37. [h] R. W. Fessenden and R. H. Schuler, *ibid.*, **43**, 2704 (1965). [i] M. T. Rogers and L. D. Kispert, **46**, 3193 (1967). [j] J. L. Hencher and S. H. Bauer, *J. Amer. Chem. Soc.*, **89**, 5527 (1967). [k] P. H. Kasai, R. J. Myers, D. F. Eggers, Jr., and K. B. Wiberg, *J. Chem. Phys.*, **30**, 512 (1959). [l] O. Bastiansen, F. N. Fritsch, and K. Hedberg, *Acta Cryst.*, **17**, 538 (1964). [m] L. Pierce and V. Dobyns, *J. Amer. Chem. Soc.*, **84**, 2651 (1962). [n] L. S. Bartell, E. A. Roth, C. D. Hollowell, K. Kuchitso, and J. E. Young, Jr., *J. Chem. Phys.*, **42**, 2683 (1965). [o] A. G. Maki and R. A. Toth, *J. Mol. Spectry.*, **17**, 136 (1965). [p] M. G. Krishna Pillai, *J. Annamallai Univ.*, **25**, 126 (1964). [q] T. Cole, H. O. Pritchard, N. R. Davidson, and H. M. McConnell, *Mol. Phys.*, **1**, 406 (1958). [r] L. Andrews and G. C. Pimentel, *J. Chem. Phys.*, **47**, 3637 (1967). [s] A. P. Cox, L. F. Thomas, and J. Sheridan, *Spectrochim. Acta*, **15**, 542 (1959).

TABLE III

BOND ANGLES AND CARBON HYBRIDIZATION IN FLUOROMETHYLENE GROUPS

	∠FCC	∠FCH	∠FCO	C—F, sp	C—F, Å	Ref
CH_2=CHF	120°54′	115°24′		2.53	1.334 ± 0.002	*a*
cis-CHF=CHF	122°	114°		2.49	1.335 ± 0.002	*b*
CH_3CF=O	110°44′ ± 1°		121°22′ ± 1°	3.32	1.348 ± 0.015	*c*
CHF=O		109°54′ ± 3°	122°46′ ± 30′	3.50	1.338 ± 0.005	*d*

[a] B. Bak, D. Christensen, L. Nygard, and J. R. Anderson, *Spectrochim. Acta*, **13**, 120 (1958). [b] See footnote *f*, Table II. [c] L. Pierce and L. C. Krishner, *J. Chem. Phys.*, **31**, 875 (1959). [d] R. F. Miller and R. F. Curl, Jr., *ibid.*, **34**, 1847 (1961).

butane,[17] with a standard heat of reaction of −50 kcal/mol,[18] while the corresponding reaction with ethylene (which has a theoretical heat of reaction of −18.7 kcal/mol, *vide infra*) has not been observed. Hexafluoro-1,3-butadiene undergoes thermal cyclization to form hexafluorocyclobutene,[19] while in the protonated analog the equilibrium lies on the side of the more stable 1,3-butadiene.[20] Perfluoropropene, chlorotrifluoroethylene, and 1,1-dichloro-2,2-difluoroethylene also dimerize thermally to four-membered-ring systems.[16] Neither of the 1,2-difluoroethylenes nor 1,1-difluoroethylene has been observed to dimerize. TFE also codimerizes with many nonfluorinated olefins, often more readily than it dimerizes with itself.[16] The heats of addition of halogens and halogen acids to perfluoroolefins are observed to be more exothermic than in the case of the corresponding hydrocarbon systems.[21] The heat of polymerization of TFE is 17 kcal/mol more exothermic than that of ethylene.[22]

It is clearly seen that the *gem*-difluoro group (CF_2=), or more specifically the group (CF_2=CF–), has a very marked effect on the position of olefin–cyclobutane equilibria. The greater exothermicity in going from C=C bonds to C—C bonds in fluorocarbon systems is large enough to offset the effects of ring strain. Two possible alternative explanations for this behavior have been clearly summarized by Schlag and Peatman,[23] namely, that the instability of the fluoro olefin system is due to (a) the C—F bonds being weaker than those in saturated systems (because the carbon HAO's are sp^2 hybridized) or (b) the C=C bond is weaker than a normal C=C double bond.

Cox has suggested that the double-bond strength is the same in fluorinated and nonfluorinated olefins, but that the C—F bonds in perfluoro olefins are weaker than in saturated fluorocarbons.[24] Peters has also made this assumption, theorizing that the C—F bond should be weaker because the fluorine should be less able to remove p electrons from an sp^2-hybridized carbon HAO than from an sp^3-hybridized carbon HAO;[25] *i.e.*, he assumed *a priori* that the carbon HAO's in fluoro olefins are sp^2 hybridized, although at one point in his argument he envisions nonorthogonal carbon HAO's.

Hine has suggested that on the basis of double bond–

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no bond resonance the C—F bonds attached to an unsaturated carbon should be weaker than those attached to a saturated carbon atom.[26] This also assumes, however, that the unsaturated carbon is sp^2 hybridized and not sp^3 hybridized.

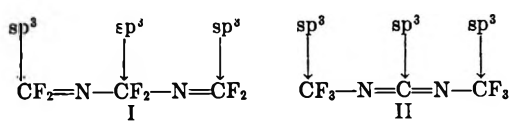
Schlag and Kaiser have concluded from a study of the heat of *cis–trans* isomerization of perfluorobutene-2 that the low activation energy, relative to butene-2, was due to the C=C bond being weaker in the perfluoro case.[27] They argued that, if the strain were in the C—F bonds rather than in the C=C bond, the activation energies should be about the same.

LMO Theory of Strained Fluorocarbons.—From the available structural data it appears that *the attachment of two fluorines to normally sp^2-hybridized carbon centers changes the hybridization to sp^3*. Such a hybridization change in olefins and cyclopropanes can be visualized in either of two equivalent LMO descriptions. For every possible σ—π bond description of the double bond there is an *equivalent* bent bond LMO description,[28] and for every Walsh-type[29] description of the cyclopropyl ring there is an *equivalent* bent bond LMO description.[4] The hybridization in ethylene is essentially sp^2, *i.e.*, three sp^2 HAO's and an unhybridized p orbital at each carbon in the σ—π bond description or, equivalently, two sp^2 HAO's and two sp^5 HAO's at each carbon in the equivalent bent bond description (the sp^5 HAO's used in forming the C=C bond). The angle between two sp^5 HAOs is 101°32′.[4] It is here suggested that the hybridization of the carbon HAO's in tetrafluoroethylene, and in other olefins containing *gem*-difluoro groups, is essentially sp^3, *i.e.*, two sp^3 HAO's (used in forming the C—F bonds) and an sp HAO along with any unhybridized p orbital (the former used in forming the σ bond and the latter the π bond), or, equivalently, four sp^3 HAO's at each carbon in the bent bond LMO description.[28b] The angle between two sp^3 HAO's is, of course, 109°28′.

From available thermochemical data it is possible to calculate the strain energies in tetrafluoroethylene and perfluorocyclobutane. Using a value of −98.1 kcal/mol for the standard heat of formation of a saturated $-CF_2-$ group,[30–32] the strain energy in tetrafluoroethylene is found to be 41.2 kcal/mol, while that in ethylene is 22.39 kcal/mol.[32,33] From the heat of formation of perfluorocyclobutane[18,34] its strain energy is found to be 32.0 kcal/mol, compared with 26.2-kcal/mol strain energy in cyclobutane.[35] With both the completely fluorinated and protonated four-membered rings having sp^3 carbon hybridization similar strain energies are not too surprising. A difference of about 3.9 kcal/mol would be expected based on the differences in the potential barrier to rotation in ethane and perfluoroethane.[35,37]

From a theoretical standpoint it would be expected that an sp^3-hybridized ethylene would be more "strained" than ethylene with sp^2–sp^5 hybridization. The increased C—H bond strength of the sp^2 C—H bonds relative to sp^3 C—H bonds [the overlap integrals using STO's are 0.734 (1.084 A) and 0.678 (1.107 Å), respectively] more than offsets the increased bond strength which would result from sp^3 bent C=C bonds rather than sp^5 bent C=C bonds [S = 0.454 and 0.449 (1.333 Å), respectively, compared with 0.650 (1.536 Å) for the sp^3 C—C bond in ethane]. Tetrafluoroethylene, having essentially sp^3 hybridization, would be expected to show a larger strain energy than ethylene, even though its C=C bent bonds should be slightly stronger than those of ethylene (the C=C bond length appears to be equal to, or slightly less than that in ethylene[37]), because its C—F bonds have not, because of the effects of Bent's rule, undergone the sort of strengthening that C—H bonds do relative to a saturated, straight-chain analog. While ethylene has stronger C—H bonds and weaker C—C bonds than $\{CH_2—CH_2\}_n$, tetrafluoroethylene can be expected to have C—F bonds which have essentially the same bond energy as those in $\{CF_2—CF_2\}_n$, and C—C bonds that are weaker. An sp^2–sp^5-hybridized TFE would be expected to have *both* weaker C—F and C=C bonds than the sp^3 case. The decrease in p character in the carbon HAO's forming the C—F bond in going from sp^3 to sp^2 would presumably lead to a decrease in the ionic contribution to the C—F bond.[1]

The driving force for the dimerization of TFE to perfluorocyclobutane, and for the dimerization and cycloaddition reactions of the CF_2=CF– group in general, can be seen to be the relief of double-bond strain, C—F bond strength remaining essentially constant. In the case of ethylene, while dimerization would lead to relief of double-bond strain, it would also lead to an increase in C—H bond "strain," or decrease in C—H bond energy, making this reaction less favorable than in the fluorinated system. The facile fluoride ion-catalyzed isomerization of perfluoro-2,4-diazapenta-1,4-diene (I) to the corresponding bis(trifluoromethyl)carbodiimide (II)[38] can also be understood from a hybridization standpoint. In going from I to II



there are in the bent bond description no hybridization changes at the carbons and, therefore, no increase in double-bond strain (other factors equal). In the protonated analogs there would be increased strain in going from the bisazomethine (with sp^2–sp^5 hybridized CH_2= groups) to the carbodiimide because of the hybridization changes. An analogous rearrangement has been reported for 1,4-perfluoropentadiene.[39]

(26) J. Hine, *J. Amer. Chem. Soc.*, **85**, 3239 (1963).
(27) E. W. Schlag and E. W. Kaiser, Jr., *ibid.*, **87**, 1171 (1965).
(28) (a) G. G. Hall and J. Lennard-Jones, *Proc. Roy. Soc.* (London), **A205**, 357 (1951). (b) R. S. Mulliken, *Tetrahedron*, **6**, 68 (1959).
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(30) W. D. Good, D. R. Douslin, D. W. Scott, A. George, J. L. Lacina, J. P. Dawson, and G. Waddington, *J. Phys. Chem.*, **63**, 1133 (1959).
(31) E. S. Domalski and G. T. Armstrong, *J. Res. Natl. Bur. Std.*, **71A**, 105 (1967).
(32) JANAF Thermochemical Tables, D. R. Stull Ed., U. S. Government Printing Office, Washington, D. C., 1967.
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(36) (a) K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951); (b) E. L. Pace, *J. Chem. Phys.* **16**, 74 (1948).
(37) J. A. Young, *Dissertation Abstr.*, **16**, 460 (1956); T. T. Broun and R. L. Livingston, *J. Amer. Chem. Soc.*, **74**, 6084 (1952).
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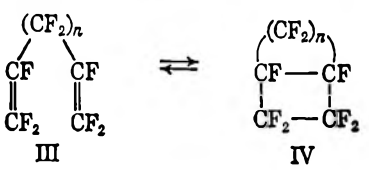
(39) W. T. Miller, W. Frass, and P. R. Resnick, *J. Amer. Chem. Soc.*, **83**, 1767 (1961).

A hybridization situation similar to that between TFE and ethylene may exist between cyclopropane and perfluorocyclopropane. While sp^2–sp^5 hybridization serves as a model for cyclopropane,[4] the carbons of perfluorocyclopropane may be more nearly sp^3 hybridized. The C—C bonds in perfluorocyclopropane would be bent by about 24°44′, while those in cyclopropane are bent by about 20°46′. Although the C—C bonds in perfluorocyclopropane would still (based on overlap integral calculations assuming equal intraatomic distances) be slightly stronger than in cyclopropane the C—F bonds would not be strengthened as would the C—H bonds. Perfluorocyclopropane would be expected to show a larger strain energy than cyclopropane.

Chemical Reactivity of Perfluorocyclopropanes.—Although little is known of the chemistry of perfluorocyclopropanes, Mitsch and Neuvar have studied the kinetics of the thermal isomerization of perfluorovinylcyclopropane, which rearranges to perfluorocyclopentene.[40] The activation energy for this isomerization was found to be 15.0 kcal/mol lower than for the corresponding hydrocarbon. These workers attributed this difference to the added strain in the perfluoro system. Atkinson and McKeagan have studied the thermal decomposition of perfluorocyclopropane to TFE and $:CF_2$ and observed this compound to be much less stable than cyclopropane.[41] Using their value of −31 kcal/mol for the heat of reaction and the heats of formation for $:CF_2$[42] and TFE,[32] the strain energy in perfluorocyclopropane is found to be 68.6 kcal/mol, compared with 27.5 kcal/mol in cyclopropane.[35] These results suggest that at temperatures below which $:CF_2$ is split out (*ca.* 250°) ring-opening reactions of perfluorocyclopropanes may be very facile; that, unlike cyclopropanes which undergo both substitution and addition reactions, perfluorocyclopropanes may only undergo addition reactions; and that because of the large strain energy perfluorocyclopropane may behave similarly to perfluoroolefins in undergoing dimerization, addition, and cycloaddition reactions. Perfluorocyclopropane reportedly reacts with hydrogen fluoride to give the 1,3-ring-opened addition product.[43]

A qualitative estimation of strain energies suggests for III that only in the case of $n = 1$ would the thermal



III IV

equilibrium lie on the side of the diene. In the case of $n = 0$ [20] and $n = 2$ [44] the equilibrium has been observed to lie on the side of the cyclic isomer. In view of the above high strain energies such compounds as perfluorocyclopropene, perfluorobicyclo[1.1.0]butane, and perfluorospiropentane should be highly strained and very reactive. The synthesis of 1,2-bis(trifluoromethyl)-3,3-difluorocyclopropene and 1,3-bis(trifluoromethyl)-2,2,4,4-tetrafluorobicyclobutane has been reported but no data is available on their strain energies.[45]

Mitsch and Neuvar have also compared the uv spectra of perfluorobutadiene, perfluorocyclopropylethylene, and perfluoropropene and concluded that the perfluorocyclopropyl moiety has π-electronic character and can enter into conjugation with unsaturated systems. Additional evidence on this point would be desirable, however. The Walsh descriptions suggest no difference in the relative conjugative abilities of the cyclopropyl and perfluorocyclopropyl groups. On the other hand the bent bond descriptions suggest that the sp^5 HAO's of the cyclopropyl ring should overlap more effectively with adjacent unsaturated groups than would the sp^3 HAO's in the perfluorocyclopropyl ring. Transformation of the Walsh description of perfluorocyclopropane to a SO description, *via* the method of Hall and Lennard-Jones,[28a] shows that the highest occupied SO's in the plane of the perfluorocyclopropyl ring have less p character than do those in cyclopropane. It should be remembered, however, that these are not "exact" quantum mechanical descriptions of the two-ring systems and based on bond angles they are probably more similar in hybridization than the above descriptions indicate. There are similar differences in the predicted conjugative abilities of the vinyl and perfluorovinyl groups.

Conclusions

In conclusion, it can be said that the widely accepted theory of sp^2-hybridized carbon HAO's in double bond, carbonyl, and cyclopropyl groups breaks down when they contain a *gem*-difluoro group. In such cases the high electronegativity of fluorine causes the hybridization of the carbon HAO's of the *gem*-difluoro group to be essentially sp^3. With these views in mind the chemical reactivity of resultant highly strained fluorocarbon systems becomes much more readily understandable.

Acknowledgment.—The author would like to thank Mr. J. W. Millin for making it possible to carry out the bond-angle–hybridization calculations with the aid of General Electric 225 computer time-sharing system, Dr. R. A. Mitsch for stimulating his interest in fluorocarbon chemistry, and Drs. J. G. Erickson and G. V. D. Tiers for reading the manuscript and making helpful suggestions. The author is also indebted to a referee for several beneficial suggestions.

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(43) J. Harmon, U. S. Patent 2,404,374 (1946).
(44) A. H. Fainberg and W. T. Miller, *J. Amer. Chem. Soc.*, **79**, 4170 (1957).
(45) W. Mahler, *ibid.*, **84**, 4600 (1962).

Synthesis and Cleavage Reactions of Some Dibenzophosphole Derivatives

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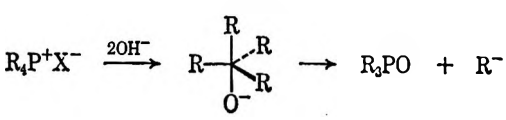
Several heterocyclic phosphine oxides and phosphonium salts have been prepared and cleaved with sodium hydroxide. Cleavage of 5-benzyl-5-phenyldibenzophospholium chloride (III) and 5-benzyl-5-methyldibenzophospholium iodide (VI) gave 5-phenyldibenzophosphole 5-oxide (II) and 5-methyldibenzophosphole 5-oxide, respectively. In these cases, the cleavage of the benzyl group appears to proceed from a position not colinear with the phosphorus–oxygen bond in the trigonal-bipyramidal intermediate. Cleavage of 5-phenyldibenzophosphole 5-oxide (II) and 5-benzyldibenzophosphole 5-oxide (V) led to exclusive ring opening for II and preferential ring opening for V. The unexpected instability of the heterocyclic ring in V suggests that this cleavage reaction does not proceed *via* a trigonal-bipyramidal intermediate but through a mechanism similar to that of an SN2 reaction.

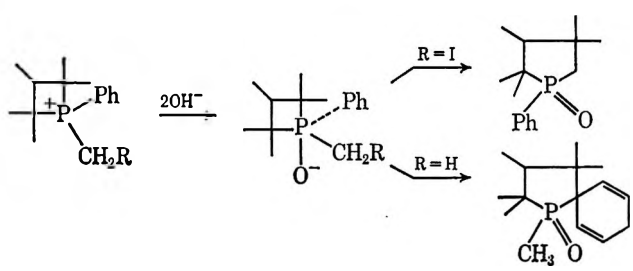
There has been considerable interest in recent years in the cleavage of various bonds in heterocyclic phosphorus compounds. The generalizations concerning both the rate and direction of cleavage for acyclic systems are often altered for cyclic compounds. Westheimer[1] has explained how ring strain can enhance the rate of hydrolysis of cyclic phosphate esters even when ring opening does not occur. This increased rate is attributed to relief of strain in going from a tetrahedral phosphorus atom to a trigonal-bipyramidal intermediate. Similarly, trigonal-bipyramidal intermediates have been proposed for the cleavage of phosphonium salts with hydroxide ion. Kinetic data,[2] which show the reaction to be first order in phosphonium salt and second order in hydroxide ion, are consistent with Scheme I. It has been shown that the

SCHEME I



carbanion is lost from the apical position colinear with the phosphorus–oxygen bond by noting that cleavage of methylethylphenylbenzylphosphonium iodide proceeds with inversion of configuration at phosphorus.[3] There appear to be two rules governing the cleavage of phosphonium salts: (1) the group that is lost is the one that is capable of forming the most stable carbanion,[4] and (2) the group is lost from the apical position of the trigonal-bipyramidal intermediate. For acyclic compounds, both conditions can always be met. Two reported ring expansions[5] of four-membered phosphetanium salts indicate that the requirement that cleavage should occur at the apical position is important. In these cases, because of ring strain, the ring must occupy equatorial–axial positions in the intermediate. In each case ring expansion occurs with cleavage of the ring from the apical position even though this means formation of the least stable carbanion. This is illustrated in Scheme II. More recently,[6] it has been

SCHEME II



shown that, when R = phenyl, the benzyl group cleaves with retention of configuration at phosphorus. This shows that, when the difference in carbanion stabilities is great enough, then the group may be lost from a position not colinear with the phosphorus–oxygen bond.

For several years we have been studying the cleavage of the carbon–phosphorus bond in compounds in which the phosphorus atom is a member of a heterocyclic system. The present paper describes the preparation and cleavage of several phosphine oxides and phosphonium salts of the 5-dibenzophosphole ring system. The method of preparation is shown in Scheme III. Tetraphenylphosphonium bromide was prepared by the method of Horner and coworkers[7] and converted into 5-phenyldibenzophosphole (I) with lithium diethylamide.[8,9] Cleavage of I with lithium to form the lithium phosphide and phenyllithium has been reported by Britt and Kaiser.[10] Our reaction scheme from I to IV is analogous to a reported method[11] for conversion of triphenylphosphine into diphenylbenzylphosphine. Compounds III, V, and VI have not been previously

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(2) M. Zanger, C. A. VanderWerf, and W. E. McEwen, *J. Amer. Chem. Soc.*, **81**, 3806 (1959).

(3) A. Bladé-Font, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **82**, 2396 (1960).

(4) For a summary, see D. W. Allen, I. T. Millar, and F. G. Mann, *J. Chem. Soc., C*, 1872 (1967).

(5) S. E. Fishwick, J. Flint, W. Hawes, and S. Trippett, *Chem. Commun.*, 1113 (1967).

(6) W. Hawes and S. Trippett, *ibid.*, 295 (1968).

(7) L. Horner, G. Mummeathey, M. Moser, and P. Beck, *Chem. Ber.*, **99**, 2782 (1966).

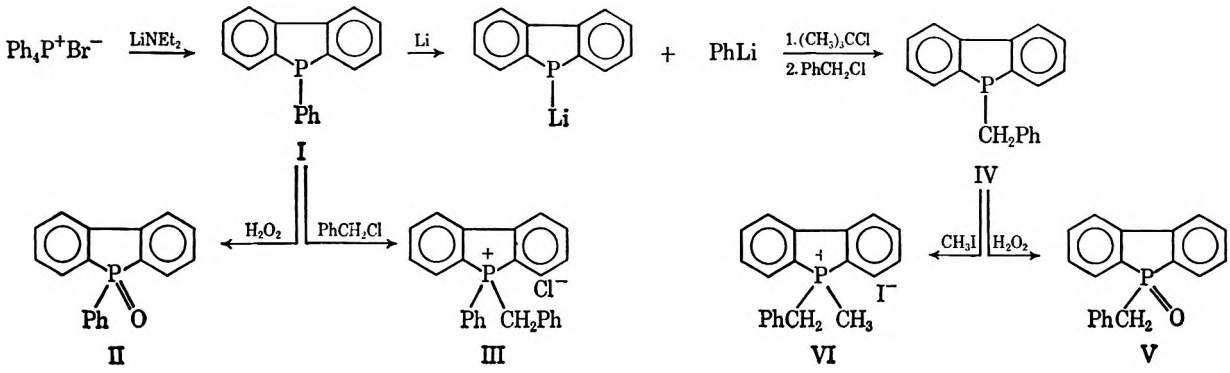
(8) H. Hoffman, *ibid.*, **95**, 2563 (1962).

(9) We have found that this reaction proceeds in the same way with the phosphonium chloride, but, when the iodide is used, only triphenylphosphine is formed. An attempt to extend this reaction to the preparation of 5-phenyldibenzoarsole and 5-phenyldibenzostibole by treatment of tetraphenylarsonium chloride and tetraphenylstibonium bromide with lithium diethylamide led to triphenylarsine and triphenylstibine, respectively.

(10) A. D. Britt and E. T. Kaiser, *J. Org. Chem.*, **31**, 112 (1966).

(11) A. M. Aguiar, J. Beisler, and A. Mills, *ibid.*, **27**, 1001 (1962).

SCHEME III

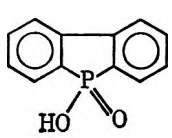


described. Compound IV, prepared by another procedure, was reported during the course of this work.[12]

Horner and coworkers[13] have shown that the fusion of a tertiary phosphine oxide with sodium hydroxide leads to cleavage of a carbon–phosphorus bond. Their

$$R_2R'PO + NaOH \longrightarrow RR'PO_2Na + RH$$

findings indicate that the group that is preferentially cleaved is the one which can form the more stable carbanion. Thus, benzyl is cleaved more readily than phenyl, while phenyl is cleaved in preference to tolyl or alkyl. These results suggested to us that it should be possible to prepare heterocyclic phosphinic acids by the preferential cleavage of the exocyclic carbon–phosphorus bond present in an appropriate heterocyclic phosphine oxide. However, when 5-benzyldibenzophosphole 5-oxide (V) was allowed to react with sodium hydroxide at 200°, we isolated from the reaction mixture a 55% yield of 2-biphenylylbenzylphosphinic acid and only 23% 5-hydroxy-5 H-dibenzophosphole 5-oxide (VII).



VII

This result was especially surprising, since it had previously been reported[13] that the fusion of sodium hydroxide with diphenylbenzylphosphine oxide leads to exclusive cleavage of the benzyl group; and we have confirmed this finding. When 5-phenyldibenzophosphole 5-oxide (II) was allowed to react with fused sodium hydroxide, only 2-biphenylylphenylphosphinic acid could be isolated from the reaction mixture. The fact that the ring is preferentially cleaved in the case of II is, perhaps, not unexpected, since the substituted biphenylyl carbanion is probably more stable than the phenyl anion. It is surprising, however, that there is no cleavage at all of the exocyclic carbon–phosphorus bond.

The unexpected instability of the dibenzophosphole 5-oxide ring system prompted us to investigate the alkaline cleavage of the dibenzophospholium salts III and VI. When these compounds were allowed to react with an aqueous acetone solution of sodium hydroxide, only the benzyl–phosphorus bond was cleaved.[14–16] Thus, III gave a quantitative yield of 5-phenyldibenzophosphole 5-oxide (II), and VI gave a 90% yield of 5-methyldibenzophosphole 5-oxide. Since the ring strain in both the dibenzophosphole 5-oxide and the dibenzophospholium systems should be comparable, it seems reasonable to conclude that fundamentally different mechanisms must be involved in the alkaline cleavage of the two classes of compounds.

The cleavage of the benzyl–phosphorus bond in the dibenzophospholium salts probably proceeds *via* a trigonal–bipyramidal intermediate such as is illustrated in Scheme I. However, the leaving benzyl carbanion probably does not occupy a position colinear with the phosphorus and oxygen atoms in this intermediate for the following reason. If the benzyl group did occupy such a position, then the carbon–phosphorus bonds of the heterocyclic ring would have to occupy diequatorial positions, and this situation would mean an appreciable increase in ring strain in going from the phospholium salt to the trigonal–bipyramidal intermediate. On the other hand, formation of a trigonal–bipyramidal intermediate with the ring in an equatorial–apical conformation[17] results in a decrease in strain energy and in placing the benzyl–phosphorus bond at right angles to the phosphorus–oxygen bond. The benzyl group in this intermediate leaves as a carbanion, and the heterocyclic ring is not opened. As we have previously mentioned, other workers[6] have obtained similar results with the four-membered benzylphosphetanium system.[18]

We would like to propose that the cleavage of the ring in 5-benzyldibenzophosphole 5-oxide (V) by means of fused sodium hydroxide does not involve a trigonal–bipyramidal intermediate. If this reaction did proceed through such an intermediate, structures VIII–X should be considered. The formation of VIII, in which the ring occupies equatorial–apical positions, would mean some decrease in ring strain and would presumably be followed by benzyl group cleavage (as is observed

(12) E. M. Richards and J. C. Tebby, *Chem. Commun.*, 957 (1967).

(13) L. Horner, H. Hoffman, and H. G. Wippel, *Chem. Ber.*, **91**, 64 (1958).

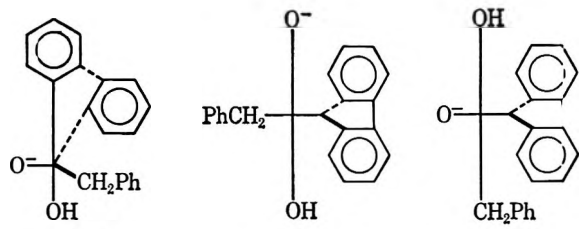
(14) Only ring opening has been previously observed[6,12,15,16] when dibenzophospholium salts were subjected to cleavage reactions; in each of these cases, ring opening resulted in formation of the most stable carbanion.

(15) E. Zbiral, *Tetrahedron Lett.*, 1649 (1964).

(16) D. W. Allen and I. T. Millar, *Chem. Ind.* (London), 2178 (1967).

(17) D. Hellwinkel [*Chem. Ber.*, **99**, 3628 (1966)] has presented evidence that the equatorial–apical conformation is definitely preferred in certain stable pentacovalent 5-dibenzophosphole derivatives.

(18) Our results may be in contrast to a preliminary report[12] which indicates that the benzyl group does not migrate during ring expansion of the 5-dibenzophosphole ring system.



with the benzyl-substituted dibenzophospholium salts). However, cleavage of the exocyclic carbon–phosphorus bond is *not* the main reaction observed when the 5-oxide V is fused with sodium hydroxide, and thus there must be some factor that inhibits the formation of VIII. It seems reasonable to suggest that the rate of formation of VIII is relatively slow because of the coulombic repulsion between the approaching hydroxide ion and the oxide oxygen atom. The existence of the trigonal–bipyramidal intermediates IX[19] or X, in both of which the ring occupies diequatorial positions, appears unlikely since there would be severe ring strain in these structures; in addition, the formation of X would involve serious coulombic repulsion. It seems probable, therefore, that the cleavage of the ring in the 5-oxide V does not proceed through a trigonal–bipyramidal intermediate. The transition state leading to ring cleavage may resemble IX and may involve the concurrent cleavage of a ring carbon–phosphorus bond and the formation of a second phosphorus–oxygen bond.

Experimental Section[20]

5-Phenyldibenzophosphole (I).—Tetraphenylphosphonium bromide was prepared in 55% yield by the method of Horner and coworkers[7] and converted into I in 62% yield by treatment with lithium diethylamide.[8] The phosphole was shown (melting point, mixture melting point, and ir spectrum) to be identical with an authentic sample prepared by another procedure.[21]

5-Benzyldibenzophosphole (IV).—5-Phenyldibenzophosphole (I, 0.0245 mol) was dissolved in 75 ml of dried tetrahydrofuran (THF) and small pieces of lithium wire (0.050 g-atom) were added. The mixture was stirred and refluxed under nitrogen for 3 hr and then cooled. *t*-Butyl chloride (0.0245 mol) in 10 ml of THF was then added dropwise with stirring. After the addition, the solution was refluxed for 10 min and then allowed to cool to room temperature. Benzyl chloride (0.025 mol) was then added dropwise with stirring. During the addition, the deep red solution changed to almost colorless. The solution was refluxed for 15 min after the addition, and then water was added. Ethyl ether (75 ml) was added, and the organic layer separated. The solvent was stripped and the residue was vacuum distilled. The product, 5.1 g, bp 165–170° (~10 μ) [lit. bp 162° (30 μ),[12] bp 175–180° (0.2 mm)[22]], was collected as a liquid which later solidified. The yield after recrystallization from methanol was 3.9 g (62%): mp 76–78°; nmr τ 6.98 (s, 2, CH_2P), 2.1–3.2 (m, 13, aromatic H).

Anal. Calcd for $C_{19}H_{15}P$: C, 83.20; H, 5.51; P, 11.29. Found: C, 83.01; H, 5.32; P, 11.14.

5-Benzyldibenzophosphole was prepared earlier[22] in this laboratory from *o,o'*-dilithiobiphenyl and benzylphosphonous dichloride[23] by a procedure similar to that of Wittig and Maercker.[24] The ir spectra of both samples were identical.

5-Benzyldibenzophosphole 5-Oxide (V).—5-Benzyldibenzophole (3.3 g) was dissolved in 30 ml of acetone and treated dropwise with 25 ml of 3% hydrogen peroxide. The solution was stirred for 1 hr after the addition, and the acetone evaporated. The reaction mixture, containing an insoluble viscous material, was extracted twice with 25-ml portions of benzene. The extracts were combined and dried with sodium sulfate. The product was then precipitated from the benzene solution by addition of petroleum ether. Recrystallization from a benzene–petroleum ether (bp 65–110°) mixture gave 3.3 g (95%) of the pure product: mp 139–141°; nmr τ 6.64 (d, J_{P-H} = 15.4 cps, 2, CH_2P), 2.2–3.1 (m, 13, aromatic H).

Anal. Calcd for $C_{19}H_{15}OP$: C, 78.61; H, 5.21; P, 10.67. Found: C, 78.55; H, 5.15; P, 10.45.

5-Phenyldibenzophosphole 5-Oxide (II).—Compound II was prepared from 5-phenyldibenzophosphole (I) by the method used for 5-benzyldibenzophosphole 5-oxide (V): yield 94%; mp 163–166° (lit.[21] mp 165–167°). The ir spectrum was identical with that of an authentic sample.[21]

Diphenylbenzylphosphine Oxide.—Diphenylbenzylphosphine was prepared from lithium diphenylphosphide and benzyl chloride by a procedure similar to that described for 5-benzyldibenzophosphole: bp 185–190° (0.75 mm); nmr τ 6.70 (s, 2, CH_2P), 2.4–3.2 (m, 15, aromatic H). The phosphine was oxidized by the procedure described for 5-benzyldibenzophosphole 5-oxide: yield, based on triphenylphosphine, 60%; mp 186–189° (lit.[11] mp 191–192°); nmr τ 6.37 (d, J_{P-H} = 14.6 cps, 2, CH_2P), 2.2–2.9 (m, 15, aromatic H).

5-Benzyl-5-phenyldibenzophospholium Chloride (III).—5-Phenyldibenzophosphole (2.0 g) was added to a large excess of benzyl chloride (20 ml) in a flask equipped with a reflux condenser. The mixture was slowly refluxed for 2 hr. The phosphonium salt, which crystallized on cooling, was collected and washed with 200 ml of ether: yield 2.8 g (94%); mp 303–306° dec.

Anal. Calcd for $C_{25}H_{20}ClP$: C, 77.62; H, 5.21; P, 8.01. Found: C, 77.60; H, 5.23; P, 8.18.

5-Benzyl-5-methyldibenzophospholium Iodide (VI).—A large excess of methyl iodide (25 ml) was added to 5-benzyldibenzophosphole (6.0 g) in a flask equipped with a reflux condenser. A vigorous reaction immediately followed the addition. The mixture was allowed to sit for 2 hr. The phosphonium salt was removed by filtration, washed with ether, and then recrystallized from an acetone–ethanol mixture: yield 6.0 g (99%); mp 239–242°; nmr τ 6.98 (d, J_{P-H} = 14.6 cps, 3, CH_3P), 4.63 (d, J_{P-H} = 16.6 cps, 2, CH_2P), 2.3–2.9 (m, 13, aromatic H).

Anal. Calcd for $C_{20}H_{18}IP$: C, 57.70; H, 4.36; P, 7.44. Found: C, 57.58; H, 4.44; P, 7.68.

Cleavage of 5-Benzyldibenzophosphole 5-Oxide (V).—The phosphine oxide V (0.0069 mol) was thoroughly mixed with finely powdered sodium hydroxide (0.014 mol) in a 25-ml pear-shaped flask fitted with a condenser. The flask was slowly heated to 200° and maintained between 200 and 210° for 30 min. During this time 0.12 ml of toluene (confirmed by ir and nmr) distilled. After cooling, the contents of the flask were dissolved in 75 ml of water, treated with charcoal, cooled, and acidified to yield 1.85 g of solid, mp 149–155°. This solid was recrystallized twice from ethanol to yield 1.17 g (55%) of 2-biphenylylbenzylphosphinic acid: mp 168–170°; nmr τ 7.12 (d, J_{P-H} = 15.6 cps, 2, CH_2P), 2.4–3.3 (m, 14, aromatic H). The acid was identified by analysis and by comparison of its melting point, mixture melting point, and ir spectrum with those of an authentic sample prepared as described below. The mother liquors from the above recrystallizations were combined to yield a solid, which, after two recrystallizations from ethanol, gave 0.34 g (23%) of 5-hydroxy-5H-dibenzophosphole 5-oxide (VII), mp 245–250°

(19) Conformation IX is favored by the fact that both oxygen atoms occupy apical positions. In general, the more electronegative groups tend to occupy these positions in a trigonal–bipyramidal molecule.[1] However, it seems unlikely that this factor can counterbalance the large amount of ring strain in IX.

(20) Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 521 spectrophotometer. Nmr spectra were taken with either a Varian HA-100 or Varian T-60 instrument; deuteriochloroform was used as a solvent with tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories.

(21) J. B. Levy, G. O. Doak, and L. D. Freedman, *J. Org. Chem.*, **30**, 660 (1965).

(22) C. N. Bean, Masters Thesis, North Carolina State University, Raleigh, N. C., 1965.

(23) P. J. Slota, Jr., Ph.D. Thesis, Temple University, Philadelphia, Pa., 1954.

(24) G. Wittig and A. Maercker, *Chem. Ber.*, **97**, 747 (1964).

(lit.[25] mp 253–257°); the acid was identified by comparison with an authentic sample.[26]

2-Biphenylylbenzylphosphinic Acid.—Thus compound was prepared[22] from 2-biphenyldiazonium tetrafluoroborate and benzylphosphonous dichloride by the method of Freedman and Doak:[27] yield 21%; mp 168–170°.

Anal. Calcd for $C_{19}H_{17}O_2P$: C, 74.02; H, 5.56; P, 10.05. Found: C, 74.20; H, 5.73; P, 9.62.

Cleavage of 5-Phenyldibenzophosphole 5-Oxide (II).—This compound (2.0 g) was cleaved by the procedure described for 5-benzyldibenzophosphole 5-oxide. 2-Biphenylylphenylphosphinic acid, 1.6 g (75%), mp 173–176° (lit.[28] mp 180–181°), was isolated and shown to be identical (mixture melting point and ir) with an authentic sample (see below). About 0.3 g (15%) of the phosphine oxide II was recovered from the reaction mixture.

2-Biphenylylphenylphosphinic Acid.—This compound was prepared from 2-biphenyldiazonium tetrafluoroborate and phenylphosphonous dichloride by the usual method:[27] yield 18%; mp 177–179° (lit.[28] mp 180–181°).

Cleavage of 5-Benzyl-5-phenyldibenzophospholium Chloride (III).—The phospholium salt III (1.4 g) was dissolved in 40 ml of a 1:1 acetone–water mixture. Sodium hydroxide (9 ml of a 20% solution) was added, and the mixture was allowed to sit for 24 hr. The acetone was evaporated and the aqueous mixture was extracted with two 15-ml portions of chloroform. The extracts were combined and stripped leaving 5-phenyldibenzophosphole 5-oxide (II): yield 1.0 g (100%); mp 162–165°. The compound was identical with the sample prepared above.

(25) L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **21**, 238 (1956).
(26) G. O. Doak, L. D. Freedman, and J. B. Levy, *ibid.*, **29**, 2382 (1964).
(27) L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **74**, 2884 (1952).
(28) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 2133 (1961).

Cleavage of 5-Benzyl-5-methyldibenzophospholium Iodide (VI).—The phospholium salt VI (2.8 g) was cleaved by the procedure described for 5-benzyl-5-phenyldibenzophospholium chloride (III). 5-Methyldibenzophosphole 5-oxide was obtained as a hemihydrate after recrystallization from benzene–petroleum ether: yield 1.3 g (90%); mp 89–91°; nmr τ 8.21 (d, J_{P-H} = 13.6 cps, 3, CH_3P), 7.42 (s, 1, H_2O), 2.0–2.8 (m, 8, aromatic H). The ir spectrum showed the O–H stretching at 3470 and 3520 cm^{-1}. The water could be removed by heating the hemihydrate for 2 hr *in vacuo* over phosphorus pentoxide; the loss of water was demonstrated by an appropriate weight loss, the disappearance of the O–H stretching in the ir, and of the τ 7.42 peak in the nmr spectrum.

Anal. Calcd for $C_{13}H_{11}OP \cdot 0.5H_2O$: C, 70.00; H, 5.42; P, 13.88. Found: C, 70.45; H, 5.57; P, 14.01.

The compound was identical (melting point, mixture melting point, and ir) with an authentic sample prepared by the procedure given below.

5-Methyldibenzophosphole 5-Oxide.—5-Methyldibenzophosphole was prepared from 5-phenyldibenzophosphole (0.029 mol) and methyl iodide (0.029 mol) by the procedure described for 5-benzyldibenzophosphole (IV): yield 44%; bp 110° (10 μ) [lit.[4] bp 103° (0.2 mm)]; nmr τ 8.69 (s, 3, CH_3P), 2.3–2.8 (m, 8, aromatic H).

Anal. Calcd for $C_{13}H_{11}P$: C, 78.77; H, 5.60. Found: C, 78.60; H, 5.73.

The phosphine was oxidized with hydrogen peroxide to the phosphine oxide hemihydrate (70%), mp 88–90°.

Registry No.—III, 19190-36-4; IV, 19190-37-5; V, 19190-38-6; VI, 19190-39-7; 5-methyldibenzophosphole 5-oxide, 19190-40-0.

Some Novel Sulfonamides. The Chlorosulfonation of Aryl Alkyl Sulfides

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The chlorosulfonation of three methylthio-substituted benzenes has been investigated. With two of the compounds, the reaction proved satisfactory for preparation of sulfonamide derivatives. In the more favorable case, 2,4-dimethylthioacetanilide readily gave a crystalline sulfonyl chloride. Subsequent oxidation gave the corresponding disulfones. Various tetrasubstituted compounds were readily characterized by bands for isolated aromatic hydrogens in their proton magnetic resonance (pmr) spectra. Lack of splitting in these bands along with the facile substitution in the presence of the two methylthio-directing groups favors assignment of a 1,2,4,5-substitution pattern for these compounds. Analysis of the pmr spectra provides a rough correlation of chemical-shift parameters for the sulfonyl and methylthio substituents.

A study of some sulfonation reactions with simple alkyl aryl sulfides has shown participation by the sulfur as a sulfonium group in attack on the aromatic ring to give diarylalkylsulfonium salts. This reaction occurs with methyl *p*-tolyl sulfide at 20°. When the ring is somewhat deactivated, as with methyl *p*-chlorophenyl sulfide, some sulfonation is observed and this occurs *ortho* to the methylthio group.[1] An earlier study of the substitution of methyl phenyl sulfide reports that both bromination and sulfonation occur primarily in the *para* position.[2]

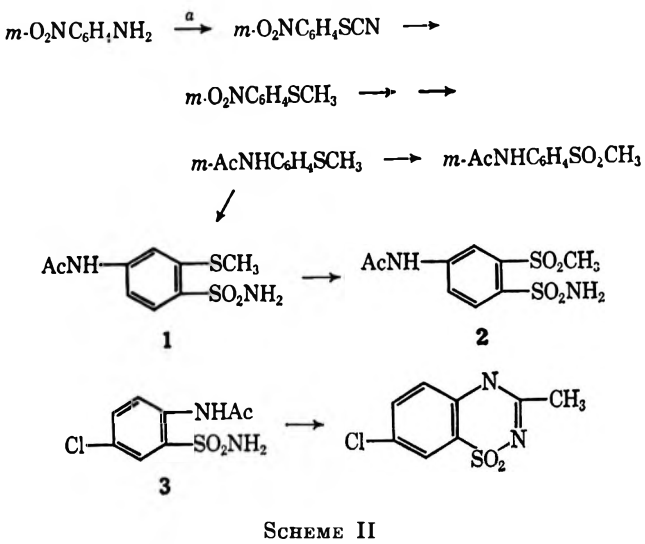
In work directed toward the preparation of new sulfonamides, chlorosulfonation of highly reactive methylthio-substituted benzenes was utilized. In addition to using cold chlorosulfonic acid, use of chloroform as a cosolvent in the two-phase procedure of Huntress and Carten[3] for characterization of aryl alkyl ethers was also used. This procedure was found to give better results than without the use of a cosolvent in the one case in which it was tried.

m-Methylthioacetanilide[4] was prepared and further characterized by oxidation with perbenzoic acid to the sulfone[4] (Scheme I). It was also chlorosulfonated followed by treatment with ammonia to give a new

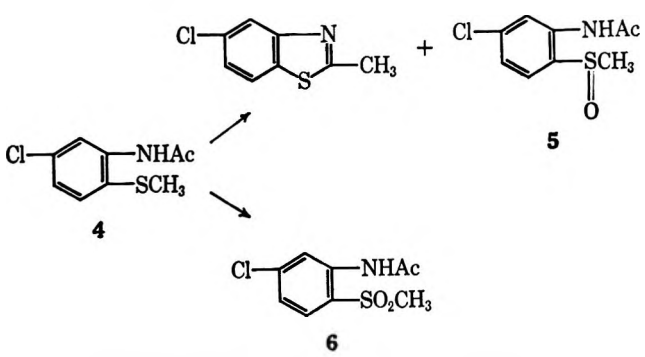
(1) F. Krollpfeiffer and W. Hahn, *Chem. Ber.*, **86**, 1049 (1953).
(2) T. Van Hove, *Bull. Sci. Acad. Roy. Belg.*, **12**, (5), 929 (1926); *Chem. Abstr.*, **21**, 2256 (1927).
(3) E. H. Huntress and F. H. Carten, *J. Amer. Chem. Soc.*, **62**, 511, 603 (1940).
(4) (a) Th. Zinke and J. Müller, *Ber.*, **46**, 775 (1913); (b) H. Gilman and G. A. Martin, *J. Amer. Chem. Soc.*, **74**, 5317 (1952).

methylthiosulfamylacetanilide (**1**).[5] This compound was further transformed to the sulfone **2**. The position

SCHEME I



SCHEME II



[a] K. Brand and H. W. Leyerzapf, *Ber.* **70B**, 284 (1937).

2-Methylthio-5-chloroacetanilide (**4**, Scheme II) was prepared from 2-methylthio-5-chloronitrobenzene[8] by stannous chloride reduction followed by acetylation with acetic anhydride–acetic acid. A single attempt at chlorosulfonation under relatively mild conditions gave no sulfonation, but did result in S demethylation and ring closure to 5-chloro-2-methylbenzothiazole.[9] Under slightly more vigorous conditions, **4** gave the benzothiazole and a small amount of a product which appeared, from its analysis and infrared[10] (ir) and pmr spectra, to be the sulfoxide **5**.

The sulfone 6 was also prepared from **4** by perbenzoic acid oxidation.

Treatment of 2,4-dimethylthioacetanilide[11] with cold chlorosulfonic acid (Scheme III) and reaction of the product (**7**) with concentrated ammonium hydroxide or dimethylamine gave the corresponding sulfamylacetanilide (**8**) and dimethylsulfamyl acetanilide (**9**).

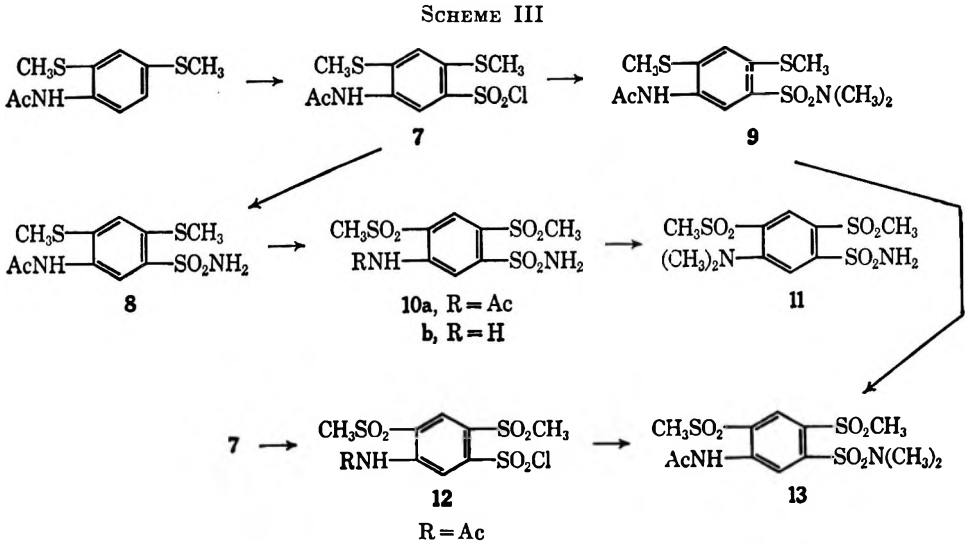
In the preparation of **7**, pure, crystalline sulfonyl halide was readily isolated when chloroform was used as a cosolvent for the chlorosulfonation.[3]

Oxidation of **8** with perbenzoic acid gave the disulfone **10a** which was hydrolyzed to the free amine **10b**.

An attempt was made to prepare the dimethylsulfonyl compound corresponding to **9** by stepwise methylation of the potassium salt of **10a** in the presence of a large excess of methyl iodide. When most of the initial equivalent of base had been used up, the process was repeated. This brought the pH to 8 from which it appeared that the methyl iodide had reacted preferentially either with hydroxide ion or with the sulfamyl anions of **10a** and further with its monomethylsulfamyl derivative.

However, two additional treatments with base and excess methyl iodide produced a 57% yield of a sub-

SCHEME III



of the sulfamyl group in **1** was inferred from its failure to undergo pyrolytic ring closure at a temperature in excess of that required for ring closure[6] of 2-sulfamyl-4-chloroacetanilide (**3**).[7]

stance with no N-acetyl and only two N-methyl substituents, though the total iodide and base used

(5) A sulfamyl derivative of *o*-methylthioacetanilide has been reported [R. Specklin and J. Meybeck, *Bull. Soc. Chim. Fr.*, 621 (1951)].

(6) (a) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960); (b) J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963).

(7) S. Suzue and S. Hayashi, *Yakugaku Zasshi*, **82**, 1192 (1962); *Chem. Abstr.*, **58**, 5689 (1963).

(8) (a) H. H. Hodgson and F. W. Handley, *J. Soc. Chem. Ind.*, **46**, 435-6T (1927); *Chem. Abstr.*, **22**, 950 (1928). (b) D. A. Skinner and E. L. Wampler U. S. Patent 2,557,520 (1951). (c) The ethylthio homolog has been described.[9]

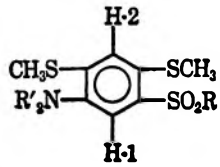
(9) H. P. Lankelma and A. E. Knauf, *J. Amer. Chem. Soc.*, **53**, 309 (1931).

(10) F. G. Bordwell and P. J. Boutan, *ibid.*, **79**, 717 (1957).

(11) H. H. Hodgson and F. W. Handley, *J. Chem. Soc.*, 162 (1928).

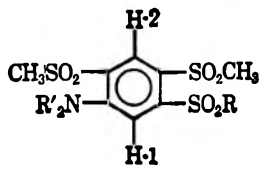
TABLE I

PROTON MAGNETIC RESONANCE PEAKS IN DMSO FOR STRUCTURES A–C



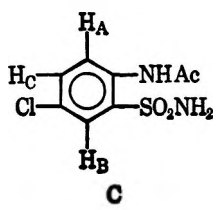
A

Compound	R′	R	δ (H-1)	δ (H-2)	δ $(NCH_3)_2$	δ (SCH_3)	δ (Ac)
8	Ac, H	NH_2	7.79	7.20		2.56, 2.59	2.07
9	Ac, H	$N(CH_3)_2$	7.70	7.15	2.74	2.57, 2.57	2.06
7	Ac, H	Cl	7.70	7.00		2.41, 2.44	2.00



B

Compound	R′	R	δ (H-1)	δ (H-2)	δ $(NCH_3)_2$	δ (SO_2CH_3)	δ (Ac)
10b	H	NH_2	7.72	8.28		3.20, 3.37	
11	CH_3	NH_2	7.46	8.38	2.95	3.32, 3.32	
13	Ac, H	$N(CH_3)_2$	8.63	8.95	2.98	3.38, 3.45	2.28
10a	Ac, H	NH_2	8.58	9.18		3.48, 3.50	2.28
12	Ac, H	Cl	8.55	8.90		3.32, 3.35	2.19



C

δ (H_A)	δ (H_B)	δ (H_C)	
8.21 (J_{AC} = 11Hz)	7.86 (J_{BC} = 3 Hz)	7.65 (J_{CA} = 8.4 Hz; J_{CB} = 2.5 Hz)	7.42

would have allowed formation of the N,N,N′,N′-tetramethyl derivative (plus 1 equiv of acetic acid on introduction of the last methyl group). Consequently, it was concluded that hydrolysis of the acetyl group occurred readily with subsequent methylation of the amino nitrogen but not of the sulfonamide anion to give **11**. It is of interest that the amino group exhibits a much greater nucleophilic reactivity than the $-SO_2NH$ anion in spite of the former's vinylogous relationship to the methylsulfonyl groups.

Since direct methylation of the sulfamyl nitrogen of **10a** could not be achieved, preliminary studies of two other routes to the dimethylsulfamyl compound **13** were made. Oxidation of **7** with 4 equiv of *m*-chloroperbenzoic acid gave a compound with the expected pmr peaks for **12** (Table I), but which also contained incompletely oxidized material to the extent of *ca.* 20% (δ 2.82, CH_3SO-). An earlier attempt to convert **7** into **12** under milder conditions gave a higher proportion (*ca.* 50% based on total acetyl methyl) of this sulfoxide methyl with, in addition, another sulfoxide methyl at δ 2.72 to the extent of *ca.* 20%.

Permanganate oxidation[12] of **9** in aqueous acetic acid gave a product which was probably **13** based on comparison of its ir spectrum with that of a crude product obtained from **12** and dimethylamine.

Proton Magnetic Resonance Spectra.—The pmr spectra for compounds of Scheme III are summarized in Table I. As no attempt was made to standardize conditions for observation of the NH_2 protons, these are not included, though their positions generally provided reliable confirmation for the sulfonamide group and for electronegatively substituted aromatic amines (see Experimental Section). The proton between the two methylthio groups of A (Table I, H-2) is clearly different from the one *ortho* to the sulfamyl and acetamido groups. The latter (H-1) is deshielded by the acetamido and sulfonamido group as predicted from structure C (Table I) in which the individual protons can be identified through their coupling constants.[13] These assignments for H-1 and H-2 in structure A (Table I) parallel also the expected *ortho* effects for electronegative and electropositive substituents in both chloroform[14] and dimethyl sulfoxide[15] (DMSO). Com-

(12) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Amer. Chem. Soc.*, **54**, 1985 (1932).

(13) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, Inc., New York, N. Y., 1966, p 770.

(14) (a) P. L. Corio and B. P. Dailey, *J. Amer. Chem. Soc.*, **78**, 3043 (1956); (b) J. S. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1722 (1963).

(15) J. B. Leane and R. E. Richards, *Trans. Faraday Soc.*, **55**, 707 (1959); also ref 13, p 767.

parison of halosulfonyl and nitrosubstituted benzenes shows that the sulfonyl group effects somewhat greater deshielding of the *ortho* position (0.1–0.2 ppm) and somewhat less deshielding at the *meta* position (*ca.* 0.2 ppm) than the nitro group.[16,14a] Thus, hydrogens *ortho* to a sulfonyl group should be deshielded by *ca.* 1.1 ppm and there should be essentially no *meta* effect (*o*-NO_2, −0.955 ppm;[14a] *m*-NO_2, −0.155 ppm[14a]). The pmr of *p*-acetamidoanisole[17] suggest that the acetamido group is somewhat deshielding to an *ortho* hydrogen (*ca.* 0.1 ppm) and has essentially no *meta* effect when reported values[14a] for methoxy are considered.

On this basis, the shielding of H-2 in structure A (especially **7**) is essentially due only to the two methylthio groups. This gives an *ortho* shielding effect of approximately 0.2 ppm per methylthio group which is somewhat less than that reported for methoxy.[14a] One would also expect, for structure A, a deshielding of H-1 by approximately 1.2 ppm due to the combined effects of the *o*-sulfonyl and *o*-acetamido groups. The lesser observed shift from benzene of 0.3–0.4 ppm is attributable to a combination of *ortho* steric effects (lowering −M for AcNH and SO_2), *meta* shielding by the CH_3S groups, and electrical interaction of the *para* substituents.

Turning to structure B, assignment of the relative positions of H-1 and H-2 is less clear. If the *meta* effect of methylsulfonyl is comparable with what is reported in the literature[16,14a] for halosulfonyl, then H-1 in **10a, 12,** and **13** should differ from that in structure A essentially by the elimination of shielding due to two *m* methylthio groups. This still requires an unusually large shielding from *m* methylthio of 0.4–0.45 ppm compared with that of methoxy[14a] of 0.1 ppm. However, accommodation of H-2 of **10a, 12,** and **13** by elimination of a shielding per methylthio group of 0.1–0.2 ppm and estimation of an *o* methylsulfonyl shielding of 0.8–0.9 is in good agreement with what one would expect from consideration of methoxy,[14a] chlorosulfonyl,[16] and nitro[16] substituents.

The *m* amino shielding parameters for H-2 of **10b** and **11** (compared with that of acetamido, **10a**) appears to be larger than reported[14a] and is undoubtedly complicated by steric effects and probably also by some hydrogen bonding in **10b** to the adjacent methylsulfonyl oxygens. Similarly, some *m* methylsulfonyl deshielding in **10b** and **11** would appear necessary to overcome the effect on H-1 of changing from acetamido (**7, 8,** and **9**) to amino (**10b** and **11**). This undoubtedly also involves some interaction of *ortho* substituents. However, it should be noted that the anomalies regarding these two parameters (*m* methylsulfonyl deshielding and *m* amino shielding) would be even more pronounced if H-1 and H-2 of **10b** and **11** were reversed. The position of H-1 in **10b** and **11** also may reflect the acidic nature of R'_2N as a vinylogous sulfonamide with the internal effect of the *o*- and *p* sulfone groups resembling closely that of acetylation of an amino function. The amino group of **10b,** when compared with **8,** using derived[13–16,13] and observed values from Table II, gives an *ortho* amino effect of 0.47 ppm which is lower than the 0.77 value previously reported[14a] for compounds without similar vinylogous interaction with, or hydrogen bonding to, electronegative substituents.

Table II

Estimates of Shielding Constants[a] for Methylthio, Methylsulfonyl, and Acetamido Groups in DMSO

	ortho	*meta*
CH_3S	−0.2	−0.1 to −0.2
CH_3SO_2	0.8–0.9	<0.2[b]
CH_3CONH	0.1	0.0

[a] Expressed as δ (parts per million) less than tetramethylsilane (TMS) as an internal standard. [b] Probably nearer to 0.0 from literature values[16,14a] for chlorosulfonyl discussed in the text.

An interesting example of resonance effects and/or *ortho* hydrogen bonding is that of 2,4-dinitroaniline. Its ring protons have been measured in DMSO[19] and give a value for the proton *ortho* to the amino group of 7.13 ppm. Allowing for the effect of *m* nitro groups,[14a] this requires an *o* amino shielding of 0.6 ppm compared with a reported value of 0.77.[14a] Thus, similar interaction of methylsulfonyl and amino groups in **10b** and **11** is not unexpected.

Experimental Section[20]

***m*-Methylthionitrobenzene.**—*m*-Nitrophenyl thiocyanate[18] (40 g) in 250 ml of methanol was treated with a solution of 40 g of potassium hydroxide in 40 ml of water and the reaction mixture was heated under reflux for 35 min in an atmosphere of nitrogen. Water (200 ml) was added followed by 42 g of dimethyl sulfate over 30 min at 25–30°. Another 10 g of dimethyl sulfate was added at this temperature, 10 g more at 55–60° which produced a neutral reaction mixture, and a final 2–3 g along with equivalent 8.5 *N* potassium hydroxide portionwise. The reaction mixture was cooled and extracted with methylene chloride. Drying and removal of solvent gave 37.5 g of *m*-methylthionitrobenzene,[18] bp 119–124° (1.5 mm).

***m*-Methylthioacetanilide.**—*m*-Methylthionitrobenzene (37.5 g) was added to a solution of 160 g of stannous chloride in 200 ml of concentrated hydrochloric acid at 10° with stirring. The reaction mixture was exothermic to 35° and was warmed to 45°. The temperature continued to rise spontaneously to 85–90°. When the exothermic reaction abated, heating was continued for 20 min at 90–95°. Cooling and addition of ice gave a solid (10–15 g) which was treated with excess 8.5 *N* potassium hydroxide and extracted with methylene chloride to give 6.0 g of the amine after removal of solvent.

The filtrate was treated with 470 ml of 8.5 *N* potassium hydroxide and extracted with methylene chloride to give an additional 25.5 g of *m*-methylthioaniline;[4b] the ir and ultraviolet (uv) spectra were identical with those of the material described above.

To a solution of 12 g of the amine in 200 ml of water and 7.2 ml of concentrated hydrochloric acid was added 10 ml of acetic anhydride and a solution of 8.5 g of sodium acetate in 48 ml of water. Ice and water were added to give 13.86 g of *m*-methylthioacetanilide, mp 80–81.5° (lit. mp 75°[4a] and 78–78.5°[4b]).

Anal. Calcd for $C_9H_{11}NOS$: N, 7.73. Found: N, 7.91.

***m*-Methylsulfonylacetanilide.**—*m*-Methylthioacetanilide (1 g) was oxidized with perbenzoic acid in benzene to give, after re-

(16) T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1218 (1960).
(17) C. Heathcock, *Can. J. Chem.*, **40**, 1865 (1962).
(18) See footnote *a*, Scheme I.

(19) Pmr data were determined in hexadeuteriodimethyl sulfoxide at 60 Mcps and are expressed as parts per million less than the field required for resonance of tetramethylsilane. Where the functional group is given, the intensity corresponds to the proper number of hydrogens.

(20) The author wishes to thank Dr. R. T. Dillon and the staff of the analytical department of G. D. Searle & Co. for the data reported. He is also grateful to Messrs. C. H. Yen and A. R. Zigman for preparation of additional quantities of certain of the compounds described herein and to Dr. Roy Bible for consultation regarding the pmr spectra.

crystallization from ethanol–ether, 680 mg of *m*-methylsulfonylacetanilide, mp 139–140° (lit. mp 137°[4a] and 136.8–137.5°[4b]).

Anal. Calcd for $C_9H_{11}NO_3S$: N, 6.57. Found: N, 6.37.

3-Methylthio-4-sulfamylacetanilide (1).—*m*-Methylthioacetanalide (1.0 g) was added portionwise to 5 ml of chlorosulfonic acid at room temperature. The reaction mixture was warmed to 45° over 10 min and then poured onto ice to give a paste from which the supernatant liquid was decanted. The residue was taken up in ethanol and the solution was saturated with ammonia and warmed for 15 min. The ethanol solution was adjusted to pH 6 by addition of dilute acid and was boiled down and filtered hot to give plates of mp 230–233°. This material was taken up in dilute potassium hydroxide and was reprecipitated by addition of hydrochloric acid. The solid was collected, washed, and dried to give 250 mg of very fine needles: mp 228–231°; $\lambda_{max}^{CHCl_3}$ 2.96, 3.22, 5.92, 7.51, 7.58, 8.62, 8.74 μ; δ[19] 2.16 (Ac), 2.57 (CH_3S), 7.36 (SO_2NH_2), 7.61, 7.66, 7.78, 7.81, 7.92, 7.95, 7.98, 8.12 (ArH multiplet), 10.23 (NH).

Anal. Calcd for $C_9H_{12}N_2O_3S_2$: C, 41.52; H, 4.65; N, 10.76. Found: C, 42.04; H, 4.70; N, 10.75.

The original ethanol filtrate gave a second crop of 80 mg, mp 222–227°, reduced to 50–60 mg by recrystallization from ethanol, mp 228–232°; the ir spectrum was identical with that of the material described above.

3-Methylsulfonyl-4-sulfamylacetanilide (2).—3-Methylthio-4-sulfamylacetanilide (270 mg) was dissolved in 2 ml of dimethylformamide and 5.5 ml of 0.7 *N* perbenzoic acid in benzene was added over 15 min. The reaction mixture was blown down on the steam bath and was triturated with 10 ml of benzene and 10 ml of water to give a solid product. Recrystallization from water and then from methanol gave 82.3 mg: mp 223.5–225.5°; λ_{max}^{KBr} 2.94, 2.98, 3.14, 3.24, 5.93, 7.25, 7.5, 7.63, 8.6, 8.75, 8.95 μ.

Anal. Calcd for $C_9H_{12}N_2O_5S_2$: N, 9.59. Found: N, 9.52.

2-Sulfamyl-4-chloroacetanilide and Its Pyrolysis.—This substance was prepared by acetylation of the amine[6b] with acetyl chloride in dioxane.[6a] From 300 mg there was obtained 218 mg of the desired product after recrystallization from methanol: mp 207–213.5° (lit.[7] mp 217–219°) [bubbling and resolidification of the melt (ring closure) began at 215–220°]; λ_{max}^{KBr} 2.96, 3.01, 3.12, 3.26, 5.91 μ; $\lambda_{max}^{CH_3OH}$ 251.5 mμ (ϵ 12,600), 295 (2410).

Anal. Calcd for $C_8H_9ClN_2SO_3$: C, 38.63; H, 3.65; N, 11.27. Found: C, 38.55; H, 3.66; N, 11.04.

Gradual heating of 43 mg of the material from 215 to 225° over 10 min in a nitrogen atmosphere gave, after trituration with hot methanol, 20 mg of 7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide, mp 324–327° (lit.[6b] mp 330–331°) which was identified by comparison (ir and uv) with an authentic sample.[6b]

Attempted Ring Closure of 3-Methylthio-4-sulfamylacetanilide (1).—3-Methylthio-4-sulfamylacetanilide (1, 74 mg) was heated gradually over 30 min from 235 to 250° under nitrogen. Trituration with methanol gave 28 mg of starting material, mp 228–230°, identified spectrally and by mixture melting point. The methanol filtrate was taken to dryness. The solid residue had mp 211–220° and ir and uv spectra identical with those of starting material.

2-Methylthio-5-chloronitrobenzene.[8a,b]—2,5-Dichloronitrobenzene (40 g) was added to a solution of 300 ml of methanol and 26 ml of 8.5 *N* potassium hydroxide which had been saturated with methyl mercaptan. An additional 23 ml of 8.5 *N* potassium hydroxide was added over 20 min while continuing the methyl mercaptan addition. Methanol (300 ml) was added and the reaction mixture was heated under reflux for 30 min. It was then poured onto ice and diluted to 3 l. to give 40.5 g of 2-methylthio-5-chloronitrobenzene, mp 135.5–136°.

Anal. Calcd for $C_6H_3Cl_2NO_2$: S, 15.75; N, 6.88. Found: S, 16.19; N, 6.94.

2-Methylthio-5-chloroacetanilide (4).—2-Methylthio-5-chloronitrobenzene (20 g) was added to a freshly prepared solution of 80 g of stannous chloride in 100 ml of concentrated hydrochloric acid. After slight warming, the reaction was quite exothermic and required external cooling. After this initial period, heating was continued at 95–100° for 10–15 min. The reaction mixture was cooled and ice and 160 g of potassium hydroxide were added alternately until the reaction mixture was basic. Extraction with methylene chloride gave 20 g of the crude amine.

The amine (17 g) in 50 ml of acetic acid and 5 ml of acetic anhydride was heated under reflux for 5 hr. The reaction mixture was diluted with water and the crude product was recrystallized from benzene–petroleum ether (bp 62–70°) to give 10.17 g of **4**, mp 96–97.5°.[21]

Anal. Calcd for $C_9H_{10}ClNOS$: S, 14.86; N, 6.50. Found: S, 14.90; N, 6.50.

Attempted Chlorosulfonation of 4. A.—Compound **4** (1 g) was added to 5 ml of chlorosulfonic acid at 5–10° and the reaction mixture was stirred for an additional 60 min at 40–45°. The reaction mixture was added gradually to ice and extracted with methylene chloride to give 0.52 g of a solid. The solid was triturated with 10 ml of concentrated aqueous ammonia solution and warmed to 50–60°. Cooling gave 370 mg of crude 5-chloro-2-methylbenzothiazole, mp 62–67°. Sublimation gave pure material of mp 68–70° (lit.[9] mp 68–69°) which was identified by mixture melting point with an authentic sample and comparison of ir spectra.

When the experiment was repeated without treatment with ammonia, the same product (46.5 mg from 340 mg) was isolated.

B.—Treatment of 2 g of **4** with chlorosulfonic acid for 10 min followed by warming at 50–55° for 1 hr gave 1.06 g, mp 143–157°. Recrystallization from methylene chloride–ether gave 200 mg of 2-methylsulfinyl-5-chloroacetanilide (**5**): mp 164–165°; $\lambda_{max}^{CHCl_3,CS_2}$ 3.1, 5.8, 7.1, 7.9, 9.5,[10] 9.7 μ;[10] $\delta_{max}^{CDCl_3}$ 2.18 (Ac), 2.89 (CH_3SO), 7.15 (multiplet, 2-ArH), 8.5 (doublet, ArH, J = 3–4 hz), 10.6 (NH).

Anal. Calcd for $C_9H_{10}ClNO_2S$: C, 46.7; H, 4.36; S, 13.87. Found: C, 46.51; H, 4.50; S, 14.12.

The residue obtained from the filtrate was essentially pure 5-chloro-2-methylbenzothiazole,[9] 530 mg, mp 66–70°.

2-Methylsulfonyl-5-chloroacetanilide (6).—Compound **4** (1 g) was dissolved in 10 ml of benzene and 28 ml of 0.94 *N* perbenzoic acid in benzene was added over 5 min. After stirring for another 15–20 min, the reaction mixture was diluted with benzene and was extracted with 5% sodium carbonate solution and water. The benzene was removed and the residue was recrystallized from acetone–ether to give 0.62 g of **6**, mp 161.5–162.5°.[22]

Anal. Calcd for $C_9H_{10}ClNO_3S$: N, 5.66; S, 12.94. Found: N, 5.52; S, 12.68.

2,4-Dimethylthio-5-sulfamylacetanilide (8).—2,4-Dimethylthioacetanilide [15 g, mp 111–113° (lit.[11] mp 114°)] was added over 15 min to 125 ml of ice-cold chlorosulfonic acid with stirring. The reaction mixture was stirred for an additional 10 min and was then quenched by dropwise addition to ice over 25 min. The aqueous mixture was extracted with methylene chloride, the solution was dried, and the solvent was evaporated to 100 ml in an evaporating dish. Concentrated ammonium hydroxide (300 ml) was added and the mixture was warmed with occasional stirring until the methylene chloride and most of the water had evaporated. After standing overnight, the residue was triturated with hot water and was cooled by addition of ice and filtered to give 14.2 g of 2,4-dimethylthio-5-sulfamylacetanilide: mp 193–195° (recrystallization from ethanol raised the melting point to 194–196.5° without change in the ir spectrum); λ_{max}^{KBr} 2.98, 5.98, 7.37, 7.53, 8.62 μ; $\lambda_{max}^{CH_3OH}$ 261.5 mμ (ϵ 27,600); δ 7.27 (SO_2NH_2), 9.40 (NH) (see also Table I).

Anal. Calcd for $C_{10}H_{14}N_2O_3S_3$: N, 9.15; S, 31.39. Found: N, 9.28; S, 31.14.

2,4-Dimethylthio-5-(N,N-dimethyl)sulfamylacetanilide (9).—2,4-Dimethylthioacetanilide[11] (510 mg) in 20 ml of dry, alcohol-free chloroform[3] was cooled in an ice bath and treated dropwise over 5 min with stirring with 3 ml of chlorosulfonic acid. After 20 min, the reaction mixture was poured onto ice and the solid which separated was collected and treated with 20 ml of cold dimethylamine in an evaporating dish. Trituration and evaporation of excess dimethylamine at room temperature gave a solid. The solid was taken up in methylene chloride–benzene and the solution was dried and clarified. On evaporation of the methylene chloride, crystallization gave 436 mg of 2,4-dimethylthio-5-(N,N-dimethyl)sulfamylacetanilide: mp 127–128.5°; $\lambda_{max}^{CHCl_3}$ 2.98, 3.32, 3.42, 5.88, and 6.42 μ; $\lambda_{max}^{CH_3OH}$ 264 mμ (ϵ 28,100) with shoulders at 277–285 and 310–322; δ 9.42 (NH) (see also Table I).

Anal. Calcd for $C_{12}H_{18}N_2O_3S_3$: C, 43.09; H, 5.42; N, 8.38. Found: C, 43.23; H, 5.42; N, 8.39.

2,4-Dimethylthio-5-chlorosulfonylacetanilide (7).—For isolation of **7**, the solid (or semisolid paste) which separated after quenching the reaction from the two-phase chlorosulfonation (above) was separated from the water and chloroform and was taken up in methylene chloride (difficultly soluble). The remaining aqueous layer was further extracted with methylene

(21) The 4-chloro isomer has been reported.[9]

(22) An isomer of **6** has been reported.[6a]

chloride and benzene and the combined organic extracts were dried (Na_2SO_4) and boiled down with benzene to induce crystallization. From 1.5 g of dimethylthioacetanilide, this gave 1.47 g, mp 183.5–184° dec. The original chloroform layer was extracted with cold water, dried, and blown down with nitrogen; crystallization from methylene chloride–benzene gave 150 mg, mp 184–186° dec, and dilution of the combined filtrates with *n*-pentane gave another 110 mg of sulfonyl halide, mp 183.5–184° dec. The first two crops were recrystallized from methylene chloride–cyclohexane to give 1.33 g, of fine, light yellow needles: mp 183.5–184° dec;[23] $\lambda_{max}^{CHCl_3}$ 2.9–2.95, 5.84 (5.88 sh), 6.92, 7.54, and 7.76 μ; $\lambda_{max}^{CH_3OH}$ 265.5 mμ (ϵ 23,500).

Anal. Calcd for $C_{10}H_{12}ClNO_3S_3$: C, 36.92; H, 3.72; Cl, 10.88. Found: C, 37.24; H, 3.90; Cl, 10.94.

2,4-Dimethylsulfonyl-5-sulfamylacetanilide (10a).—2,4-Dimethylthio-5-sulfamylacetanilide (2 g) was dissolved in hot acetic acid. The solution was stirred and cooled to approximately 60° and 150 ml of 0.28 *M* perbenzoic acid in benzene was added over 10 min with stirring. The reaction mixture was then heated for 40 min on the steam bath and cooled to give 1.9 g: mp 298–300° dec; λ_{max}^{KBr} 2.96, 2.99, 3.08, 5.84, 7.6, 8.5, 8.7 μ; δ 3.31 (NH), 7.0–8.5 (SO_2NH_2) (see also Table I).

Anal. Calcd for $C_{10}H_{14}N_2O_7S_3$: C, 32.92; H, 3.81; N, 7.56; S, 25.97. Found: C, 32.92; H, 4.07; N, 7.75; S, 25.79.

2,4-Dimethylsulfonyl-5-sulfamylaniline (10b).—2,4-Dimethylsulfonyl-5-sulfamylacetanilide (1.17 g) was suspended in 20 ml of ethanol and 3.0 ml of 8.5 *N* aqueous potassium hydroxide was added. The solution was stirred for 1.5 hr and then heated under reflux for 20 min. The reaction mixture was poured onto ice and neutralized with concentrated hydrochloric acid. The precipitate was collected and was recrystallized from pyridine–water to give 820 mg: mp 288–292° with slight decomposition; λ_{max}^{KBr} 2.86, 2.94, 3.05, 7.7, 8.55, 8.8 μ; $\lambda_{max}^{CH_3OH}$ 226 mμ (ϵ 27,600), 271 (17,650), 325 (5060); δ 7.2 (NH_2), 7.4 (SO_2NH_2) (see also Table I).

Anal. Calcd for $C_8H_{12}N_2O_6S_3$: N, 8.53; S, 29.29. Found: N, 8.31; S, 29.01.

N,N-Dimethyl(2,4-dimethylsulfonyl-5-sulfamyl)aniline (11).—2,4-Dimethylthio-5-sulfamylacetanilide (2 g), 20 ml of methanol, 5.0 ml of methyl iodide, and 0.64 ml (5% in excess of 1 equiv) of 8.5 *N* potassium hydroxide were heated under reflux with stirring for 20 min. At this point some of the starting material had not dissolved and the pH was 8–10. An additional 0.64 ml of base was added and the reaction mixture was heated under reflux for 40 min (pH 8). The reaction mixture was cooled, an additional 5.0 ml of methyl iodide was added, and two additional base treatments (0.64 ml each) with 40-min (to pH 6) and 25-min reflux periods, respectively, were made.

After cooling, dilution with water gave a product of mp 228–231°. Recrystallization from ethanol gave 300 mg: mp 231–233°; λ_{max}^{KBr} 2.85, 2.94, 7.66, 8.65 μ; $\lambda_{max}^{CH_3OH}$ 220 mμ (ϵ 20,850), 268 (18,500), 327 (5100); δ 7.36 (SO_2NH_2) (see also Table I). Resonance bands at δ 2.74 and 2.80 are in the correct position for the corresponding dimethylsulfamyl compounds. These bands and the amino band at δ 6.88 indicate approximately 15% of materials methylated on the sulfamyl nitrogen and lacking methylation on the amino nitrogen.

Anal. Calcd for $C_{10}H_{16}N_2O_6S_3$: N, 7.86; S, 26.97. Found: N, 7.51; S, 27.19.

The ethanol filtrate gave a second crop of 800 mg, mp 229–232°. The ir spectrum was identical with that of the first crop.

Oxidation of 7.—*m*-Chloroperbenzoic acid (550 mg, 10% excess) and 200 mg of **7** were dissolved in 3 ml of acetic acid. An initial vigorous reaction was followed by heating for 20 min at 65–70°. The reaction mixture was cooled and diluted with ice and water to give a solid, mp 157.5–168.5° dec. It was taken up in methylene chloride, dried, and crystallized by addition of ether to give 71 mg of **12**: mp 179.5–185° dec; $\lambda_{max}^{CH_3OH}$ 225 mμ (ϵ 27,400), 263 (14,300), 303 (6550); for δ values see Table I.

Anal. Calcd for $C_{10}H_{15}ClNO_7S_3$: C, 30.81; H, 3.10. Found: C, 31.12; H, 3.13.

2,4-Dimethylsulfonyl-5-(N,N-dimethyl)sulfamylacetanilide (13). A. **From 9.**—A solution of 150 mg of potassium permanganate (one oxygen equivalent in excess) in 3 ml of water was added dropwise to 150 mg of **9** in 2 ml of acetic acid with slight warming for the first half of the addition and then at room temperature. Ice and water were added to give a dark solid which was suspended in dilute aqueous sulfuric acid and treated with 500 mg of sodium bisulfite. This gave 50 mg of a tan precipitate, mp 128.5–129.5°, which was not further investigated.

The original filtrate was clarified by treatment with 100–200 mg of sodium bisulfite to give a clear solution which was combined with the filtrate from the tan precipitate. The solution was basified and extracted with chloroform to give a solid. The material was washed with methanol to give 46 mg, mp 233–236°. Recrystallization from dimethylformamide–water raised the melting point to 250–258° and, finally, recrystallization from pyridine–water gave 28 mg, mp 253–258° with softening from 243°.

On further standing a third crop of 68 mg, mp 228–228.5°, was obtained from the filtrate. Recrystallization from methylene chloride–methanol gave 42.5 mg of **13**: mp 226–227°; λ_{max}^{KBr} 2.99, 5.87, 6.3 (sh), 6.4, 6.7, 7.6 μ; $\lambda_{max}^{CH_3OH}$ 223.5 mμ (ϵ 27,700), 262 (ϵ 17,400), 304 (7450); for δ values, see Table I.

Anal. Calcd for $C_{12}H_{18}N_2O_7S_3$: C, 36.18; H, 4.55. Found: C, 36.41; H, 4.51.

B. **From 12.**—Trituration of 40 mg of **12** with 5–10 ml of cold dimethylamine gave a light yellow solid after evaporation of excess amine. This was dissolved in a mixture of methylene chloride, methanol, and water and the organic solvents were blown off with nitrogen. Standing overnight gave 26 mg of crystals, mp 200–233°. Attempts at further purification were unsuccessful. A crop of 4 mg, mp 184–216°, had an ir spectrum similar to that of **13** obtained in A (above), but with considerably diminished bands at 2.99 and 5.87 and additional absorption at 2.90 μ (NH_2), suggesting that hydrolysis to the free amine of **13** had occurred in part.

Registry No.—**1**, 19185-64-9; **2**, 19185-65-0; **4**, 19185-66-1; **5**, 19185-67-2; **6**, 19185-68-3; **7**, 19185-69-4; **8**, 19185-70-7; **9**, 19185-71-8; **10a**, 19185-72-9; **10b**, 19185-73-0; **11**, 19185-74-1; **12**, 19185-75-2; **13**, 19185-76-3; 2-sulfamyl-4-chloroacetanilide, 19185-77-4.

(23) This and the earlier samples resolidified immediately after very rapid decomposition (bubbling) to a light reddish brown amorphous solid. This material partially liquified further to *ca.* 220° showing further resolidification and darkening above 250°.

Beckmann Rearrangement of Some Benzophenone Oximes Having an *ortho*-N-Substituted Carboxamide or Sulfonamide Group Leading to Cyclization[1]

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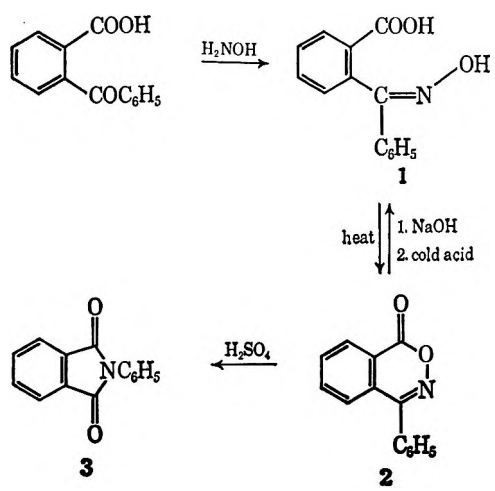
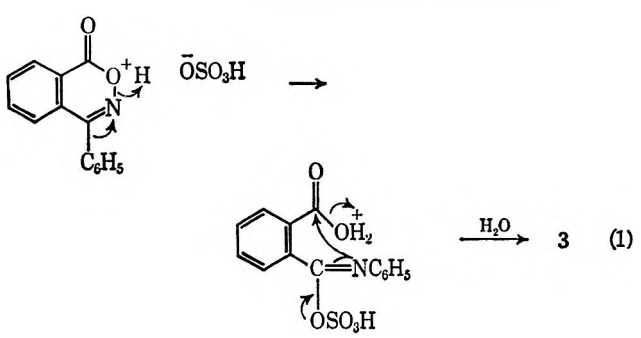
Although oximation of *o*-benzoylbenzoic acid is accompanied by cyclization to form the lactone, ring opening of this lactone with sodium hydroxide and lithiobenzylamine to form the corresponding oxime acid and oxime amide was achieved. These *ortho*-substituted benzophenone oximes underwent Beckmann rearrangement, accompanied by cyclization, with phosphorus pentachloride to form phthalanil; also, the intermediate diamide was isolated from the oxime amide. In contrast, benzophenone oximes having an *ortho*-N-substituted sulfonamide group were prepared by oximation of corresponding imine sulfonamides and found to undergo rearrangement accompanied by a different type of cyclization, with phosphorus pentachloride to form saccharin anils. Possible mechanisms and reasons for the different modes of cyclization are considered, and the synthetic utility of some of the reactions is indicated.

It has previously been shown that oximation of *o*-benzoylbenzoic acid to form oxime acid **1** is accompanied by cyclization to give lactone **2**,[2,3] and that treatment of **2** with concentrated sulfuric acid affords phthalanil (**3**)[4] (Scheme I).

SCHEME I



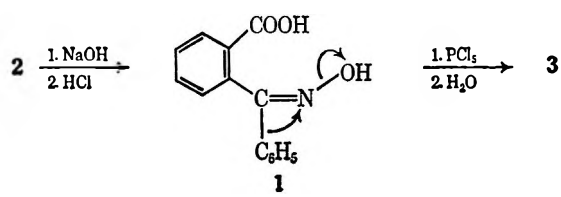
The conversion of lactone **2** into phthalanil (**3**) was apparently assumed to involve ring opening to form oxime acid **1** which underwent a Beckmann rearrangement accompanied by cyclization.[4] However, rearrangement of lactone **2** without intermediate formation of **1** now seems more likely (eq 1).



In the present investigation oxime acid **1** and, more significantly, certain related oxime amides and oxime sulfonamides were found to undergo interesting rearrangement-cyclizations with phosphorus pentachloride.

Although oxime acid **1** was not prepared satisfactorily by oximation of *o*-benzoylbenzoic acid (see Scheme I),[2] **1** was obtained by ring opening of lactone **2** with aqueous sodium hydroxide, and found to undergo rearrangement–cyclization with phosphorus pentachloride in tetrahydrofuran (THF) to form phthalanil (**3**) (Scheme II).

SCHEME II



Similarly, oxime amide **4** was prepared by ring opening of lactone **2** with lithiobenzylamine in THF and found to undergo rearrangement and/or rearrangement–cyclization with phosphorus pentachloride in ether or THF to form diamide **5** and phthalanil (**3**), respectively (Table I). Diamide **5** was independently synthesized from N-benzylbenzamide (**6**) and phenyl isocyanate by means of *n*-butyllithium (Scheme III).[5]

TABLE I

YIELDS OF DIAMIDE 5 AND PHTHALANIL (3) FROM OXIME AMIDE 4 WITH PHOSPHORUS PENTACHLORIDE UNDER VARIOUS CONDITIONS

Solvent	Reaction temp, °C	Nature of medium	Yields % 5	Yields % 3
Ether	0[a]	Heterogeneous	90	
Ether	35	Heterogeneous	6	85
THF	0[a]	Homogeneous		74
THF–ether	0[a]	Homogeneous	10	60

[a] The latter part of the reaction may have occurred at 25–30° (see Experimental Section).

(1) Supported by Army Research Office (Durham) and by the National Science Foundation.

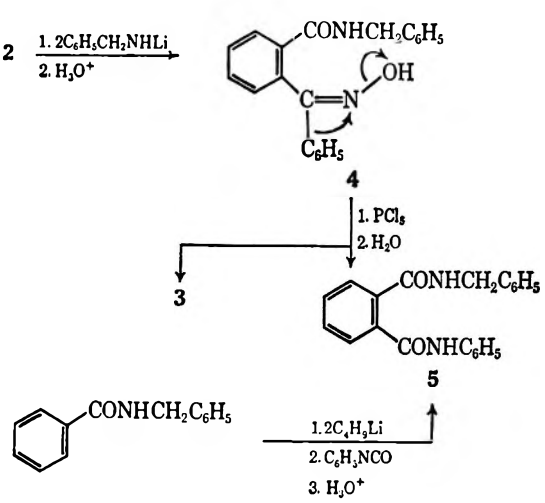
(2) F. H. Thorp, *Ber.*, **26**, 1795 (1893). Isolation of intermediate oxime acid **1** has more recently been reported by no yield was given: M. V. Patiyardhan, N. L. Phalnikar, and B. V. Bhide, *J. Univ. Bombay*, **18** (Pt. 5, Sect. A), 22 (1950).

(3) We have observed that oximation of *o*-benzoylbenzanilide is similar accompanied by cyclization to form lactone **2**.

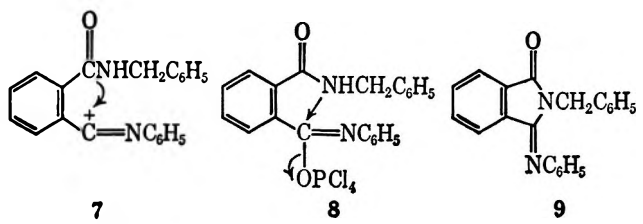
(4) J. Meisenheimer and J. H. Meis, *Ber.*, **57**, 289 (1924). For similar results with ring substituted lactone **2**, see B. Oddo and D. Curti, *Gass. Chim. Ital.*, **54**, 577 (1924).

(5) For related condensations at the *ortho* position of N-methylbenzamide see W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

SCHEME III



Although diamide **5** was the expected rearrangement product, phthalanil (**3**) was not necessarily the anticipated rearrangement–cyclization product. Since the indicated rearrangement of oxime amide **4** (see Scheme III) should form carbonium ion **7** or phosphorus chloride complex **8**, direct cyclization to give anil **9** seemed possible. That **9** was not produced as an intermediate and then converted into phthalanil (**3**) was shown by a blank experiment with **9** and phosphorus pentachloride with which **9** was found to be stable; **9** was prepared by a known method.



The formation of phthalanil (**3**) is suggested to involve cyclization of complex **10** to form **11** which affords **3** on hydrolysis (eq 2); complex **10** is a protonated species of complex **8**. Of course protonation of oxime amide **4** may occur leading directly to complex **10** on rearrangement. Also, diamide **5** could arise by hydrolysis of complex **10**.

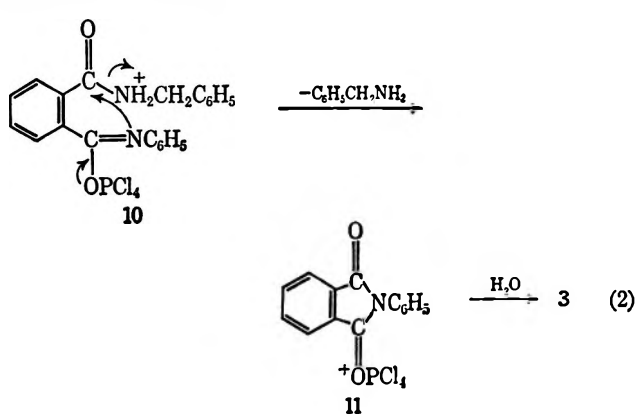


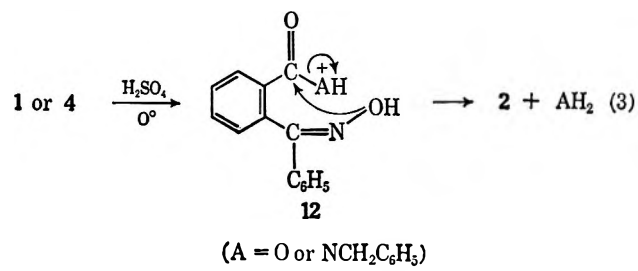
Table I shows that the relative yields of diamide **5** and phthalanil (**3**) were dependent on the temperature at which the reaction was effected and on the solvent used. Appratently the greater solubility of the reactants in THF favored cyclization to form **3**.

As might be expected, diamide **5** underwent cyclization to form phthalanil (**3**) with phosphorus pentachloride. However, conversion of **5** into **3** occurred more slowly than that of oxime amide **4** to **3** (see Experimental Section). This indicates that intermediate formation of an enol-type complex such as **10** is required for the cyclization. Also, diamide **5** was cyclized to form **3** with refluxing hydrochloric acid.

In contrast to phosphorus pentachloride, concentrated sulfuric acid failed to effect rearrangement of oxime acid **1** or oxime amide **4** at 0–25°; instead, cyclization occurred to regenerate lactone **2**, the protonated species **12** presumably being an intermediate (eq 3).

This regeneration of lactone **2** by sulfuric acid may be regarded as indirect evidence that the conversion of **2** into phthalanil (**3**) by this acid observed earlier[4] (presumbaly under more drastic conditions) did not involve the intermediate formation of oxime acid **1** (see above).

The indicated configurations of oxime acid **1** and oxime amide **4** in which phenyl and hydroxyl are *trans* were supported, not only by migration of phenyl group in the rearrangements, but also by the ring openings with nucleophiles and ring closure with cold sulfuric acid (see Schemes II and III and eq 3).



(A = O or $NCH_2C_6H_5$)

In contrast to oxime acid **1** and oxime amide **4**, oxime sulfonamides **14a** and **14b** were prepared by an oximation reaction and found to undergo Beckmann rearrangement accompanied by a different type of cyclization than that observed with **1** and **4**. Thus, **14a** and **14b** were obtained from imine sulfonamides **13a** and **13b**[6] and hydroxylamine and found to undergo rearrangement and/or rearrangement–cyclization with phosphorus pentachloride in ether or ether–THF to form *o*-sulfamylbenzanilides **17a** and **17b** and/or saccharin anils **16a** and **16b**, respectively (Table II). The latter compounds, which presumably arose through cyclizations of phosphorus chloride complexes **15a** and **15b** or the corresponding chloride or carbonium ions, underwent acid-catalyzed hydrolysis to give *o*-sulfobenzoic imides **18a** and **18b** respectively (Scheme IV). The indicated *trans* configuration of the oximes **14a** and **14b** was supported by migration of the phenyl group in the rearrangement.

Table II shows that the saccharin anils **16a** and **16b** were obtained exclusively under three of the four conditions studied but that the uncyclized *o*-sulfamylbenzamide **17b** was isolated in good yield when the reaction was effected in ether–THF at 0° for only 3.5 hr. Although *o*-sulfamylbenzanilide **17a** was not found under these conditions, it presumably could be isolated under milder conditions. Evidently phosphorus chlo-

(6) For preparation and ring-chain tautomerism of these compounds, see H. Watanabe, C.-L. Mao, I. T. Barnish, and C. R. Hauser, *J. Org. Chem.*, **34**, 919 (1969).

TABLE II

YIELDS OF *o*-SULFAMYLBENZANILIDES **17a** AND **17b** AND SACCHARIN ANILS **16a** AND **16b** FROM OXIME SULFONAMIDES **14a** AND **14b** WITH PHOSPHORUS PENTACHLORIDE

					Yields			
Oxime	Solvent	Temp, °C	Time, hr	Nature of medium[a]	Product	%	Product	%
14a	Ether	25–30	16	Heterogenous	**17a**	0	**16a**	88
14a	Ether–THF	0	3.5	Homogenous	**17a**	0	**16a**	89
14b	Ether	35	24	Heterogenous	**17b**	0	**16b**	93
14b	Ether–THF	0	3.5	Homogenous	**17b**	54	**16b**	42

[a] At the end of the reaction period.

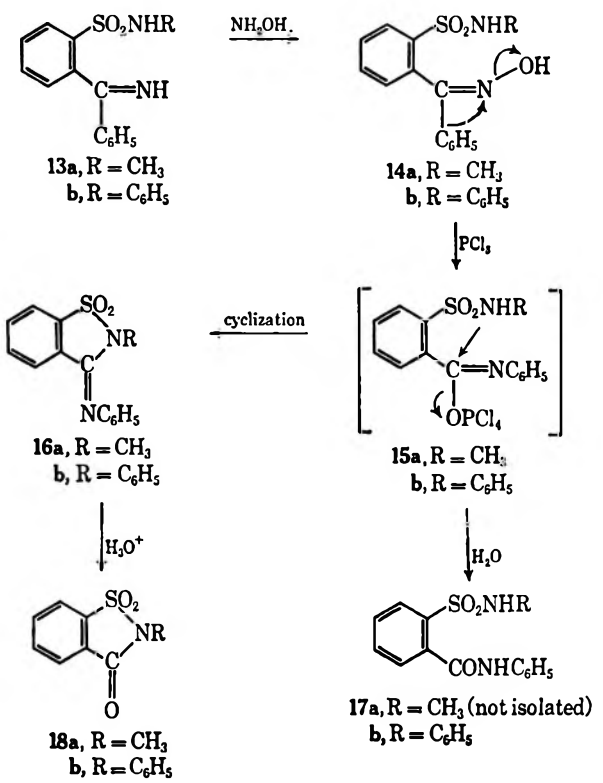
TABLE III

YIELDS OF SACCHARIN ANILS **16a** AND **16b** FROM *o*-SULFAMYLBENZANILIDES **17a** AND **17b** WITH PHOSPHORUS PENTACHLORIDE AND OXYCHLORIDE

						Yields	
Anilide	Reagent	Solvent	Temp, °C	Time, hr	Nature of medium	Product	%
17a	PCl_5	Ether	35	24	Heterogenous	**16a**	22
17a	PCl_5	Ether–THF	0	3.5	Heterogenous	**16a**	0
17a	$POCl_3$	$POCl_3$	107[a]	0.5	Homogenous	**16a**	80
17b	PCl_5	Ether	35	24	Heterogenous	**16b**	54
17b	PCl_5	Ether–THF	0	3.5	Homogenous	**16b**	0
17b	$POCl_3$	$POCl_3$	107[a]	0.5	Homogenous	**16b**	84

[a] Refluxing temperature of phosphorus oxychloride.

SCHEME IV



ride complex **15a** underwent cyclization more readily than complex **15b**, but this is not surprising since the N-methyl group should be a better nucleophile than the N-phenyl group.

Both of the *o*-sulfamylbenzanilides **17a** and **17b** were synthesized more conveniently from sulfonamides **19a** and **19b** and phenyl isocyante by means of *n*-butyllithium;[7] they were then cyclized with phosphorus pentachloride or, preferably, with phosphorus oxychloride to form the saccharin anils **16a** and **16b**, respectively (Scheme V, Table III).

SCHEME V

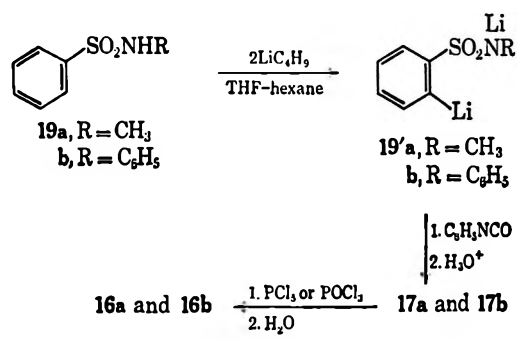
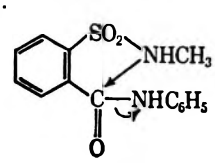


Table III shows that, when phosphorus pentachloride was used, the yields of the saccharin anils **16a** and **16b** from the *o*-sulfamylbenzanildes **17a** and **17b** were considerably lower than those obtained from oximes **14a** and **14b** even under milder conditions. This indicates that, before the cyclization could occur, conversion of **17a** and **17b** into enol-type intermediates such as **15a** and **15b** is required. Actually, good yields of the saccharin anils **16a** and **16b** were obtained from **17a** and **17b** only with phosphorus oxychloride, but this reagent was employed at a much higher temperature than phosphorus pentachloride (see Table III).

Whereas carboxamide sulfonamides **17a** and **17b** underwent cyclization with phosphorus pentachloride or oxychloride to form saccharin anils **16a** and **16b** (see Scheme V), carboxamide sulfonamide **17a** was found to undergo thermal cyclization to give *o*-sulfobenzoic imide **18a** and aniline (eq 4). Indeed this method of preparation of **18a** is preferable to that involving hydrolysis of the saccharin anils (see Scheme IV).



→ **18a** + $C_6H_5NH_2$ (4)

(7) For related condensations by this method, see H. Watanabe and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).

In contrast to phosphorous pentachloride, concentrated sulfuric acid failed to effect the Beckmann rearrangement of oxime sulfonamides **14a** and **14b** at 0–100°; at 100°, **14a** was converted into the corresponding ketone sulfonamide.

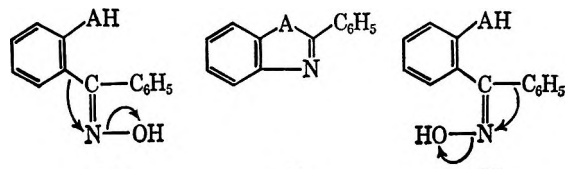
Discussion

The fact that Beckmann rearrangements of oxime amide **4** and axime sulfonamides **14a** and **14b** were accompanied by different types of cyclization is interesting. Apparently protonation at the amide nitrogen of **4** before rearrangement or of carbonium ion **7** or complex **8** after rearrangement prevented the type of cyclization indicated in **7** and **8**, since such protonation at the sulfonamide nitrogen of **14a** and **14b** or of complexes **15a** and **15b** should occur to a much less extent. Moreover, even if such protonation of **14a** and **14b** or **15a** and **15b** did occur, the type of cyclization indicated in complex **10** involving the carbonyl group should not be expected with the sulfonamide, since the sulfonyl group is known to be much less susceptible to such a nucleophilic attack.

Although the *trans* configuration of the oxime amide **4** seems well established, especially by the nucleophilic ring opening of lactone **2** (see Scheme III), that of the oxime sulfonamides **14a** and **14b** might be questioned. Thus, had the latter compounds had the *syn* configuration, they might have undergone isomerization accompanied by Beckmann rearrangement of phenyl because of expected reluctance of the aryl group containing the strongly electron-attracting sulfonyl substituent to rearrange. Apparently, there is no well-established example of a Beckmann migration of an aryl group having a strongly electron-attracting substituent; this would require isolation of both of the isomers of the oxime in order to preclude the possibility of isomerization prior to rearrangement. An attempt to prepare the second isomer of oxime sulfonamide **14a** so that the configuration could be definitely established was unsuccessful.

Several of the types of reaction described above appear to be of synthetic value. They include the ring opening of lactone **2** with nucleophiles (see Schemes II and III), the rearrangement and *n*-butyllithium methods of preparation diamides such as **5** (see Scheme III), the oximation of imine sulfonamides and rearrangement of the resulting oxime sulfonamides (see Scheme IV), and, especially, the *n*-butyllithium method of synthesis of *o*-sulfamylbenzanilides and their cyclization to saccharin anils (see Scheme V). *o*-Sulfamylbenzanilide **17b** has previously been prepared by a rather tedious method.[8] Our method is, not only much simpler, but also more general. The cyclization of **17b** with phosphorous oxychloride to form saccharin anil **16b** has been reported earlier.[8]

It should be mentioned that only one other type of Beckmann rearrangement–cyclization appears to have been reported previously;[9] this involved compounds of type **20** where A is oxygen or nitrogen to form a cyclic product of type **21** (A = O or NH). The isomeric oxime **22** underwent rearrangement without cyclization to form the corresponding benzanilides.



20 **21** **22**

Experimental Section[10]

Preparation of Oxime Acid 1.—Lactone **2**[2] (2.0 g) was dissolved (stirred) in 50 ml of 6 *N* sodium hydroxide at 60–70°. The clear solution was cooled and poured onto an ice–hydrochloric acid mixture (stirred). The precipitate was collected, washed with water, and redissolved in aqueous sodium bicarbonate solution. The solution was acidified with ice-cooled hydrochloric acid, and the resulting precipitate was collected to give 1.75 g (81%) of oxime acid **1**: mp 120–125° dec (lit.[2] mp 118°); ir 2800–3480 (broad, COOH) and 1700 cm^{-1} (C=O). The melting point sample resolidified to form lactone **2**, mp 162–164° (lit.[2] mp 163°).

Rearrangement–Cyclization of Oxime Acid 1 with Phosphorus Pentachloride.—To a stirred solution of 1.2 g (0.005 mol) of oxime acid **1** in 50 ml of THF[11] in an ice bath was added 1.5 g (0.0075 mol) of phosphorus pentachloride. After 2 hr, the ice bath was removed and the mixture was stirred at room temperature for 8 hr. The yellowish reaction mixture was poured onto ice–water. The layers were separated. The organic layer and two ethereal extracts of the aqueous layer were combined, dried (K_2CO_3), and evaporated. The residue was recrystallized from acetone–ethanol to give 0.9 g (80%) of phthalanil (**3**), mp and mmp 206–208° (lit.[12] mp 206°).

Preparation of Oxime Amide 4.—To a stirred solution of 4.46 g (0.02 mol) of lactone **2** in 100 ml of THF[11] was added 0.04 mol of lithiobenzylamine, prepared from 0.04 mol each of benzylamine and *n*-butyllithium[13] in THF–hexane. After 2 hr, the reaction mixture was poured onto 10 ml of concentrated hydrochloric acid and 300 g of crushed ice. The layers were separated. The organic layer and ethereal extracts of the aqueous layer were combined and dried (K_2CO_3). The solvent was removed, and the residue was recrystallized from ethanol–benzene to give 4.1 g (62%) of oxime amide **4**: mp 175–176° dec; ir 3400 (NH and OH) and 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.62; H, 5.53; N, 8.40.

Rearrangement of Oxime Amide 4 with Phosphorus Pentachloride.—In Table I are summarized the results obtained from this reaction under various conditions. The details are described below.

A. In Ether.—To a stirred suspension of 2.0 g of **4** in 200 ml of anhydrous ether cooled in an ice bath was added 2.5 g of phosphorus pentachloride. After 3 hr, the ice bath was removed, and stirring was continued at room temperature for 8 hr. The reaction mixture was poured onto ice–water, and the layers were separated. The organic layer (containing suspension) was combined with ethereal extracts of aqueous layer. The resulting solution was dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was recrystallized from acetonitrile–dimethylformamide (DMF) to give 1.8 g (90%) of diamide **5**: mp 182–184°; ir 3470, 3450 (NH), 1690, and 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.10; H, 5.53; N, 8.42.

In another experiment, the mixture was refluxed for 6 hr and

(8) I. Remsen and J. H. Hunter, *Amer. Chem. J.*, **18**, 809 (1896).

(9) See A. H. Blatt, *J. Org. Chem.*, **20**, 591 (1955).

(10) Melting points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich. Ultraviolet (uv) spectra were produced on a Beckman DB-G spectrophotometer using ethanol solvent. Infrared (ir) spectra (KBr method) were produced on a Perkin-Elmer Infracord Models 137 and 237. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (δ 0 ppm) as an internal standard.

(11) Freshly distilled from lithium aluminum hydride.

(12) Porai-Koshitz, *Trans. Leningrad Chem.-Tech. Inst.*, **1**, 135 (1934).

(13) Foote Mineral Co., Exton, Pa.

then poured onto ice–water. The resulting suspension was filtered. The solid was combined with the residue obtained from the organic layer and fractionally crystallized from acetonitrile–DMF to give **5** and **3** (see Table I).

B. In THF.—To a stirred solution of 1.0 g of **4** in 100 ml of THF[11] cooled in an ice bath was added 1.0 g of phosphorus pentachloride to produce a yellow solution. After 2 hr, the ice bath was removed, and stirring was continued at room temperature for 8 hr. The reaction mixture was poured onto ice and worked up essentially as described in method A to give, after recrystallization from acetone–ethanol, 0.7 g (74%) of **3**, mp 206–208° (lit.[12] mp 206°).

Anal. Calcd for $C_{14}H_9NO_2$: C, 75.32; H, 4.07; N, 6.28. Found: C, 75.02; H, 4.04; N, 6.12.

The reaction was repeated in equal volume of THF[11] and ether to give **5** and **3** (see Table I).

Independent Synthesis of Diamide 5 from N-Benzylbenzamide and Phenyl Isocyanate by Butyllithium.—To a stirred solution of 0.01 mol of N-benzylbenzamide (**6**) in 50 ml of THF[11] at 0° was added 0.02 mol of *n*-butyllithium in hexane[13] under nitrogen atmosphere followed, after 30 min, by 0.01 mol of phenyl isocyanate in 10 ml of THF.[11] After 30 min, the reaction mixture was poured onto ice–water and worked up to give 0.67 g (20%) of diamide **5**, mp and mmp 182–184°. This yield could probably be improved.

Blank Experiment with Anil 9 and Phosphorus Pentachloride.—Anil **9** was prepared as described previously[14] and treated with excess phosphorus pentachloride under the conditions employed for the rearrangement of oxime amide **4** and, also, in the presence of a little water to form hydrogen chloride which would presumably be produced in the rearrangement of **4**. In all cases 90% or more of the starting anil **9** was recovered.

Cyclization of Diamide 5 with Reagents. A. With Phosphorus Pentachloride.—To a stirred solution of 0.5 g of diamide **5** in 50 ml of THF[11] at 0° was added 0.6 g of phosphorus pentachloride. After 2 hr, the reaction mixture was stirred at room temperature for 48 hr, then poured onto ice–water, and worked up to give 0.25 g (74%) of phthalanil (**3**), mp and mmp 205–207°.

When the reaction mixture was allowed to stir for only 8 hr at room temperature, only starting diamide **5** was recovered.

B. With Concentrated Hydrochloric Acid.—Diamide **5** (0.5 g) was refluxed with 20 ml of concentrated hydrochloric acid for 2 hr. After cooling, the reaction mixture was worked up to give 0.27 g (80%) of phthalanil (**3**), mp 206–208°, and some benzylamine (identified by ir spectrum).

Cyclization of Oxime Acid 1 and Oxime Amide 4 with Sulfuric Acid.—Oxime acid **1** (1.0 g) was dissolved in 10 g of concentrated sulfuric acid at 0°. After 30 min, the solution was poured onto ice. The resulting precipitate was collected, washed with 5% of sodium bicarbonate solution, and then water, and recrystallized from 95% ethanol to give 0.8 g (86%) of lactone **2**, mp and mmp 163–165° (lit.[2] mp 163°).

Similarly, oxime amide **4** (1.0 g) was dissolved in 10 g of concentrated sulfuric acid at 0°, but the solution was then allowed to warm to room temperature. After 2 hr, the yellow solution was poured onto ice, and the resulting white precipitate was collected and recrystallized to give 0.6 g (82%) of lactone **2**, mp and mmp 162–164°.

Preparation of Oxime Sulfonamides 14a and 14b.—A solution containing 5.50 g (0.02 mol) of imine sulfonamide **13a**,[6] 2.23 g (0.032 mol) of hydroxylamine hydrochloride, and 8.16 g (0.06 mol) of sodium acetate hydrate ($3H_2O$) in 200 ml of 70% (by weight) aqueous ethanol was refluxed for 24 hr and then cooled. The ethanol was evaporated in a current of air under a hood to leave an aqueous mixture containing an oil, which solidified on scratching. The mixture was stirred with 100 ml of water and filtered. The solid was washed with water and dried in air to give, after two recrystallizations from methanol, 4.28 g (75%) of *o*-(N-methylsulfamyl)benzophenone oxime (**14a**): mp 156.5–158.5°; ir 3400 (OH), 3230 (NH), 1310, and 1358 cm^{-1} (SO_2); nmr (acetone-d_6) δ 10.53 (s, 0.9, OH), 8.20–7.00 (m, 10.0, aromatic), 5.45 (broad, 1.1, NH), and 2.50 ppm (d, 3.0, J = 4.0 cps, NCH_3).

Anal. Calcd for $C_{14}H_{14}N_2SO_3$: C, 57.91; H, 4.86; N, 9.65. Found: C, 57.53; H, 4.80; N, 9.40.

Similarly, a solution of 3.03 g (0.009 mol) of imine sulfonamide **13b**, 1.26 g (0.018 mol) of hydroxylamine hydrochloride, and 3.69 g (0.027 mol) of sodium acetate hydrate in 150 ml of 70% aqueous ethanol was refluxed for 24 hr. Evaporation of the solvent left a solid, which was collected, washed with 95% ethanol, and dried to give 2.95 g (93%) of *o*-(N-phenylsulfamyl)-benzophenone oxime (**14b**): glittering fine leaflets; mp 220–221° dec; ir 3420 (OH), 3180 (NH), 1320 and/or 1310 (SO_2), and 1155 cm^{-1} (SO_2).

Anal. Calcd for $C_{19}H_{16}N_2SO_3$: C, 64.75; H, 4.58; N, 7.95. Found: C, 64.82; H, 4.53; N, 7.67.

Attempts to condense the corresponding ketone sulfonamides with hydroxylamine under similar conditions or in the presence of sodium hydroxide were unsuccessful, and the starting ketones were recovered.

Rearrangement of Oxime Sulfonamides 14a and 14b with Phosphorus Pentachloride.—In Table II are summarized the results obtained under various conditions. The details are described below.

A. Rearrangement of 14a to Form 16a.—To a stirred mixture of 1.0 g of oxime sulfonamide **14a** in 100 ml of dry ether cooled in an ice bath was added 1.0 g of phosphorus pentachloride. After stirring at room temperature for 16 hr, the reaction mixture (faint yellow solution with white solid) was poured onto 50 g of crushed ice. The acidic mixture was made basic with potassium carbonate, and the layers were separated. The ethereal layer was combined with ethereal extracts of the aqueous layer. The ethereal solution was washed with saturated sodium chloride solution and dried ($MgSO_4$) and the solvent was removed. The residue was recrystallized from methanol to give 0.82 g (88%) of N-methyl saccharin anil (**16a**): prismatic crystals; mp 139–140.5°; uv λ_{max} 335 mμ (log ϵ 3.7) and 238 (4.5); ir 1660 (strong, C=N), 1320 and/or 1290 (SO_2), and 1185 and/or 1175 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.10–6.70 (m, 9.4, aromatic) and 3.30 ppm (s, 2.8, NCH_3).

Anal. Calcd for $C_{14}H_{12}N_2SO_2$: C, 61.74; H, 4.44; N, 10.29. Found: C, 61.80; H, 4.67; N, 10.10.

Similarly, a solution of 0.3 g of oxime sulfonamide **14a** in 15 ml of THF[11] and 10 ml of dry ether was treated at 0° with 0.3 g of phosphorus pentachloride. After stirring at 0° for 3.5 hr, the pale yellow solution was poured onto 10 g of crushed ice and worked up to give **16a** (see Table II).

B. Rearrangement of 14b to Form 16b and 17b.—To 0.50 g of oxime sulfonamide **14b** in 100 ml of dry ether was added 0.50 g of phosphorus pentachloride, and the mixture was refluxed for 24 hr. The solid dissolved but soon a faint yellow precipitate formed. After cooling, the reaction mixture was poured onto crushed ice, and the resulting mixture was shaken with 30 ml of benzene. After making basic with potassium carbonate, the layers were separated. The organic layer was combined with a 50:50 benzene–ether extract of the aqueous layer; the solution was washed with saturated sodium chloride solution and dried ($MgSO_4$). The solvent was removed, and the residue was recrystallized from 95% ethanol to give 0.44 g (93%) of N-phenyl saccharin anil (**16b**): yellow prismatic crystals; mp 190.5–192° (lit. mp 189.5°,[8] 187–189°[15]); uv λ_{max} 338 mμ (log ϵ 3.7) and 238 (shoulder) (4.6); ir 1660 (strong, C=N), 1320 and/or 1295 (SO_2), and 1177 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.20–6.60 ppm (m, aromatic).

Anal. Calcd for $C_{19}H_{14}N_2SO_2$: C, 68.24; H, 4.22; N, 8.38. Found: C, 68.21; H, 4.59; N, 8.27.

Similarly, a solution of 0.40 g of oxime sulfonamide **14b** in 30 ml of THF[11] and 10 ml of dry ether at 0° was treated with 0.40 g of phosphorus pentachloride. After stirring at 0° for 3.5 hr, the faint yellow solution was poured onto 15 g of crushed ice and made basic with sodium carbonate and most of the organic solvent was evaporated in air (hood). The resulting solid was collected, washed with water, and dried in air. The solid (0.46 g) was fractionally crystallized from 95% ethanol to give, first, 0.16 g (42%) of N-phenyl saccharin anil (**16b**), fine yellow crystals, mp 185–189° and 189–191° after recrystallization from ethanol, and, second, 0.21 g (54%) of *o*-sulfobenzdianilide (**17b**), fine needles, mp 186–191° and 191–193.5° after recrystallization from methanol.

Hydrolysis of Saccharin Anils 16a and 16b to Form *o*-Sulfobenzoic Imides 10a and 10b.—A mixture of 0.30 g of saccharin anil **16a** and 16 ml of 20% hydrochloric acid was refluxed for

(14) I. K. Kormendy, *Acta Chim. Acad. Sci. Hung.*, **17**, 255 (1958).

(15) J. A. Jesurun, *Ber.*, **26**, 2292 (1893).

30 min and then cooled in an ice bath. The precipitate was collected, washed with water, and dried to give 0.15 g (69%) of N-methyl-*o*-sulfobenzoic imide (**18a**), fine needles, mp 126–128° and 130.5–131.5° after recrystallization from 95% ethanol. Admixture with an authentic sample[7] of **18a** (mp 131.5–132°) showed no depression (mmp 130.5–132°) and the ir spectra of the two samples were identical.

The acidic filtrate (and washings) was concentrated and treated with sodium hydroxide and benzoyl chloride to give 0.14 g (62%) of benzanilide, mp and mmp 162–164°.

Similarly, 0.40 g of saccharin anil **16b** was refluxed with 10 ml of concentrated hydrochloric acid for 1 hr. After cooling, the mixture was filtered. The solid was washed with water and dried to give 0.28 g (90%) of N-phenyl-*o*-sulfobenzoic imide (**18b**), mp 188–190° and 191–192° after recrystallization from 95% ethanol. Admixture with an authentic sample[7] of **18b** (mp 192–192.5°) showed no depression (mmp 191–192°) and the ir spectra of the two samples were identical.

Aniline was isolated from the filtrate as benzanilide, mp 162–164°, in 49% yield.

Synthesis of *p*-Sulfamylbenzanilides by *n*-Butyllithium Method.—To a stirred suspension of dilithiosulfonamide **19'a** in THF–hexane at 0° under nitrogen,[7] prepared from 0.025 mol of N-methylbenzenesulfonamide (**19a**) and 37 ml (0.055 mol) of 1.6 *M* *n*-butyllithium in hexane,[13] was added a solution of 3.57 g (0.03 mol) of phenyl isocyanate in 30 ml of THF.[11] After 30 min, the reaction mixture was decomposed with water followed by 5% hydrochloric acid. After evaporation of THF in air, the mixture was filtered. The solid was washed with ether and dried to give 4.86 g (67%) of *o*-(N-methylsulfamyl)benzanilide (**17a**), mp 202.5–204.5°, and 4.76 g (66%) of **17a**: fine prismatic crystals; mp 204–206° after recrystallization from acetone–methanol; ir 3323 (NH in SO_2NH), 3250 (NH in CONH), 1660 and 1642 (CO), and 1320 and 1160 cm^{-1} (SO_2).

Anal. Calcd for $C_{14}H_{14}N_2SO_3$: C, 57.91; H, 4.86; N, 9.65. Found: C, 58.17; H, 4.94; N, 9.87.

Similarly, dilithiosulfonamide **19'b**, prepared from N-phenylbenzenesulfonamide (**19b**) and *n*-butyllithium,[7] was treated with phenyl isocyanate to give 4.70 g (53%) of *o*-sulfobenzdianilide (**17b**): prismatic crystals, mp 190–194° and 193.5–195.5° after recrystallization from acetone–methanol (lit. mp 196°,[16a] 192°[16b]); ir 3320 (NH in SO_2NH), 3200 (NH in CONH), 1650 (CO), and 1320 and 1160 cm^{-1} (SO_2); nmr (acetone-d_6) δ 7.95–6.80 ppm (m, aromatic).

Anal. Calcd for $C_{19}H_{16}N_2SO_3$: C, 64.75; H, 4.58; N, 7.95. Found: C, 64.66; H, 4.60; N, 7.90.

Admixture with a sample obtained in the rearrangement described above (under B) showed no depression (mmp 193–195°) and the ir spectra of the two samples were identical.

Cyclizations of *o*-Sulfobenzdiamides 17a and 17b to Form Saccharin Anils 16a and 16b.—In Table III are summarized the results obtained under various conditions. The details are described below.

A. Phosphorus Pentachloride Method.—To a suspension of 1.0 g of *o*-sulfobenzdiamide **17a** in 100 ml of dry ether was added 1.0 g of phosphorus pentachloride, and the mixture was stirred and refluxed for 24 hr. After cooling, the precipitate was collected and washed with ether to give 0.46 g (46%) of the recovered starting compound **17a**, mp 203.5–205°. The filtrate (and ethereal washings) was poured onto 20 g of crushed ice. The acidic mixture was made basic with sodium carbonate, and the solvent was removed in air (hood). The solid was collected to give a little more of recovered **17a**. The filtrate (and ethereal washings) was evaporated to give 0.21 g (22%) of N-methyl saccharin anil (**16a**), mp 138.5–139.5° after recrystallization from methanol. Admixture with a sample of **16a** obtained in the rearrangement described above showed no depression (mmp 138.5–139.5°) and the ir spectra of the two samples were identical.

Similarly, 1.0 g of *o*-sulfobenzdiamide **17b** in 100 ml of dry ether was treated with 1.0 g of phosphorus pentachloride. After stirring and refluxing for 24 hr, the mixture was poured onto crushed ice and made basic and most of the solvent was evaporated. The resulting solid was collected, washed with water, and dried in air. The solid was fractionally crystallized from methanol to give, first, 0.51 g (54%) of N-phenyl saccharin anil (**16b**), yellow fine leaftets, mp 187–189.5° and 188–189.5° after recrystallization from acetone–methanol, and second, 0.31 g (31%) of the recovered starting compound of **17b**, mp 187–188°. Admixture of the N-phenyl saccharin anil with a sample of **16b** obtained in the rearrangement described above showed no depression (mmp 189.5–190.5°) and the ir spectra of the two samples were identical.

Attempts to cyclize 0.40 g of *o*-sulfobenzdiamides **17a** and **17b** with 0.40 g of phosphorus pentachloride in 30 ml of THF[11] and 10 ml of dry ether at 0° for 3.5 hr, as described in the rearrangements of **14a** and **14b**, were unsuccessful, and the starting amides were recovered.

B. Phosphorus Oxychloride Method.—A mixture of 0.60 g of *o*-sulfobenzdiamide **17a** and 2.00 g of phosphorus oxychloride was refluxed for 30 min, and most of the excess oxychloride was distilled off under reduced pressure. The hot liquid residue was spread (by swirling) over as much surface of the flask as possible. After a few minutes, 50 g of ice–water was added and the resulting mixture was stirred. The yellow solid was collected, washed with water, and dried in air to give 0.45 g (80%) of N-methyl saccharin anil (**16a**), mp 133–137°, and 0.42 g (75%) of prismatic crystals, mp 138–140° after recrystallization from methanol (charcoal). Admixture with a sample of **16a** obtained in the rearrangement described above showed no depression (mmp 138–140°) and the ir spectra of the two samples were identical.

Similarly, 0.60 g of *o*-sulfobenzdiamide **17b** was treated with 2.00 g of phosphorus oxychloride[8] and worked up to give 0.57 g (100%) of N-phenyl saccharin anil (**16b**), mp 178–186°, and 0.48 g (84%), mp 188–189°, as yellow prismatic crystals after recrystallization from acetone–methanol (charcoal). Admixture with a sample of **16b** obtained in the rearrangement described above showed no depression (mmp 188–190°) and the ir spectra of the two samples were identical.

Thermal Cyclization of *o*-Sulfobenzdiamide 17a to Form 18a.—A 1.0-g sample of *o*-sulfobenzdiamide **17a** was heated on a Wood's metal bath at 240–250° for 5 hr in a slow stream of nitrogen and then cooled. The solid mass was washed with water and dried in air to give 0.59 g (82%) of N-methyl-*o*-sulfobenzoic imide (**18a**), mp 126–130°, and 0.46 g (68%), mp 130.5–132°, as fine prismatic plates after recrystallization from 95% ethanol. Admixture with an authentic sample[7] of **18a** showed no depression (mmp 131–132°) and the ir spectra of the two samples were identical. Aniline (0.04 g) was collected from the wall of the outlet tube of the reaction flask and identified by ir.

Attempt to Rearrange Oxime Sulfonamide 14a by Sulfuric Acid.—A solution of 0.20 g of **14a** in 2 ml of concentrated sulfuric acid was heated at 100° for 1 hr to give, on work-up, 0.17 g (90%) of *o*-(N-methylsulfamyl)benzophenone, mp 114–117° and 119–120.5° after recrystallization from ethanol. Admixture with an authentic sample[6] of this ketone sulfonamide (mp 119–120.5°) showed no depression, and the ir spectra of the two samples were identical.

When the reaction was effected at 0°, the starting oxime sulfonamide **14a** was recovered. Similar treatment of oxime sulfonamide **14b** at 0 or 100° afforded water-soluble material.

Attempt to Prepare Second Isomer of Oxime Sulfonamide 14a.—A 0.20-g sample of **14a** was dissolved in 30 ml of dry, refluxing ether. After cooling to 5°, the solution was saturated with dry hydrogen chloride but no precipitate formed; 90% of **14a** was recovered on work-up.

Registry No.—**1**, 19298-28-3; **2**, 19298-29-4; **3**, 520-03-6; **4**, 19298-31-8; **5**, 16497-40-8; **14a**, 19298-33-0; **14b**, 19298-34-1; **16a**, 19298-35-2; **16b**, 19298-36-3; **17a**, 19298-37-4; **17b**, 19298-38-5; **18a**, 15448-99-4.

(16) (a) I. Remsen and C. E. Coates, Jr., *Amer. Chem. J.*, **17**, 316 (1895); (b) I. R. Remsen and E. P. Kohler, *ibid.*, **17**, 340 (1895).

Organic Disulfides and Related Substances. XXVII. Reactions and Synthetic Utility of Cyclic Disulfides, Dioxides, and Tetroxides[1a-c]

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Hydrolysis, polarographic reduction, and other reactions were studied of the unsubstituted five-, six-, and seven-membered disulfides, the 1,1-dioxides, and the 1,1,2,2-tetroxides. 1,2-Dithiane 1,1,2,2-tetroxide reacted less readily with thiophenol than the 1,1-dioxide but oxidized a thiolate quantitatively to the disulfide by a mild method of possible general use; its reactivity with nucleophiles resembled that of a disulfide, except for greater susceptibility to alkali (all three tetroxides were readily cleaved at pH 8); its pyrolysis gave tetrahydrothiophene dioxide but in low yield. Generalizations are difficult but seem usually to be for easier cleavage of the five-membered systems than of the six-membered ones (with the seven-membered systems variable) and for greater resistance to self-polymerization or to attack of a thiol by the more oxidized forms but for lesser resistance to hydrolysis and electrochemical reduction. The dioxides and tetroxides are quite promising intermediates for synthesis. 1,2-Dithiane 1,1-dioxide underwent "oxodisulfide cleavage" by thiolate ion to give disulfides **1**, **2**, and **3** containing a sulfinate moiety, which in turn were converted into alkyl sulfones (**4** and **5**), an aryl sulfone (**6**), or a sulfonate (**8**). A typical disulfide product (**4**) disproportionated to the symmetrical disulfides comparably with resistant classes, affording a synthesis of a disulfide sulfone. 1,2-Dithiane tetroxide underwent "oxodisulfide cleavage" with alkali to give a sulfonate salt containing a sulfinate moiety (**11**), which was converted into a disulfide dioxide (**12**). Product **3** was active as an antiradiation drug.

The previous paper in this series compared syntheses for the five-, six-, and seven-numbered cyclic disulfides (1,2-dithiolane, 1,2-dithiane, and 1,2-dithiepane), their 1,1-dioxides, and their 1,1,2,2-tetroxides.[1c] The present paper first considers relative stabilities and reactivities of these substances under various circumstances. It then demonstrates utility of such substances for synthesis of a variety of structures otherwise difficultly obtainable. Whether the future will justify the hope that model reactions of the types described will prove general for cyclic disulfides and their oxidation products remains to be seen, but we are optimistic that these prototypes will suggest useful approaches for many ring-size and ring-substitution situations.

Instability of 1,2-dithiolane, apparently at least partly a consequence of repulsion between nonbonding electrons on the two sulfur atoms,[2] originally led us to wonder whether the 1,1,2,2-tetroxide would be likewise destabilized (made more reactive) by interaction of the four negatively charged oxygen atoms and how the 1,1-dioxide would compare with the disulfide and tetroxide (since it lacks these nonbonding electrons of the disulfide on one of its sulfur atoms and the two oxygen atoms of the tetroxide on the other). Some evidence on these points was adduced previously: 1,2-dithiolane monoxide is stable as a liquid for at least 2 hr and the dioxide for at least a month,[1c] in contrast to 1,2-dithiolane which polymerizes rapidly if solvent is removed.[2,3] That 1,2-dithiolane 1,1,2,2-tetroxide is quite stable (melting point unchanged after 9 months) also is noteworthy;[1c] the fact that it is a solid probably is important to its stability, but no polymerization was evident when either the dioxide or tetroxide was recrystallized.[1c] Other questions also are intriguing, such as reactivity of the oxides with nucleophiles. Even though it may be some time before rigorously satisfying answers to such questions as the foregoing can be had, information bearing on them seems likely to have fairly immediate practical use.

The desire for convenient, preparatively significant assessments of the influence of ring size and oxidation level on properties of the disulfides, the 1,1-dioxides, and the 1,1,2,2-tetroxides led first to a study of hydrolysis in refluxing aqueous dioxane. Although the hydrolyses undoubtedly are complicated by side reactions (*e.g.*, of sulfenic and sulfinic acids), the speed with which acidic groups were formed (measured by alkali consumption) was taken as a reasonable measure of reactivity in hydrolysis for the dioxides and tetroxides. Results are shown in Figure 1.

The three disulfides were followed by using uv spectra instead of by titration. Since all apparently were characterized by nearly complete resistance to the hydrolytic conditions, results with them are shown for comparison as the flat base line in Figure 1. Thus, after 50 hr, 100% of 1,2-dithiolane survived and change was insignificant even after 70 hr (in confirmation of identity at the latter point, a sample underwent 90% decrease in its optical density at 330 mμ upon exposure to sunlight, a property useful for distinguishing the dithiolane).[1c] 1,2-Dithiane and 1,2-dithiepane showed no change in absorption after 48 and 52 hr, and only little after 120 hr.

Figure 1 suggests that the dioxides were hydrolyzed more readily than the disulfides but still relatively slowly. Qualitative checks on this conclusion, obtained by allowing the dioxides to react with excess thiol and titrating the sulfinic acid formed in the manner of Barnard and Cole,[4] revealed that 84% of the dithiane dioxide remained after 75 hr, 72% of the dithiolane dioxide after 51 hr, and 62% of the dithiepane dioxide after 46 hr; both these results and the data shown in Figure 1 suggest that 1,2-dithiane dioxide is the least reactive of the three dioxides, but that all are fairly resistant and roughly comparable.

Figure 1 suggests that the tetroxides are hydrolyzed much more readily than the dioxides, and that reactivity increases in order six < seven < five. For these three,

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (b) Taken mainly from the Ph.D. dissertation of R. B. B., Vanderbilt University, Aug 1968; the dissertation may be consulted for greater detail. (c) Paper XXVI: L. Field and R. B. Barbee *J. Org. Chem.*, **34**, 36 (1969). (d) Eastman Kodak Fellow, 1965–1966.

(2) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954).

(3) A. Schöberl and H. Gräfje, *Ann.*, **614**, 66 (1958).

(4) D. Barnard and E. R. Cole, *Anal. Chim. Acta*, **20**, 540 (1959).

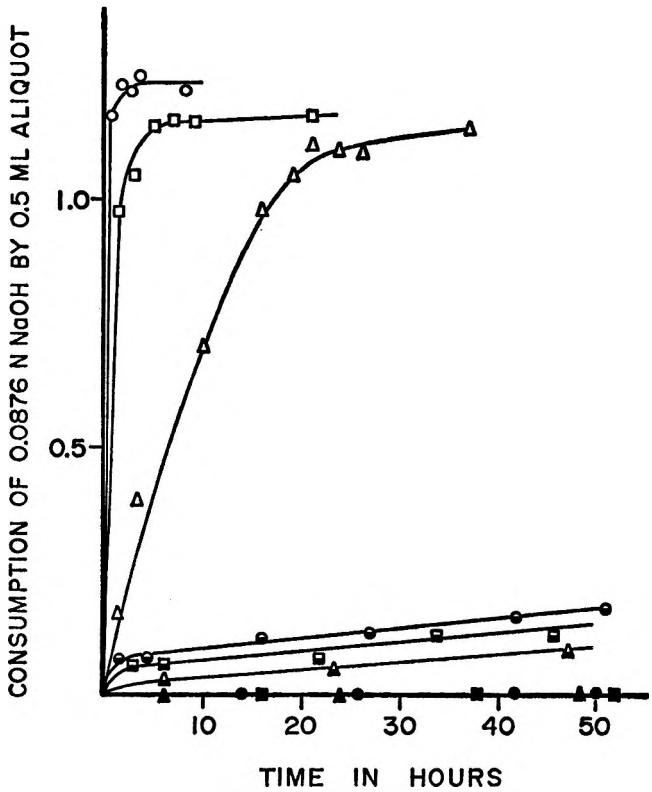


Figure 1.—Hydrolysis of 0.11 *M* solutions in 2:1 dioxane–water of cyclic sulfur compounds at 100°: O, five-membered ring; △, six-membered ring; □, seven-membered ring; filled figure, disulfide; half-filled figure, disulfide dioxide; open figure, disulfide tetroxide. Hydrolysis of the cyclic disulfides was followed spectroscopically.

incidentally, alkali consumption (after a nearly constant value was observed) amounted to 87, 90, and 96%, respectively, of expectation of hydrolysis, assuming that eq 1 applies. Recovery of only 19% of 1,2-dithiane

$$(\overline{CH_2)_nSO_2SO_2} + H_2O \longrightarrow HO_3S(CH_2)_nSO_2H \quad (1)$$

1,1,2,2-tetroxide after 21 hr qualitatively confirmed its relatively rapid hydrolysis, and recovery of 85% of 1,2-dithiane 1,1-dioxide after 21 hr confirmed that a dioxide is less reactive than a tetroxide.

Reactions of the dioxides and tetroxides with nucleophiles were considered next. Like arenethiolsulfonates,[5] 1,2-dithiane 1,1-dioxide reacted with thiophenol in ether according to eq 2 but, again similarly, not to very

$$(\overline{CH_2)_4SO_2S} + C_6H_5SH \longrightarrow HO_2S(CH_2)_4SSC_6H_5 \quad (2)$$

great extent. After 1 hr with 1 molar proportion of thiophenol, the reaction of the dioxide was about 16% complete, based on an average from unreacted thiophenol, titration of sulfinic acid formed, and isolation of the unchanged dioxide; phenyl benzenethiolsulfonate reacted under rather similar conditions to the roughly comparable extent of 27–31%.[5] The extent of reaction of the dithiane dioxide increased to 65% in ethanol and to 86% in ethanol with 2 molar proportions of thiophenol, points noteworthy for their possible general applicability to reactions of disulfide dioxides.

In contrast to the reaction extent of 86% in ethanol shown by the dioxide (1 hr, *ca.* 25°), only 15% of 1,2-dithiane tetroxide reacted in 4 days; since the tetroxide was only partly soluble in ethanol, however, the reaction also was done homogeneously for 1 hr in acetonitrile, but no more than 7% reacted. In a 20-hr experiment (different concentrations), 9% reacted. In an identical 20-hr experiment, but in ethanol, 1,2-dithiepane tetroxide also was unreactive with thiophenol, 10% reacting. Dithiolane tetroxide was more reactive than the other two tetroxides, however, reacting to the extent of 50% (20 hr, ethanol); unlike the other two tetroxides, it also gave a positive acidic reaction with thiophenol in the Barnard–Cole test for disulfide dioxides.[4]

Although the 1,2-dithiane tetroxide resisted thiophenol, it was readily cleaved by 2 equiv of sodium thiophenoxide, with quantitative formation of phenyl disulfide and disodium 1,4-butanedisulfinate (eq 3).

$$(\overline{CH_2)_4SO_2SO_2} \xrightarrow{C_6H_5SNa} [NaO_2S(CH_2)_4SO_2SC_6H_5] \xrightarrow{C_6H_5SNa} NaO_2S(CH_2)_4SO_2Na + (C_6H_5S)_2 \quad (3)$$

This mild means of quantitatively oxidizing a thiol to its disulfide has attractive general possibilities worthy of further exploration, particularly for biochemical systems.

To gain guidelines to its relative reactivity with typical nucleophiles, 1,2-dithiane tetroxide was treated with several potassium salts in aqueous acetonitrile. Starting material unconverted to a sulfinate salt (removed with water) then was recovered (*cf.* eq 3). To the extent such recovery signifies the order of reactivity, relative S nucleophilicities were in the following order: $C_6H_5S^-$, $OH^- > CN^- > SCN^-$, I^-.

Except that OH^- is much higher in this series, the order is that for attack upon an aryl disulfide;[6] formation of a sulfene intermediate with the tetroxide may explain the greater reactivity of OH^- and, indeed, cannot be discounted for other ions in the series. Since potassium hydroxide dissolved only partly, and perhaps because of unrecognized complications as well, this order is best regarded merely as an approximation of S nucleophilicity, pointing only to high reactivity of cyanide, hydroxide, and thiophenoxide ions and low reactivity of iodide and thiocyanate ions.

In initial attempts to carry this aspect further by comparing stabilities of the three tetroxides toward hydroxyl ion, 1,2-dithiane tetroxide reacted very rapidly at 60° (conversely, the pH of an aqueous alcoholic solution of the dioxide at pH 10 did not change during 2 hr at 60°, reflecting again the lower reactivity of the dioxide noted in the discussion of Figure 1).

Relative reactivities of the cyclic disulfide tetroxides with alkali at room temperature therefore were examined by using a pH-Stat to follow the amount of alkali required to maintain pH 8. The times at which uptake of alkali ceased (in parentheses) suggest the following order of increasing reactivity for the three tetroxides: six (30 min) < five (20 min) ≲ seven (15 min); since the curves for the five- and seven-membered compounds were much alike however,[1b] as they were in Figure 1, their difference probably is less significant than the times imply. In this reaction, too, sulfene intermediates

(5) T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).

(6) A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3071 (1960).

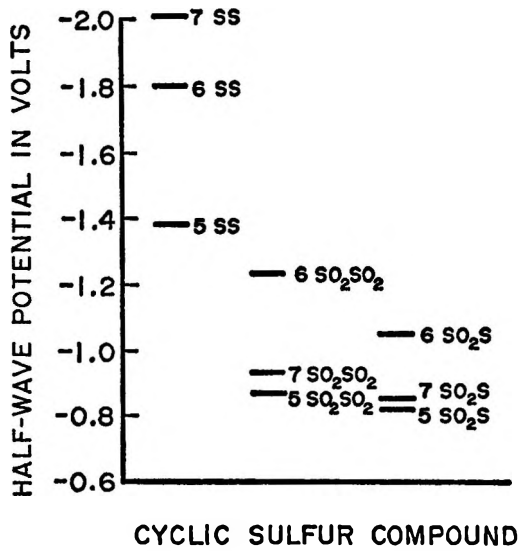


Figure 2.—Correlations of oxidation state and ring size of cyclic sulfur compounds with polarographic meaurements in diglyme.

can by no means be excluded at present; they are well established in not dissimilar reactions,[7] and indeed we found 1,2-dithiane tetroxide to be destroyed by triethylamine in refluxing acetonitrile (1 hr), with development of a striking red color seen also during formation of a sulfene.[8]

The polarographic behavior of the disulfides, dioxides, and tetroxides next was examined, because of its possible bearing on the relative reactivity of the various ring sizes and oxidation levels. Figure 2 depicts relationships which emerged from the polarographic reduction of the nine compounds in diglyme.[9] Figure 2 implies that increasing ease of reduction falls in the order SS < SO_2SO_2 < SO_2S; Lindberg and Bergson likewise found a dithiolane to be more resistant toward reduction than its dioxide at pH 7.2 (although less so at pH 1.2).[10] Figure 2 also implies that, although the potentials for reduction of the six- and seven-membered rings of a given oxidation level varied relative to each other, these rings always were more resistant to reduction than the five-membered ring. The polarographic waves of all nine compounds showed that each compound was irreversibly reduced, and thus that the reduction processes are slow in diglyme.

With the disulfides, the apparent increasing ease of electrochemical reduction of the rings (seven < six < five) agrees with data of Nygård and Schotte for the α,α'-dicarboxylic acids in buffer.[11] Although Nygård and Schotte stated that a greater ring stability was apparent for the six- and seven-membered cyclic disulfides compared with the five-membered one,[11a] Schotte pointed out that apparent involvement of intermediate mercury complexes made a direct comparison inadequate for establishment of possible differences in ring stability.[11b]

(7) T. J. Wallace, *Quart. Rev.* (London), 67 (1966).

(8) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3231 (1963).

(9) We are indebted for these measurements to Dr. L. C. Hall and Dr. G. J. Clark of Vanderbilt University. Details may be found in the forthcoming Ph.D. dissertation by G. J. Clark. Thanks also are due to Dr. Hall and Dr. Clark for many helpful discussions on interpretation of the results.

(10) B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965).

(11) (a) B. Nygård and L. Schotte, *Acta Chem. Scand.*, **10**, 469 (1956); (b) L. Schotte, *Ark. Kemi*, **9**, 441 (1956).

Although the half-wave potentials for the unsubstituted disulfides (seven, −2.01 V; six, −1.80 V; five, −1.36 V) are higher than values of Nygård and Schotte for their substituted disulfides (seven, −0.92 V; six, −0.75 V; five, −0.33 V),[11a] the order is the same; ethyl disulfide in diglyme had a half-wave potential of −1.99 V.

With the dioxides, reduction waves were characterized by a second small wave near −1.8 V of undetermined origin. The half-wave potentials of the primary waves suggests the following order of increasing ease of reduction (half-wave potentials in volts in parentheses): six (−1.05) < seven (−0.85) < five (−0.83).

With the tetroxides, the polarographic waves were characterized by a small wave prior to the appearance of the normal wave, suggesting adsorption. Apparent ease of reduction increased in the order six (−1.23) < seven (−0.93) < five (−0.88).

For rigorous comparison of half-wave potentials, the mechanism of electrode processes must be the same. This requirement seems satisfied in comparing potentials of those cyclic sulfur systems which contained the same electroactive group. Thus the implication of the data seems valid that in any one oxidation level the six- or seven-membered ring is less easily reduced than the five-membered one. Unfortunately for comparison of relative reactivity of the linkages –SS–, –SO_2S–, and –SO_2SO_2– in a given ring size, differences in the polarographic curves suggest that different mechanisms of reduction may be operative. Hence the conclusion from Figure 2 that the ease of electrochemical reduction necessarily increases in the order SS < SO_2SO_2 < SO_2S must be regarded with considerable caution, since "Any comparison of the reactivity based on a comparison of half-wave potentials corresponding to different groups following different reduction paths is only a rough approximation."[12]

An effort to trace patterns in the effects of ring size and oxidation level may be ventured, but with a strong reminder of possible pitfalls and exceptions noted both earlier[1c] and above. With respect to *ring size*, the tendency usually seems to be for the six-membered systems to be the least reactive of the three, and for the five-membered systems to be the most reactive, with the seven-membered systems taking a variable position. Among the disulfides, the order of Schöberl and Gräfje for increasing reactivity (six < seven < five)[3] was seen earlier in that the six-membered disulfide could be formed in situations where the five- and seven-membered disulfides formed in low yield or not at all, in oxidation of the six-membered-disulfide to the dioxide in higher yield, and in that only the six-membered disulfide could be oxidized directly to the tetroxide;[1c] presumably, the five- and seven-membered systems are more reactive, and hence more prone to undergo undesired reactions. Among the dioxides, the trend toward increasing ease of ring cleavage in the order six < seven < five seemed to be reflected for the more nearly coplanar five-membered one in its longer wavelength uv absorption[1c] and its easier electrochemical reduction, and for the six-membered one in better conversion of the dioxide into tetroxide[1c] and in its

(12) P. Zuman, *Chem. Eng. News*, **46** (No. 13), 94 (1968).

somewhat greater resistance to simple hydrolysis. Among the tetroxides, the six-membered system followed the order of increasing reactivity six < seven < five in simple hydrolysis and in reaction with alkali, and the five-membered system did so in reaction with a thiol. Since the oxides of the disulfides thus seem to follow the reactivity sequence of the disulfides, it may be reasonable to conclude that destabilizing effects in the disulfides have counterparts in the oxides. Respecting the effect of *oxidation level*, the presence of oxygen atoms seemed to increase resistance toward thiols and toward self-polymerization (making the five-membered cyclic monoxide, dioxide, and tetroxide tractable, in contrast to the unstable disulfide,[1c] and probably improving resistance of the six-membered systems as well). On the other hand, presence of oxygen atoms seemed to decrease resistance toward hydrolysis and toward electrochemical reduction in diglyme.

Elimination of sulfur dioxide by thermal decomposition has been reported for a variety of organic sulfur compounds.[13] Such a reaction occurs when 1,2-dithiane tetroxide is heated briefly at 280° (eq 4). The yield of

$$(CH_2)_4SO_2SO_2 \longrightarrow (CH_2)_4SO_2 + SO_2 \qquad (4)$$

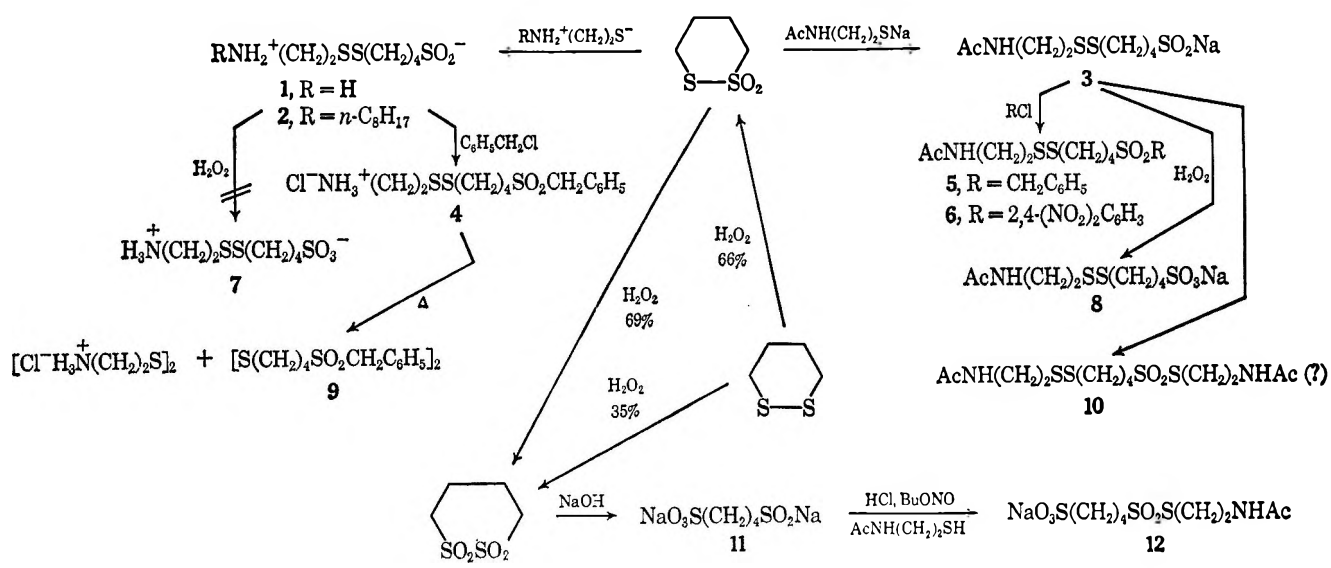
tetrahydrothiophene 1,1-dioxide was only 12%, however, and could not be improved. Both this tetroxide and 1,2-dithiane 1,1-dioxide actually are rather stable thermally, being recovered in 92–95% yield after 7 days in chlorobenzene at 132°. 1,2-Dithiepane 1,1,2,2-tetroxide apparently gave no pentamethylene sulfide 1,1-dioxide when heated at 280° for 10 min; the dithiolane tetroxide was not tried because of insufficient material.

Several applications of 1,2-dithane dioxide and tetroxide to synthesis of otherwise difficultly obtainable classes of disulfides are shown in Scheme I. Thus the dioxide led to disulfides containing sulfininate, sulfonate, and aryl or alkyl sulfone moieties, and the tetroxide led to a disulfide dioxide containing the sulfonate moiety. (Yields of the dioxide and tetroxide shown are previous results.)[1c] Presumably, preparation of similar products containing a varied number of substituted or unsubstituted methylene groups greater than two separating the –SS– moiety and a functional group is possible, since cyclic disulfides containing from three to thirteen methylene groups are known.[3] Use of other known reactions of disulfide dioxides and tetroxides hopefully should permit extension of the general approach, which for convenience is called "oxodisulfide cleavage," to other nucleophiles than thiols to afford an even more broadly useful new synthetic tool.

Acetamido- and aminothiols were used as models in these studies, as shown in Scheme I, in the hope that the products also might be of interest as antiradiation drugs (*cf.* earlier papers in this series). 2-Aminoethanethiol and 2-(*n*-octylamino)ethanethiol were sufficiently nucleophilic to convert 1,2-dithiane 1,1-dioxide into the disulfide sulfinates **1** and **2** in 86 and 97% yields, respectively; **1** and **2** are formulated in Scheme I as dipolar ions (but are named as aminosulfinic acids in the Experimental Section for convenience). 2-Acetamidoethanethiol was converted into the thiolate with a sodium alkoxide for an otherwise similar synthesis of the disulfide sulfinate **3** (94%). Infrared spectra of **1**, **2**, and **3**, as well as of other products described below were consistent with the structures assigned to Scheme I. The hydrochlorides of the aminothiols also could be used to prepare **1** and **2** in the presence of 1 equiv of sodium alkoxide.

"Oxodisulfide cleavage" can lead to products which are themselves useful intermediates. Formation of the disulfide sulfone **4** (11%) from the sulfinate **1** and benzyl chloride is an illustration. Sulfones such as **4** were of interest, since activity of prototypes as antiradiation drugs could lead to use of this flexible route for preparing a wide variety of ring-substituted counterparts. The reaction of disulfide sulfinate **3** with benzyl chloride similarly gave the disulfide sulfone **5** (57% yield). Homogeneity of **4** and **5** was confirmed by thin

SCHEME I



(13) J. L. Kice in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, New York, N. Y., 1966, p 115.

layer chromatography (tlc). Conversion of disulfide sulfinate **3** into an aryl sulfone (**6**) was effected by its reaction with 2,4-dinitrochlorobenzene, but sulfone **6** proved extremely difficult to purify.

A further extension is the oxidation of disulfide sulfinates to form a third class of compounds, the disulfide sulfonates (Scheme I). Oxidation of disulfide sulfinate **3** with aqueous hydrogen peroxide produced the desired disulfide sulfonate **8** (26% yield). The major product appeared to be a disproportionation product, $[NaO_3S(CH_2)_4S]_2$, however, since it had strong ir absorption only at 1200 and 1060 cm^{-1} (characteristic of sulfonic acid salts) and contained no nitrogen. A similar result occurred upon oxidation of disulfide sulfinate **1** with hydrogen peroxide, although here only the presumed disproportionation product was isolated; the ir absorption spectra of the bissulfonate disproportionation product from oxidation of both **1** and **3** were identical. Sodium metaperiodate proved better for oxidizing the disulfide sulfinate **3** to the disulfide sulfonate **8**; the yield was 57%, with no observable disproportionation. With disulfide sulfinate **1** and the metaperiodate, however, disproportionation still predominated and little if any of the disulfide sulfonate **7** seemed to result.

Another use of the disulfide sulfinate **3** involved an attempt to convert it into a disulfide disulfide-dioxide (**10**) by a method introduced by Kresze and Kort[14] and subsequently developed for 2-acetamidoethanethiol by Field and Lacefield.[15] The method involves simultaneous oxidation of a thiol and a sulfinic acid by an alkyl nitrite. In it, disulfide sulfinate **3** was converted *in situ* into the sulfinic acid (ordinarily unstable as such) using hydrochloric acid, which in turn seemingly was converted into the disulfide dioxide hemihydrate **10** (37% yield). The identity as **10** was suggested by elemental analysis, the ir spectrum, and a molecular weight of 383 (calcd 398) by the method of Barnard and Cole,[4] and its homogeneity was indicated by tlc; however, a completely satisfactory elemental analysis could not be obtained despite several attempts and some reaction products showed two close tlc spots.

The susceptibility of 1,2-dithiane tetroxide to nucleophilic attack suggested the synthetic application outlined in Scheme I. Cleavage of the tetroxide by alkali provided the sulfinate sulfonate **11**, from which the sulfinic acid was generated *in situ* with mineral acid. Application of the Kresze–Kort reaction to this acid and acetamidoethanethiol gave the disulfide dioxide sulfonate **12** (79% yield), which gave a positive disulfide dioxide test;[4] some difficulty was encountered in separation of the sodium salt **12** from sodium chloride. Sulfinate sulfonates like **11** should have numerous other uses as intermediates.

Compound **1** was rated no better than slightly active as an antiradiation drug (dose, 150 mg/kg; LD_{50}, 500 mg/kg), and **8** was rated only "fair" (dose, 800 mg/kg; LD_{50}, 1200 mg/kg).[16] However, the disulfide sulfinate **3** gave particularly promising results ("good," 87–100% survival, at a dose level of 47 mg/kg; LD_{50}, 694 mg/kg);[16] the other compounds are still to be tested.

Earlier papers of this series have considered factors which influence disproportionation of unsymmetrical disulfides to two symmetrical ones. To rank compounds of the present type among those studied earlier, the disulfide sulfone **4** was chosen as a representative, because one of the products, cystamine dihydrochloride, should be easily separable from the other (**9** of Scheme I) by washing with water. Thermal disproportionation of **4** was effected by heating it in water at 100° for 72 hr (Scheme I). The extent of disproportionation, determined by isolation of the water-insoluble **9**, was 79%. The value of 79% for **4** is comparable with that of 80% under much the same conditions obtained with 1,4-bis(2-aminoethyldithio)butane dihydrochloride.[19] This result suggests that compounds like **4** should be among the most stable of the disulfides studied.[19] The result also both confirms the structure of **4** and demonstrates a useful synthesis of disulfide sulfones typified by **9**.

Experimental Section[20]

Stability in Refluxing Aqueous Dioxane.—Each sulfur compound (1,2-dithiolane, 1,2-dithiane, and 1,2-dithiepane, their dioxides, and tetroxides) was dissolved in enough 66% dioxane–water to give an 0.11 *M* solution, which then was heated under reflux (100°). Samples of the dioxides and tetroxides (0.50 ml), withdrawn at suitable intervals, were titrated with 0.0876 *N* NaOH, and base consumption in milliliters for the 0.5-ml aliquot was plotted *vs.* time in Figure 1. With cyclic disulfide dioxides, the end point was determined using a Beckman pH meter with a calomel–glass electrode pair. The end point of each aliquot containing tetroxide was determined using bromophenol blue indicator; the Bernard–Cole titrations[4] for the dioxides were done after similar preliminary neutralization. With the cyclic disulfides, lack of hydrolysis was concluded by following the characteristic uv maxima at 330 mμ for 1,2-dithiolane, at 288 mμ for 1,2-dithiane, and at 258 mμ for 1,2-dithiepane.[1c] Isolations by evaporating a sample, washing the solid with water, and drying gave 1,2-dithiane 1,1-dioxide in 75% yield and the 1,1,2,2-tetroxide in 18% yield after 21 hr; reliability of this isolation in turn was checked by isolating the dioxide from an unheated control solution in 88% yield and the tetroxide in 93% yield [so that the corrected value for survival of the dioxide is (75)(100)/88 = 85%, and for the tetroxide is (18)(100)/93 = 19%].

Reaction of 1,2-Dithiane 1,1-Dioxide with Thiophenol.—In a typical experiment, thiophenol (0.110 g, 1.00 mmol) and 1,2-dithiane 1,1-dioxide (0.152 g, 1.00 mmol) were stirred in 5 ml of dry ether at *ca.* 25° for 1 hr. Ether and unreacted thiol then were distilled at 1 mm into a Dry Ice chilled trap. Iodine titration of the trap contents showed presence of 85% of the original thiophenol, representing a reaction not more than 15% complete. The undistilled residue was titrated with 0.5 ml of 0.0876 *N* NaOH to a bromophenol blue end point, which represents a reaction extent of not less than 4%. The solution then was extracted with ether and the extract was washed with water, dried, and evaporated to give 0.109 g (72%) of 1,2-dithiane 1,1-dioxide, mp 47–48° (lit.[21] mp 56–57°), indicating a reaction extent of not

(14) G. Kresze and W. Kort, *Chem. Ber.*, **94**, 2624 (1961).

(15) L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 599 (1966).

(16) These results were kindly provided by Dr. D. P. Jacobus, Dr. T. R. Sweeney, and Dr. E. A. Steck of the Walter Reed Army Institute of Research. General procedures, the meaning of activity ratings, etc., are referred to in previous papers.[17,18]

(17) L. Field, H. K. Kim, and M. Bellas, *J. Med. Chem.*, **10**, 1166 (1967).

(18) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *ibid.*, **7**, 39 (1964).

(19) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).

(20) Details were as given in footnote 24 of ref 1c. Polarographic measurements were made of the five-, six-, and seven-membered disulfides, 1,1-dioxides, and tetroxides in diglyme with a Sargent polarograph Model XXI at 25° by Dr. Larry C. Hall and Dr. Gale J. Clark.[3] Tetrabutylammonium perchlorate was used as supporting electrolyte with a modified calomel electrode as reference. Glpc analyses were performed on an F & M Model 720 gas chromatograph with thermal conductivity detector using a 2-ft column packed with 5% silicone-gum rubber on Chromosorb-P. Thin layer chromatography was conducted on silica gel (Eastman Chromagram Type K 301R), with acetone for development and with location of spots by exposure to iodine vapor. Preparations were as described previously for 1,2-dithiolane, 1,2-dithiane, 1,2-dithiepane, their 1,1-dioxides, and their 1,1,2,2-tetroxides.[1c]

(21) N. Isenberg, Ph.D. Thesis, Rensselaer Polytechnic Institute, 1963.

more than 28%. From these percentages, the average value of 16% was estimated.

Reactions of Cyclic Disulfide Tetroxides with Thiophenol.—The procedure used with 1,2-dithiepane 1,1,2,2-tetroxide also illustrates that used with the tetroxide of 1,2-dithiolane and (as a complete solution in acetonitrile) with that of 1,2-dithiane.

Thiophenol (49 mg, 0.44 mmol) and 1,2-dithiepane tetroxide (31 mg, 0.16 mmol) were stirred in ethanol (10 ml) at *ca.* 25° for 20 hr. Solvent and excess thiophenol were evaporated, and residue was washed with ether to remove phenyl disulfide and with water to remove any sulfinic acid; 28 mg (90%) of 1,2-dithiepane tetroxide remained, mp 157–159° (lit.[1c] mp 159–160°).

Reaction of 1,2-Dithiane 1,1,2,2-Tetroxide with Sodium Thiophenoxide.—1,2-Dithiane tetroxide (0.500 g, 2.71 mmol) was suspended in 25 ml of 95% ethanol, and sodium thiophenoxide (5.44 mmol) in 25 ml of methanol was added dropwise (15 min) at 25°. The solution then was heated to reflux for 15 min and let cool (reaction occurs rapidly and completely without reflux however). After a stirring period of 5 hr more, the solvent was evaporated, and the remaining solid was washed with benzene to remove phenyl disulfide, leaving a white residue, yield 0.67 g (107%); in both melting point behavior (charring, 335°) and ir absorption (990 cm^{-1}, s), the properties were those of authentic disodium 1,4-butanedisulfinate.[15] The benzene wash contained 0.610 g (103%) of phenyl disulfide, identical in melting point, mixture melting point (56–58°), and ir absorption with an authentic sample.

Reactions of Nucleophiles with 1,2-Dithiane 1,1,2,2-Tetroxide.—1,2-Dithiane tetroxide (0.543 mmol) in 10 ml of 4:1 acetonitrile–water was stirred for 30 min at *ca.* 25° with 1.09 mmol of nucleophile (KCN, KOH, KI, KSCN, and KSC_6H_5); complete solution resulted in all instances, except with KOH. Removal of solvent, washing of the residue with 10 ml of water, and drying gave recovered tetroxide. After reaction of the tetroxide with potassium thiophenoxide, the residue first was extracted with ether to remove phenyl disulfide before being washed with water. The amount of tetroxide (identified by melting point and ir spectrum) isolated from each reaction, given in order of the nucleophiles above, was 0.014 g (14%), 0.004 g (4%), 0.090 g (90%), 0.086 g (86%), and 0.001 g (1%).

Stability of Cyclic Disulfide Tetroxides at pH 8.—Each cyclic disulfide tetroxide (0.036 mmol) was dissolved in 80% acetonitrile–water (7.2 ml). By means of a pH-Stat (Fisher automatic titrimeter),[22] 0.0876 *N* NaOH was added as rapidly as possible to a pH of 8 at *ca.* 25°. More alkali then was added automatically to maintain pH 8. The approximate milliequivalents of alkali required, before uptake ceased, with times for that point in parentheses follow: for 1,2-dithiane tetroxide, 0.057 mequiv (30 min, alkali uptake still not quite complete); for 1,2-dithiolane tetroxide, 0.066 mequiv (20 min); for 1,2-dithiepane tetroxide, 0.064 mequiv (15 min).[1b]

Pyrolysis of 1,2-Dithiane 1,1,2,2-Tetroxide.—1,2-Dithiane tetroxide (0.300 g, 1.63 mmol) was heated under N_2 at 275–280° for 10 min. Decomposition occurred immediately. Chloroform extracted from the resulting dark solids 0.045 g of yellow paste. Extraction of the paste with water left 0.014 g (5% recovery) of 1,2-dithiane tetroxide, mp 239° dec, and removed 0.028 g (14%) of crude tetrahydrothiophene 1,1-dioxide which contained all the ir bands of authentic material and had a melting point of *ca.* 5° (lit.[23] mp 20–21°). Glpc analysis[20] of this material indicated 85% purity for the main component (retention time, 50 sec), which was shown to be tetrahydrothiophene 1,1-dioxide by peak enhancement using authentic material; the yield therefore was 14%(0.85) = 12%.

A decomposition time of 40 min gave essentially the same result. Pyrolysis in nitrobenzene at 190–210° for varied lengths of time gave no improvement in yield, nor did addition of $AlCl_3$. Pyrolysis, with sand or chlorobenzene, also gave no improvement (132°, 7 days; 95% recovery of tetroxide, mp 238° dec); when 1,2-dithiane 1,1-dioxide was similarly heated in chlorobenzene, the recovery was 92%, mp 54–56°.

4-(2-Aminoethyldithio)butanesulfinic Acid (1).—2-Mercaptoethylamine (0.25 g, 3.3 mmol) and 1,2-dithiane 1,1-dioxide (0.50 g, 3.3 mmol) were stirred together for 30 min in 15 ml of 95% ethanol. The solid formed was removed to give 0.64 g (86%) of **1**, mp 157–159°. Recrystallizations from methanol–ether gave **1** with a constant melting point of 163–164° and ir absorption at 1640, 1560, and 1000 (s) cm^{-1}.

Anal. Calcd for $C_6H_{15}NO_2S_3$: C, 31.42; H, 6.59; N, 6.11; S, 41.93. Found: C, 31.13; H, 6.56; N, 5.99; S, 42.13.

Much the same result was obtained by use of 2-mercaptoethylamine as its hydrochloride (using also 1 equiv of an alkoxide), but with much greater difficulty in purification owing to presence of sodium chloride.

4-[2-(*n*-Octylamino)ethyldithio]butanesulfinic Acid (2).—A solution of 1,2-dithiane 1,1-dioxide (1.00 g, 6.60 mmol) and 2-(*n*-octylamino)ethanethiol[24] (1.24 g, 6.55 mmol) in 20 ml of absolute ethanol was stirred for 2 hr and then was cooled in an ice bath. The product, **2**, which precipitated then was removed by filtration and quickly returned to a flask before it could melt. Residual solvent then was removed, leaving 2.17 g (97%) of **2** having mp 25–30°. Several recrystallizations (absolute ethanol) gave rather waxy **2** with a melting point of 35–39°, which was not improved by further recrystallization, and ir absorption at 1620, 1000 (s), and 960 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{31}NO_2S_3$: C, 49.22; H, 9.15; N, 4.10; S, 28.16. Found: C, 49.10; H, 9.06; N, 4.25; S, 28.25.

After 2 weeks, the melting point had changed from *ca.* 35 to 73–78°, either because of decomposition (became pale green) or, more likely, because of progressive crystallization with some (but slight) decomposition, since the ir spectrum did not change significantly.

Sodium 4-(2-Acetamidoethyldithio)butanesulfinate (3).—Methanolic sodium methoxide (1.3 *N*) was added dropwise to 1,2-dithiane 1,1-dioxide (14.3 g, 93.9 mmol) and 2-acetamidoethanethiol (11.2 g, 93.9 mmol) in 250 ml of ethanol until the solution became basic to moist pH test paper (67.7 ml, 88 mmol). Removal of solvent left 26.0 g (94%) of crude **3**, mp 205–210°, with softening at 90°. For recrystallization, this **3** was dissolved in a minimum of methanol, to which acetone was added to precipitate 24.3 g (88%) of **3**, mp 210–220° dec, with softening at 110°. Purification for analysis was effected by adding ether to a solution of the latter in a minimum of methanol at 25° until a little precipitate formed; precipitate was removed, and more ether then was added to the filtrate to precipitate a second fraction. Continuation of this process produced several fractions, the largest of which was again fractionally precipitated similarly. Three such fractionations gave **3** with mp 215–220° dec and ir absorption at 3300 (s), 1650 (s), 1550, and 1000 (s) cm^{-1}.

Anal. Calcd for $C_8H_{16}NNaO_3S_3$: C, 32.75; H, 5.50; N, 4.77; S, 32.78. Found: C, 32.63; H, 5.53; N, 4.54; S, 32.57.

4-(2-Aminoethyldithio)butyl Benzyl Sulfone Hydrochloride (4).—A mixture of benzyl chloride (1.85 g, 14.6 mmol) and **1** (3.00 g, 13.1 mmol) in 350 ml of methanol was heated under reflux for 9 hr and let stand for 3 days. Solvent then was evaporated, and the residue was taken up in water (50 ml). Extraction with ether removed unreacted benzyl chloride. Benzene (50 ml) was added, followed by 3.5 ml of 3.4 *N* KOH solution (11.9 mmol).[25] The organic layer was separated, washed with water (10 ml), and filtered into 7 ml of ice-cold 3.4 *N* HCl, with which it was shaken well. A white precipitate formed immediately. The alkali layer was extracted twice more with benzene and the extract also was shaken with the acid. The total precipitate then amounted to 0.507 g (11%), mp 162–163°. Three recrystallizations from methanol–ether gave **4** having a melting point of 164–164.5° and ir absorption at 1600, 1500, 1310 (s), 1280 (s), and 1140 (s) cm^{-1}; tlc showed only one spot, R_f 0.36.

Anal. Calcd for $C_{13}H_{22}ClNO_2S_3$: C, 43.86; H, 6.23; N, 3.94; S, 27.02. Found: C, 44.11; H, 6.22; N, 4.04; S, 27.04.

4-(2-Acetamidoethyldithio)butyl Benzyl Sulfone (5).—A mixture of benzyl chloride (1.52 g, 12.0 mmol) and **3** (3.00 g, 10.2 mmol) in 225 ml of ethanol was heated under reflux for 3 hr and let stand at 25° for 24 hr. Sodium chloride then was removed by filtration, and the solvent was evaporated. The residue was rubbed well with hot acetone which, when evaporated, gave 2.10 g (57%) of **5**, mp 80–85°. Four recrystallizations from 95% ethanol gave **5** with mp 82–83° and ir absorption at 3300, 3220, 1640 (s), 1560, 1320, 1290 (s), 1130 (s), 780, and 700 cm^{-1}; tlc showed only one spot, R_f 0.76.

(22) We thank Dr. M. M. Jones of Vanderbilt University for use of this equipment.

(23) H. J. Backer and C. C. Bolt, *Rec. Trav. Chim. Pays-Bas*, **54**, 538 (1935).

(24) We thank the Walter Reed Army Institute of Research for supplying this material.

(25) It is probably quite important to minimize the time during which **4** is present as a free base, since our experience has been that free bases of aminoalkyl disulfides rapidly disproportionate to the symmetrical disulfides.

Anal. Calcd for $C_{15}H_{23}NO_8S_3$: C, 49.83; H, 6.41; N, 3.87; S, 26.60. Found: C, 50.34; H, 6.45; N, 3.88; S, 26.30.

4-(2-Acetamidoethyldithio)butyl 2,4-Dinitrophenyl Sulfone (6).—2,4-Dinitrochlorobenzene (3.46 g, 17.1 mmol) and **3** (5.0 g, 17.0 mmol) were heated under reflux for 30 min in 150 ml of ethanol. After 7 days, solvent was evaporated, and the residue was taken up into acetone and filtered to remove sodium chloride. Evaporation of acetone left 7.9 g (106%) of crude **6**, mp 60–67°. The **6** was a poorly crystalline material which proved very difficult to purify, even partly. Thus numerous recrystallizations using isopropyl alcohol, *t*-butyl alcohol, and chloroform–carbon tetrachloride failed to give **6** with a constant melting point, the last recrystallization yielding still somewhat impure yellow solid with mp 85–88° and strong ir bands at 3300, 3110, 1650, 1550, 1360, 1330, 1310, and 1160 cm^{-1}. Chromatography on both alumina and silica gel also did not improve the melting point.

Anal. Calcd for $C_{14}H_{19}N_3O_7S_3$: C, 38.43; H, 4.38; S, 21.99. Found: C, 39.42; H, 4.66; S, 22.36.

Sodium 4-(2-Acetamidoethyldithio)butanesulfonate (8). A. *Via* Hydrogen Peroxide.—Hydrogen peroxide (1.6 ml of "30%" solution, 8.8 *M*, 14.1 mmol) in 25 ml of water was added dropwise (30 min) to **3** (4.0 g, 13.6 mmol) in 100 ml of water at *ca.* 25°. After 2 days, the water was evaporated and the residue was dissolved in a minimum of methanol. Acetone then was added until a small amount of precipitate formed. This precipitate was removed and more acetone was added to precipitate a second fraction. Repetition of this process produced several fractions, which were combined into two different groups according to similar infrared spectra. The first fractions (2.0 g, mp 280° dec) showed only two strong bands at 1200 and 1060 cm^{-1}, but not at 3300, 1650, or 1550 cm^{-1} as is characteristic of **8**, indicating they were the disproportionation product, $[NaO_3S(CH_2)_4S]_2$; a negative test for nitrogen was obtained after sodium fusion. The last fractions were the desired product **8**, yield 1.1 g (26%). Purification of similarly prepared **8** was achieved by precipitating fractions from methanol at 25° using ether, as described for the sulfinate salt **3**. Four such fractionations gave **8**, which showed ir absorption at 3300, 1650 (s), 1550, 1200 (s), and 1060 (s) cm^{-1}; **8** had no well-defined decomposition point. Oxidation of $-SO_2Na$ to $-SO_3Na$, rather than of $-SS-$ to $-S(O)S-$, is shown by disappearance of the 1000-cm^{-1} ir band of **3** and appearance of the 1060- and 1200-cm^{-1} bands in **8**.

Anal. Calcd for $C_8H_{16}NNaO_4S_3$: C, 31.06; H, 5.21; N, 4.53; S, 31.09. Found: C, 31.01; H, 5.22; N, 4.30; S, 30.82.

B. ***Via* Sodium Metaperiodate.**—Sodium metaperiodate (0.48 g, 2.2 mmol) in 10 ml of water was added to **3** (0.45 g, 1.5 mmol) in 10 ml of water at *ca.* 25°. After 15 hr, the water was evaporated, and the residue was extracted with 15 ml of hot methanol. Acetone was added to the methanolic solution until a small amount of precipitate formed. Since the ir spectrum of this first fraction was identical with that of **8** described in A, apparently little disproportionation had occurred. Addition of more acetone precipitated the remaining **8**, which was combined with the first fraction to give 0.27 g (57%) of disulfide sulfinate **8**.

Acetamidoethyl 4-(2-Acetamidoethylsulfenylsulfonyl)butyl Disulfide (10) Hemihydrate.—The disulfide sulfinate **3** (5.00 g, 17.0 mmol) was dissolved in 60 ml of ethanol and concentrated HCl (17.0 mmol) was added. A solution of 2-acetamidoethanethiol (2.03 g, 17.0 mmol) and *n*-butyl nitrite (2.65 g, 25.7 mmol) in 50 ml of anhydrous ethanol was heated at reflux for 15 min. An intense red color developed. *n*-Butyl nitrite (2.65 g, 25.7 mmol) then was added in one portion, followed by dropwise addition (30 min) of the above acidic solution. The reaction mixture was heated under reflux until the red color disappeared and evolution of nitric oxide ceased (1 hr). The mixture was cooled, the solvent was evaporated, and the residue was washed with 25 ml of ether, then with three 40-ml portions of water, and dried to yield crude hemihydrate **10**: 2.5 g (37%); mp 58–60°; ir absorption at 3300, 1650, 1550, 1320, 1300, and 1125 cm^{-1}. Equivalent weight determination[4] gave 383 (calcd 398 for **10** hemihydrate). Recrystallization from nitromethane and isopropyl alcohol gave **10** hemihydrate with mp 77–78°; tlc gave a single spot, R_f 0.40.

Anal. Calcd for $C_{12}H_{24}N_2O_4S_4 \cdot 0.5H_2O$: C, 36.25; H, 6.34; N, 7.04; S, 32.26. Found: C, 36.11; H, 6.26; N, 7.07; S, 33.02.

When this work was repeated on a larger scale and the crude product was recrystallized several times from isopropyl alcohol–water, a solid with mp 55–58° was obtained which contained two components by tlc indicating possible disproportionation. Recrystallization of the crude product several times from water alone gave solid with mp 90–91.5°, which probably was mainly disproportionation product, $[CH_3C(O)NH(CH_2)_2SSO_2(CH_2)_4S]_2$.

Disodium 1,4-Butanesulfinatesulfonate (11).—An aqueous solution of sodium hydroxide (21.5 ml, 0.97 *M*, 20.8 mmol) was added dropwise (15 min) to 1,2-dithiane 1,1,2,2-tetroxide (2.00 g, 10.9 mmol) suspended in 75 ml of 66% dioxane–water mixture, at which point pH test paper showed a pH of *ca.* 7 for at least 10 min. Evaporation of solvent left **11** as white solid, yield 2.83 g (106%). An approximate molecular weight of 280 (calcd 246) was obtained by titrating part of this **11** (after acidification with sulfuric acid) using sodium nitrite to a positive starch–iodide test.[26] Purification was effected by dissolving crude **11** in a minimum of methanol and adding acetone until *ca.* 70% of the solid had been precipitated. This solid was removed, redissolved in methanol, and reprecipitated with acetone. Several repetitions gave analytically pure **11**: strong absorption at 1195, 1050, and 980 cm^{-1}; no well-defined decomposition point.

Anal. Calcd for $C_4H_8Na_2O_8S_2$: C, 19.51; H, 3.27; S, 26.05. Found: C, 19.59; H, 3.30; S, 26.25.

Sodium 4-(2-Acetamidoethylsulfenylsulfonyl)butanesulfonate (12).—The disodium salt **11** (5.32 g, 21.6 mmol) was dissolved in 600 ml of methanol and 1.80 ml (21.6 mmol) of 12 *N* HCl was added. The mixture was stirred for 20 min. A solution of 2-acetamidoethanethiol (2.58 g, 21.6 mmol) and *n*-butyl nitrite (3.32 g, 32.2 mmol) in 50 ml of anhydrous ethanol was heated at reflux for 15 min, at which time the red color had become intense. *n*-Butyl nitrite (3.32 g, 32.2 mmol) then was added in one portion, followed by dropwise addition (40 min) of the above sulfinic acid solution. The color disappeared after the addition of the sulfinic acid, but reflux was continued for 30 min, after which the mixture was allowed to cool and stand overnight. Evaporation of solvent then gave white solid, which was washed with two 50-ml portions of acetone and extracted with 400 ml of hot ethanol. Removal of the ethanol gave 5.83 g (79%) of **12**, mp 126–128°. Recrystallization from ethanol of similarly prepared material gave **12** with a constant melting point of 128–129.5° and ir absorption at 3310, 1650 (s), 1550, 1325, 1210, 1165 (s), 1125, and 1070 cm^{-1}.

Anal. Calcd for $C_8H_{16}NNaO_6S_3$: C, 28.14; H, 4.72; N, 4.10; S, 28.17. Found: C, 27.94; H, 5.14; N, 3.97; S, 27.93.

Disproportionation of 4-(2-Aminoethyldithio)butyl Benzyl Sulfone Hydrochloride (4).—The benzyl sulfone **4** (0.287 g, 0.806 mmol) in 10 ml of water was heated at 100° for 72 hr in a sealed vial wrapped with aluminum foil, and the vial then was chilled in ice. Insoluble material was extracted into benzene, which was dried and evaporated to give 0.156 g (79%) of 1,14-diphenyl-2,7,8,13-tetrathiatetradecane-2,2,13,13-tetroxide (**9**), mp 118–118.5°. The water containing the remaining products was evaporated leaving 0.129 g of residue, mp 194–199°, the ir spectrum of which was consistent with that expected of a mixture of **4** (mp 164–164.5°) and cystamine dihydrochloride, mp 218–220°. The disulfide **9** gave a single tlc spot (R_f 0.68); elemental analysis showed absence of nitrogen but presence of sulfur. The water-soluble material on tlc produced two spots, one consistent with cystamine dihydrochloride (R_f 0.00) and the other with **4** (R_f 0.36) (authentic samples were done simultaneously).

The per cent of disproportionation (79%) was calculated as (100 × 2 × moles of disulfide **9** isolated)/(0.806 mmol of disulfide **4**).

Similarly prepared disulfide **9**, recrystallized from methanol, gave **9** with a constant melting point of 120–120.5°.

Anal. Calcd for $C_{22}H_{30}O_4S_4$: C, 54.29; H, 6.21. Found: C, 54.41; H, 5.98.

Registry No.—**1**, 19293-54-0; **2**, 19293-55-1; **3**, 19293-56-2; **4**, 19293-57-3; **5**, 19293-91-5; **6**, 19293-92-6; **8**, 19293-93-7; **9**, 19293-94-8; **10**, 19293-95-9; **11**, 19293-96-0; **12**, 19293-97-1; 1,2-dithiane 1,1,2,2-tetroxide, 18321-18-1; thiophenol, 108-98-5; sodium thiophenoxide, 930-69-8.

(26) J. L. Kice and K. W. Bowers, *J. Amer. Chem. Soc.*, **84**, 605 (1962).

Biologically Oriented Organic Sulfur Chemistry. I. Reactions of Thiols with Highly Reactive Carbonyl Compounds[1]

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Approximate equilibrium constants (K) were obtained for the uncatalyzed reaction of 1-propanethiol with various carbonyl compounds in methylene chloride solution, leading to the formation of α-hydroxy sulfides. Many of the carbonyl compounds were of a highly reactive type, typified by a propensity to form isolable hydrates. The values of K obtained ranged from nearly 0 to in excess of 10^4. In instances where values of K were equal to or greater than about 10^2, the α-hydroxy sulfides formed could not be converted in the presence of acid catalyst and excess thiol into mercaptals or mercaptoles. However, where K values were in the range of about 0–10^2, the well-established conversion into mercaptals or mercaptoles could be achieved readily in the presence of hydrogen chloride or boron trifluoride. Values of K with chloral and tertiary thiols were similar to those with 1-propanethiol. 1-Dodecanethiol was much more sluggish in its reaction with chloral than were short-chain primary or tertiary thiols.

For some years we have been interested in substances which would react with radioprotective aminoalkanethiols in such a way as to reduce toxicity and improve protective activity of the thiol, thereby enhancing the usefulness of the structure for protection against otherwise lethal effects of ionizing radiation.[2] A similar approach deserves investigation with the tertiary thiol, penicillamine, which is of interest in relation to rheumatoid arthritis (as well as to other diseases), but which unfortunately has problems of toxicity associated with its use.[3]

Since a number of reactive carbonyl compounds have long been known to form isolable hydrates, it seemed that they might similarly form hemimercaptals or hemimercaptoles (α-hydroxy sulfides) with radioprotective thiols, or with penicillamine, as shown in eq 1. Such products might have worthwhile medicinal properties in being stable solids of reduced toxicity and/or improved activity.

$$R^1SH + R^2R^3CO \rightleftharpoons R^2R^3C(OH)SR^1 \qquad (1)$$

Knowledge of the relative stability of α-hydroxy sulfides thus was desirable as a basis for attempted preparation of those which might be reasonably stable, as well as to suggest carbonyl compounds which would exemplify as great a range of stabilities as feasible (because of the possible variation of medicinal activity with stability). A study of equilibrium constants (K) for eq 1 therefore was undertaken.

Comparatively little attention has been given to the formation of α-hydroxy sulfides. Johns and Hixon measured the dissociation constants of hemimercaptals formed in the reaction in benzene of chloral with several thiols by a method based on depression of freezing points.[4] Moore later obtained results similar to those of Johns and Hixon, using a vapor pressure method.[5] Lienhard and Jencks recently determined rate and equilibrium constants for the reaction of a series of thiols with acetaldehyde and several other simple carbonyl compounds to form the corresponding α-hydroxy sulfides in aqueous media.[6] They followed the reactions by changes in the uv absorbance of the carbonyl group. They suggested that reaction occurred by specific base catalyzed and general acid catalyzed pathways and that the mechanism of the general acid catalyzed reaction involves proton donation to the unhydrated carbonyl group. The rather limited amount of preparative work on α-hydroxy sulfides has been summarized by Reid[7] and by Schöberl and Wagner.[8]

For our purpose, study of carbonyl compounds which are sufficiently reactive to give isolable hydrates seemed more promising than of normal carbonyl compounds, although some of the latter type, such as acetone, acetaldehyde, ethyl acetoacetate, and benzaldehyde, were included for comparison.

Selection of 1-propanethiol for use in this study was made after investigating the reaction of chloral with 1-dodecanethiol, 2-acetamidoethanethiol, and 1-propanethiol. 1-Dodecanethiol was an unsuitable choice since it did not react with chloral in methylene chloride solution in 14 days, whereas 1-propanethiol came to equilibrium under corresponding conditions within one day. The hemimercaptal from the reaction of 1-dodecanethiol with chloral was readily formed by mixture of the liquid reactants,[9] but when it was dissolved in methylene chloride its rate of dissociation was so slow that the system was never observed to come to equilibrium, although, under similar conditions in the presence of 0.2 M boron trifluoride etherate, the system came to equilibrium within 3 days. A possible explanation for this abnormally low reactivity is that, owing to the long aliphatic sidechain, an entropy factor unfavorably retards both the formation and dissociation of the hemimercaptal. The other two thiols reacted quite rapidly with chloral in the neat state in quite exothermic reactions; similar behavior occurred with the other carbonyl compounds. Another factor favoring 1-propanethiol was its lack of polar groups which might influence the stability of an α-hydroxy sulfide, if formed, or which might lead to ir absorption maxima which could confuse ir interpretations.

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(2) *Cf.* Paper XXVII and earlier papers in the series entitled "Organic Disulfides and Related Substances:" L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

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(4) I. B. Johns and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1333 (1934).

(5) F. B. Moore, *Iowa State Coll. J. Sci.*, **16**, 99 (1941); *Chem. Abstr.*, **36**, 4396 (1942).

(6) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).

(7) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co. Inc., New York, N. Y. ,1960, p 320.

(8) A. Schöberl and A. Wagner, in "Methoden der Organischen Chemie (Houben-Weyl)," Vol. 9, E. Müller Ed., G. Thieme Verlag, Stuttgart, 1955, p 199.

(9) *Cf.* R. L. Frank, S. S. Drake, P. V. Smith, Jr., and C. Stevens, *J. Polym. Sci.*, **3**, 50 (1948).

TABLE I

APPROXIMATE EQUILIBRIUM CONSTANTS (K) FOR THE REACTION OF PRIMARY THIOLS WITH CARBONYL COMPOUNDS[a]

Parent carbonyl compound	ν_{max} of C(O), cm^{-1}	K, approx	Methods	ν_{max} (O–H), cm^{-1}	ν_{max} (C–OH), cm^{-1}	Product in presence of acid catalyst
Ketones						
CH_3COCH_3	1720	0, 0	*b, c; b, d*			Mercaptole[e]
CF_3COCF_3	1800	*ca.* 10^3–10^5	*b, f*	3530	1085	α-Hydroxy sulfide
$C_2H_5O_2CCOCO_2C_2H_5$	1770	$>10^3$, ($>10^4$)	*b, c (c, g)*	3490	1035	α-Hydroxy sulfide
CH_3COCO_2H	1798	2×10^0	*b, c*	Weak	Weak	Mercaptole[e]
$CH_3COCH_2CO_2C_2H_5$	1740	*ca.* 0	*b, c*			Mercaptole
o-$C_6H_4(CO)_3$	1750 or 1760	$>10^3$, $>10^3$	*b, c; g, h*	3510	Uncertain	α-Hydroxy sulfide
Aldehydes						
C_6H_5COCHO	1738	$>10^3$, $>10^3$	*b, c; c, g*	3480	1070	α-Hydroxy sulfide
Br_3CCHO	1748	3×10^1, 3×10^1	*b, c*	3525	1040	Mercaptal?
Cl_3CCHO	1770	3, 5, 8×10^2	*b, d, i*	3540	1055	α-Hydroxy sulfide
j		8×10^2	*b, j*	3450	1085	α-Hydroxy sulfide
k		1×10^2	*b, k*	3540	1055	α-Hydroxy sulfide
CH_3CHO	1730	0	*b, d*			Mercaptal[e]
C_6H_5CHO	1700	5×10^0	*b, d*	Weak	Weak	Mercaptal
C_6F_5CHO	1720	5×10^0	*b, c*	3575	1025	Mercaptal

[a] At ambient temperatures of *ca.* 28°. 1-Propanethiol was used in all instances unless otherwise specified. [b] Method using ir absorption. [c] Calculated after dilution of the neat mixture of 1 molar proportion of carbonyl compound and 2.5 molar proportions of 1-propanethiol with CH_2Cl_2 and equilibration by dissociation. [d] Calculated after equilibration of a mixture of solutions in CH_2Cl_2 of 1 molar proportion of carbonyl compound and 2.5 molar proportions of 1-propanethiol. [e] Residual carbonyl absorption in the ir suggested incomplete conversion into mercaptal or mercaptole. [f] Excess hexafluoroacetone was condensed into 2.16 g of 1-propanethiol at *ca.* −70°. The mixture was evacuated briefly at room temperature to constant weight (yield of the α-hydroxy sulfide, 101%), dissolved in CH_2Cl_2, and allowed to equilibrate by dissociation. [g] Measured using uv. [h] Procedure as in footnote c, but using benzene as solvent. [i] Values of 3×10^2, 5×10^2, and 8×10^2 were obtained in replicate experiments. [j] As in footnote *c* but using 1 molar proportion of 2-acetamidoethanethiol. [k] As in footnote c but using a 1 molar proportion of 1-dodecanethiol in a solution 0.2 *M* with respect to boron trifluoride etherate (which, of course, may have had an effect on the value of K); the ir frequencies of OH and C–OH were determined in the absence of the boron trifluoride.

For the evaluation of K, a Beer's law curve for the selected carbonyl compound in methylene chloride was prepared either using a suitable uv absorption maximum or the carbonyl ir absorption maximum in the range of 1700–1800 cm^{-1} (*cf.* Table I). The carbonyl compound usually was then mixed with about 2.5 molar proportions of 1-propanethiol (in the absence of acid or solvent) and characteristics of the reaction such as evolution of heat, formation of water, color change, etc., were observed, as described in the Experimental Section (where behavior of other carbonyl compounds unsuitable for inclusion in Table I also is mentioned). The mixture then was dissolved in methylene chloride and its uv or ir spectrum was examined from time to time until equilibrium by dissociation was achieved. The equilibrium constants (K), calculated as described in the Experimental Section, are given in Table I. They are considered to be rather approximate values because the temperature was not rigorously controlled, because the amount of carbonyl compound left after reaction often was too small to be measured accurately using our methods, and occasionally because of other features mentioned later or as footnotes to Table I. Nevertheless, the values of 3–8 × 10^2 for chloral and 1-propanethiol (Table I) agree reasonably with those of 4–6 × 10^2 determined by Johns and Hixon for ethane- and butanethiol.[4]

The production of O–H and C–OH ir absorption maxima in the regions 3450–3575 and 1025–1085 cm^{-1}, respectively (Table I), confirmed the formation of α-hydroxy sulfides, but the frequency of the absorption seemed to show no useful correlation with the value of K. The carbonyl frequency itself also showed no useful correlation with K. In some instances, K values were measured after achieving equilibration by both dissociation of preformed α-hydroxy sulfide in CH_2Cl_2 and by reaction of the carbonyl compound in CH_2Cl_2 with thiol in CH_2Cl_2, good agreement being observed in all cases investigated. That α-hydroxy sulfides, rather than mercaptals or mercaptoles, were initial products is further confirmed by the literature cited above, by remarks below dealing with subsequent formation of mercaptals and mercaptoles, and by isolation of α-hydroxy sulfides from reaction of several compounds of high K value with 2-aminoethanethiol hydrochloride.[10]

Coupled with these observations, in each instance we thought it of added value to study similar systems in the presence of acid catalyst (hydrogen chloride or boron trifluoride) to observe the possibility of conversion of the α-hydroxy sulfide into mercaptal or mercaptole, as estimated by formation of water or by spectral changes.

In the instances of the carbonyl compounds which do not form isolable hydrates (*i.e.*, acetone, ethylacetoacetate, pyruvic acid, acetaldehyde, pentafluorobenzaldehyde, and benzaldehyde), Table I shows that little or no α-hydroxy sulfide was formed ($K \sim 0$), as was evidenced by only small initial changes in the carbonyl absorbance. However, upon addition of the acid catalyst the expected substantial conversion into a mercaptal or mercaptole occurred in most cases, as indicated by virtually complete disappearance of the carbonyl absorption and separation of considerable amounts of water from the methylene chloride used as the solvent.

In marked contrast, Table I shows that the carbonyl compounds which are well known to form isolable

(10) Details to be published elsewhere.

hydrates, and in this sense are "highly reactive," underwent substantial conversion into the α-hydroxy sulfides. These α-hydroxy sulfides could not be significantly converted into mercaptals or mercaptoles in the presence of the acid catalysts and the remaining approximately 1.5 molar proportions of 1-propanethiol. Some support for this conclusion was afforded by our inability to note any formation of water, although an amount corresponding to less than 1% conversion of the α-hydroxy sulfide can be seen easily in pure methylene chloride. Since the solubility of water in the actual systems seemed rather variable, however, a firmer basis for the conclusion is that the ir absorption spectra of solutions of the stable α-hydroxy sulfides showed no significant change after addition of the acid catalyst.

These observations suggest the generalization that carbonyl compounds which are sufficiently reactive to form isolable hydrates also are sufficiently reactive to form α-hydroxy sulfides, rather than mercaptals or mercaptoles, and that these α-hydroxy sulfides indeed cannot even be readily converted into mercaptals or mercaptoles; Table I suggests that this behavior holds when the value of K equals or exceeds about 10^2. The converse also seems true, that carbonyl compounds which show relatively little tendency to form isolable hydrates show little tendency to form α-hydroxy sulfides (K below about 10^2) and show the usual marked tendency to form mercaptals or mercaptoles in the presence of an acid catalyst. One should bear in mind, however, that changes in circumstances could have a marked effect on these generalizations. For example, the hemimercaptole of hexafluoroacetone and 1-propanethiol disappeared rather rapidly under vacuum; dissociation to the gaseous ketone might be involved, as well as volatilization; irreversible dissociation also would be expected if a thiol component were readily oxidized.

The main factor leading to stabilization of an α-hydroxy sulfide of 1-propanethiol appears to be the presence of an electron-withdrawing group in the α position. The results presented in Table I suggest that the stabilities decrease in this order: $C_6H_5C(O)$, bis CO, bis CO_2Et, $CF_3 > CCl_3 > CBr_3 > C_6F_5$, $C_6H_5 > CH_3(CO_2H) > CH_3(CH_2CO_2Et)$, CH_3. This order resembles that which might be expected from the order of Taft polar substituent constants, where data are available (*e.g.*, $CCl_3 > CHF_2 > CO_2ME \gg C_6H_5 > CH_3$).[11] If the stabilizing group is in the β position (*e.g.*, CO_2Et in ethyl acetoacetate), the stabilizing effect is very greatly reduced.

The most attractive explanation for the inability of α hydroxy sulfides having α-electron-withdrawing groups to be further converted in the presence of acid into mercaptals or mercaptoles is that the electron-withdrawing group, which perhaps strengthens the C–OH bond and reduces the basicity of the OH, destabilizes the transition state leading to the formation of the carbonium ion, which presumably is essential in the conversion. Steric influences also may play a role; for example, hexachloroacetone which on reaction with a thiol might be expected to yield a stable α-hydroxy sulfide, was completely unreactive.

(11) J. Hine, "Physical Organic Chemistry," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 97.

Because of the interest mentioned in tertiary thiols like penicillamine, it was desirable also to study the reaction of a tertiary thiol with a carbonyl compound having a value of K intermediate among those which formed α-hydroxy sulfides. The reaction system chosen was that of chloral with 2-methyl-2-propanethiol (penicillamine itself is too sparingly soluble in methylene chloride). The K value (measured by either formation or dissociation) for this reaction was 1.5×10^2, approximately one-third of the value obtained using 1-propanethiol. The rapidity of equilibration was roughly comparable for the primary and tertiary thiols. Since it was available to us,[10] the thiol $HSC(CH_3)_2CH_2CH_2OH$ also was studied with chloral. In this instance, a K value of 1.3×10^3 was obtained (about three times the value obtained using 1-propanethiol and nearly ten times that using 2-methyl-2-propanethiol). The alternative product, $Cl_3CCH(OH)O(CH_2)_2C(CH_3)_2SH$, cannot be excluded entirely, but seemed unlikely to be more than a minor component, at most, since no ir frequency for SH was seen at equilibrium. This enhanced stability may reflect a stabilizing effect of the side-chain hydroxyl group on the α-hydroxy sulfide. This reaction when carried out neat appeared to be somewhat more exothermic than the one using 2-methyl-2-propanethiol. Cyclization to significant amounts of 2-(trichloromethyl)-4,4-dimethyl-1,3-oxathiane with this thiol seems unlikely, since the ir spectrum was consistent only with the α-hydroxy sulfide structure and since no water formation was detected, even after the product had been kept in methylene chloride for 4 days. In this case, equilibration following either reaction of the aldehyde and thiol or dissociation of the adduct seemed to occur about ten times faster with the hydroxythiol than with 2-methyl-2-propanethiol. The observations of a more noticeable exothermic reaction and a more rapid occurrence of equilibration for systems with a higher value of K were consistent with impressions from the studies using 1-propanethiol.

Experimental Section[12]

Determination of Values of K.—For each carbonyl compound studied, either the C=O ir stretching frequency or an appropriate uv absorption maximum was used to construct a Beer's Law curve and this in turn was used to determine residual content of carbonyl compound after reaction with the thiol; therefrom, the constant K, measured at equilibrium (*i.e.*, at constancy of absorbance) for the particular reaction, was calculated using

$$K = [R^2R^3C(OH)SR^1]/[R^2R^3CO][R^1SH] \qquad (2)$$

which $[R^2R^3CO]$ was taken as the concentration of carbonyl compound measured, $[R^2R^3C(OH)SR^1]$ as equal to the decrease in $[R^2R^3CO]$, and $[R^1SH]$ as $[R^1SH]$ initial $- [R^2R^3C(OH)SR^1]$. Measurements and calculations were carried out in the same fashion irrespective of whether the thiol and carbonyl compounds were first mixed in CH_2Cl_2 or, for dissociation, were first mixed neat and later diluted (dissociation then usually being evidenced by increased absorption on standing). Simultaneous observations of semiquantitative kinetic and other characteristics also were made, and comments on these are made below.

(12) Infrared spectra were obtained using a Beckman Model IR-10 spectrophotometer with a matched pair of 0.1-mm NaCl cavity cells. Unless otherwise specified, methylene chloride (Matheson Coleman and Bell "Spectroquality") was used as solvent. Ultraviolet or visible spectra were obtained using a Cary Model 14 spectrophotometer. All starting materials were the best commercial grades, unless otherwise mentioned; they were suitably purified when necessary.

In several experiments using di- or tricarbonyl compounds, overlapping C=O bands in the ir hindered accurate quantitative measurements and, consequently, K values were measured, in these instances, using absorption bands in the visible or uv regions.

Description of an experiment will illustrate the general methods used and some of the deviations necessary. Freshly redistilled diethyl oxomalonate (0.428 g, 2.46 mmol) and 1-propanethiol (0.443 g, 5.82 mmol; approximately 2.4 molar proportions) were mixed. (This method was usually followed as an alternative to mixture in solution, as a convenient check, because formation of the product is rapid and more nearly complete, and because by use of the neat reactants dissociation of a product was involved and the equilibration seemed more certain.) There was evolution of much heat and the diethyl oxomalonate was immediately decolorized. After 20 min the mixture was made up to 25 ml with CH_2Cl_2 and the spectrum of the solution was examined. The absorption bands at 1770 (shoulder) cm^{-1} in the ir and the uv absorption band at 369 mμ (log ϵ 1.49) had disappeared. The ir spectrum showed bands at 3490 (OH), 1035 (C—OH), and 1750 (ester –CO–) cm^{-1}. Because of the proximity of the ir absorption of the ketone carbonyl (1770 cm^{-1}) to that of the ester, only an approximate minimum value of K could be determined by the ir technique. K was better approximated using a uv band at 369 mμ (log ϵ 1.49). When equilibrium was assured by constancy of the uv spectrum (*ca.* 1 hr in this instance) the amount of residual oxomalonate was too small to be measured. An estimate from the Beer's law plot suggested that a concentration of 0.0003 mol/l. would have been barely detectible and this value was used for $[R^2R^3CO]$ in eq 2; taking $[R^2R^3C(OH)SR^1]$ as 0.0981 mol/l. and $[R^1SH]$ as 0.1347 mol/l. thus gave $K = 2.4 \times 10^3$; the actual value must have exceeded this. The value of $>10^4$ (Table I) was obtained similarly but at a higher concentration. Subsequent passage of HCl caused no changes in the ir spectrum and no visible formation of water, hence the conclusion (Table I) that the α-hydroxy sulfide was unchanged.

Reaction of Particular Carbonyl Compounds with 1-Propanethiol. A. Ketones. Acetone.—In the absence of HCl there was no diminution of carbonyl absorption in the ir. The mercaptole was formed when HCl gas was introduced, as evidenced by an exothermic reaction, by formation of water (none visible earlier), and by ir spectral changes not attributable to formation of an α-hydroxy sulfide.

sym-**Dichloroacetone.**—This reacted rapidly and exothermically with 1-propanethiol, liberating both HCl and H_2O; an intense red color developed within minutes. The ir spectrum suggested formation of an unstable mercaptole, but the cause of the red color is not understood. Perhaps this reaction is autocatalyzed by acid.

1,1,1-Trifluoroacetone.—Surprisingly, the ir spectrum showed that, in the absence or presence of HCl, no reaction occurred.

Hexafluoroacetone.—The reaction of hexafluoroacetone with 1-propanethiol was followed by the procedure described in footnote *f* of Table I. Because of the slight solubility of hexafluoroacetone in CH_2Cl_2 the concentration of the carbonyl compound had to be estimated using a Beer's law curve constructed for acetone or hexachloroacetone. Because of the nature of these assumptions the calculated value of K should be regarded as approximate at best. Interestingly, 7.3 g of the liquid hemimercaptole of hexafluoroacetone and 1-propanethiol disappeared in 5 hr at a pressure of 5 mm and in 30 min at one of 1 mm (*ca.* 28°); there was no ebullition, but the hemimercaptole could be recovered in a receiver cooled with liquid N_2.

Hexafluoroacetone Trihydrate.—No reaction was apparent with 1-propanethiol in the absence or presence of HCl. This illustrates the high stability of such hydrates; it can be compared with our observation that trifluoroacetaldehyde hydrate did not react with 2-aminoethanethiol hydrochloride.[10]

Hexachloroacetone.—No reaction occurred with 1-propanethiol in the absence or presence of HCl under any conditions tried.

Diethyl Oxomalonate.—This ester was freshly redistilled from its hydrate over P_2O_5.[13] It reacted extremely rapidly and exothermically with 1-propanethiol giving the α-hydroxy sulfide as described above. Study of the reaction in the uv of a 0.0163 M solution of diethyl oxomalonate in CH_2Cl_2 with a 0.042 M solution of 1-propanethiol in CH_2Cl_2 suggested a time of half-reaction of *ca.* 8 min.

Pyruvic Acid.—An exothermic reaction occurred with 1-propanethiol. An ir spectrum of the neat mixture suggested some conversion into the α-hydroxy sulfide. However, on dilution with $CHCl_3$, the α-hydroxy sulfide dissociated almost completely; the value of K obtained after dissociation is given in Table I. In the presence of HCl, some conversion into the mercaptole was achieved.

Ethyl Acetoacetate.—The α-hydroxy sulfide could not be detected in the neat state or in CH_2Cl_2. A neat mixture of the carbonyl compound and 1-propanethiol gave, in the presence of HCl, a typical exothermic reaction in which water was formed. Examination of the ir spectrum of a CH_2Cl_2 solution of the mixture then suggested virtually complete conversion into the mercaptole.

Indan-1,2,3-trione.—This compound was insufficiently soluble in CH_2Cl_2 for accurate ir measurements, although the α-hydroxy sulfide formed when it reacted with 1-propanethiol was quite soluble in CH_2Cl_2. Coupled with this, the presence of three carbonyl bands at 1730, 1750, and 1760 cm^{-1} in the ir spectrum of indan-1,2,3-trione in CH_2Cl_2 made interpretation of changes in this region difficult. As a consequence of these observations, benzene was used as solvent, advantage being taken of the maximum of the triketone at 612 mμ (log ϵ 1.46). The reaction neat of the purple triketone with 1-propanethiol was exothermic and, within seconds, gave solid α-hydroxy sulfide as pale yellow needles. The C–OH frequency of the product was displaced by over 80 cm^{-1} from the usual range and no definite assignment could be made.

B. Aldehydes. Phenylglyoxal Monomer.—This was distilled from phenylglyoxal hydrate or from polyphenylglyoxal.[14] The monomer was used within 24 hr of distillation. Its reaction with 1-propanethiol forming an α-hydroxysulfide was rapid and exothermic, decolorization being virtually instantaneous. The ketone carbonyl absorption at 1680 cm^{-1} overlapped at its base with the aldehyde carbonyl absorption at 1738 cm^{-1} and quantitative measurement by ir of K was not precise. However, by using the absorption maximum at 425 mμ (log ϵ 1.32) of phenylglyoxal in CH_2Cl_2 a minimum K value of 10^3 was obtained. After saturation of the mixture with HCl, no conversion into mercaptal or mixed mercaptal–mercaptole was observed. Although conversion into α-hydroxy sulfide was essentially complete, solutions were pale yellow, apparently because of the tail of an intense absorption band in the near-uv.

Bromal.—Mixture with 1-propanethiol in the usual way (neat) gave an α-hydroxy sulfide which was stable in CH_2Cl_2 for several days (no change in the ir spectrum). In the presence of HCl the mixture gradually became brown and H_2O separated; the brown solution then showed an unexplained second ir absorption maximum at 1732 cm^{-1} in addition to the maximum of bromal at 1748 cm^{-1}. Treatment with HCl resulted in the complete and immediate loss of the absorption maxima of the α-hydroxy sulfide at 3525 and 1040 cm^{-1}. These results suggest the formation of an unstable mercaptal, although side reactions may have been significant.

Chloral.—Chloral reacted rapidly and exothermically in the neat state with 1-propanethiol, 2-acetamidoethanethiol, or 1-dodecanethiol[9] to give the respective α-hydroxy sulfides. The α-hydroxy sulfides from 1-propanethiol and 1-dodecanethiol absorb in the ir at 3540, 1055, and 1763 (weak) cm^{-1}, while, in the spectrum of the α-hydroxy sulfide from 2-acetamidoethanethiol, the corresponding frequencies occur at 3450 and 1085 cm^{-1}. A solution of chloral (0.2 M) in CH_2Cl_2 equilibrated with 1-propanethiol (0.3 M) within 1 day and with 2-acetamidoethanethiol (0.3 M) within 4 days, but no reaction whatever could be detected with 1-dodecanethiol after 14 days. In the presence of acid catalyst (HCl saturation or 0.2 M with respect to boron trifluoride etherate) in CH_2Cl_2, 1-propanethiol and 2-acetamidoethanethiol reacted rapidly to give the α-hydroxy sulfides, but the trend of decreasing –CO– absorbance suggested that 1-dodecanethiol would have taken at least 300 days to equilibrate. The α-hydroxy sulfide from 1-dodecanethiol was prepared using the method of Frank, Drake, Smith, and Stevens[9] and came to equilibrium in CH_2Cl_2

(13) R. S. Curtiss and E. K. Stracham, *J. Amer. Chem. Soc.*, **33**, 396 (1911).

(14) H. A. Riley and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 509.

containing boron trifluoride etherate (0.2 M solution) in about 3 days. The calculated K was about 10^2, in contrast to the value of 3–8 $\times$ 10^2 for the reactions of 1-propanethiol or 2-acetamidoethanethiol. The value of 3–8 $\times$ 10^2 compares favorably with those of 4–6 $\times$ 10^2 measured by Johns and Hixon for the reaction of chloral with ethanethiol or 1-butanethiol using a freezing point depression method.[4]

The reaction of chloral with 2-methyl-2-propanethiol also was studied for comparison and gave a K of *ca.* 1.5 $\times$ 10^2 in CH_2Cl_2; the spectrum of the α-hydroxy sulfide which resulted had maxima at 3540 and 1055 cm^{-1}. The time of equilibration (*ca.* 2 days) of the neat chloral–thiol mixture appeared to be about double that of the corresponding chloral-1-propanethiol mixture. The reaction of the tertiary thiol $HSC(CH_3)_2CH_2CH_2OH$ with chloral gave a K value of 1.3 $\times$ 10^3, the time of equilibration under the conditions used with 2-methyl-2-propanethiol being about 4 hr. The ir spectrum of this α-hydroxy sulfide had maxima at 3520 and 1085 cm^{-1}.

Acetaldehyde.—This did not react in any amount detected with 1-propanethiol, 2-acetamidoethanethiol, or 1-dodecanethiol in CH_2Cl_2 in the absence of acid. In the presence of HCl or boron trifluoride etherate the corresponding mercaptal formed (see footnote *e*, Table I).

Formaldehyde.—Paraldehyde or *s*-trioxane with 1-propanethiol showed no reaction. In the presence of HCl, exothermic conversion into mercaptal occurred.

Benzaldehyde.—In the absence of HCl, slight conversion into an α-hydroxy sulfide occurred, as indicated by diminution in the –CO– absorption at 1700 cm^{-1} and by weak absorptions produced at 3510 and 1100 (1085) cm^{-1}. In the presence of HCl, substantial conversion into the expected mercaptal occurred.

Pentafluorobenzaldehyde.—This gave a reaction similar to that given by benzaldehyde, the spectrum of the mixture in CH_2Cl_2 having absorption maxima of medium intensity at 3575 and 1025 cm^{-1}. However, the calculated K was only 5 $\times$ 10^0 (benzaldehyde, 5 $\times$ 10^0). This lower K than expected must be due to a cancellation of electronic effects on the aromatic ring.

Registry No.—1-Propanethiol, 107-03-9.

Methanesulfenyl Chloride. V. The Spontaneous Decomposition of Methanesulfenyl Chloride and Methylsulfur Trichloride[1a]

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Methanesulfenyl chloride, CH_3SCl, on standing for a few hours at room temperature begins to decompose into methyl chloride, methyldisulfur chloride, methyl disulfide, methyl trisulfide, and methyl tetrasulfide as major products as indicated by the nmr spectra of decomposition mixtures. Minor peaks in the spectrum correspond to the δ chemical shifts of methyl chloromethyl disulfide and dichloromethyl methyl sulfide. Other products were hydrogen chloride, sulfur dichloride, elementary sulfur, and, in some cases, on long standing an unidentified solid. Methylsulfur trichloride decomposes rapidly when the crystalline solid is heated a few degrees above room temperature. The nmr spectrum of the decomposition mixture indicates that the principal products are chloromethanesulfenyl chloride (*ca.* 60%) and methanesulfenyl chloride (*ca.* 20%). Other products identified by their peaks in the nmr spectrum are methyldisulfur chloride, methyltrisulfur chloride, methyltetrasulfur chloride, bischloromethyl disulfide, and dichloromethanesulfenyl chloride. In addition, hydrogen chloride and sulfur dichloride were also products of the decomposition. Uncertainty exists as to whether the decomposition of CH_3SCl takes place by an ionic or free-radical mechanism. An esr study of the decomposition showed no signals to indicate an appreciable concentration of free radicals. Methyl disulfide, irradiated at liquid nitrogen temperature, produced an esr spectrum with clearly defined signals believed to indicate the $CH_3S\cdot$ radical. This radical appears to be highly reactive and cannot be stabilized on Vycor glass at room temperature. The failure to observe esr signals in decomposing CH_3SCl may possibly be due to the high reactivity of radical intermediates resulting in a low steady state concentration.

Methanesulfenyl chloride, CH_3SCl, and methylsulfur trichloride, CH_3SCl_3, are two highly reactive compounds which, if treated properly, enter into stoichiometric reactions and yield products which can be isolated in high yield.[2,3] If CH_3SCl is allowed to stand a few hours, or if CH_3SCl_3 is warmed only a few degrees above room temperature, however, the compounds undergo profound decompositions, yielding mixtures which defy separation or analysis by conventional means.

Since the two original compounds contain single carbon atoms, most of the decomposition products are capable of yielding sharp singlet peaks in the nmr spectra. Recent experience in our laboratory as well as previous studies by others have shown that nmr affords an excellent means for identifying individual closely related sulfur compounds in complex mixtures.[4,5]

Although there remain a number of uncertainties regarding the identity of some products formed in the decompositions, and the mechanisms by which the products are formed, it seems appropriate to report at this time the products identified. Later work may clarify some of the unsolved questions but the departure of the junior authors and the stinking character of the materials involved discourage further work at the present time.

There are previous reports concerning the instability of these compounds. In his original description of

(1) (a) Taken in part from the Ph.D. Thesis of R. V. Norton, University of Maine, 1967, and from the M. S. Thesis of R. L. Weichman, University of Maine, 1966. (b) To whom inquiries concerning this paper may be sent. (c) To whom the senior author is indebted for carrying out the esr study of the decomposition of CH_3SCl at Princeton University.

(2) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, **22**, 536 (1957).

(3) I. B. Douglass and W. J. Evers, *ibid.*, **29**, 419 (1964), and prior publications.

(4) J. R. Van Wazer and D. Grant, *J. Amer. Chem. Soc.*, **86**, 1450 (1964).

(5) D. Grant and J. R. Van Wazer, *ibid.*, **86**, 3012 (1964).

TABLE I

PRODUCTS OF THE SPONTANEOUS DECOMPOSITION OF METHANESULFENYL CHLORIDE[a]

	Mol %							
Time, days	CH_3SCl	CH_3SSCl	CH_3Cl[b]	CH_3SSCH_3	CH_3SSSCH_3	$CH_3SSSSCH_3$	$ClCH_2SSCH_3$	Cl_2CHSCH_3
0	100	0	0	0	0	0	0	0
1	45	16	5	18	2	4	5	3
2	26	29	5	15	4	6	7	10
7	10	31	6	17	9	9	10	8
10	7	29	5	16	12	11	10	11
17	6	29	5	13	12	14	10	10
38	4	27	4	11	12	21	11	11

[a] Hydrogen-containing components of the liquid fraction. [b] The decomposition was allowed to proceed at atmospheric pressure and most of the methyl chloride escaped from the decomposition mixture.

CH_3SCl, Brintzinger mentioned that, when the compound was allowed to stand or was distilled at ordinary pressure, a high boiling residue was formed.[6] Schneider[7] exposed a 20-g sample of CH_3SCl in a sealed tube to sunlight for 3 days at room temperature. On opening the tube he noted the escape of a large amount of gas which he reported as being hydrogen chloride, but which probably consisted in large part of methyl chloride. Mayer and Frey[8] heated aliphatic sulfenyl chlorides to 100° and found that they readily decomposed to alkyl chlorides.

In an early paper[9] describing methylsulfur trichloride and analogous compounds two principal types of decomposition were noted. One was a reversible decomposition into sulfenyl chloride and chlorine (eq 1).

$$RSCl_3 \rightarrow RSCl + Cl_2 \quad (1)$$

The other, shown by the alkylsulfur trichlorides, involved the splitting out of hydrogen chloride with the formation of an α-chloroalkanesulfenyl chloride (eq 2). The present study indicates that the decomposition also follows several other paths.

$$RCH_2SCl_3 \rightarrow HCl + RCHClSCl \quad (2)$$

In carrying out our study the two compounds were allowed to decompose; samples of the resulting mixtures were diluted with carbon tetrachloride (CCl_4) containing tetramethylsilane (TMS) and subjected to pmr analysis. The δ shifts of the peaks in the resulting spectra were then matched against the δ shifts of known compounds and, when possible, tests were made on the decomposition mixtures to isolate specific compounds or to cause an individual component to react in such a way that its presence could be demonstrated.

The principal products of the decomposition of CH_3SCl proved to be methyl chloride, methyldisulfur chloride (CH_3SSCl), methyl disulfide, methyl trisulfide, and either methyl tetrasulfide or methyltrisulfur chloride. (Methyltrisulfur chloride has a chemical shift identical with that of methyl tetrasulfide but tests on the mixture indicate the presence of the tetrasulfide.) Minor peaks in the pmr spectrum of every decomposition mixture corresponded to the δ values characteristic of methyl chloromethyl disulfide, CH_3SSCH_2Cl, and dichloromethyl methyl sulfide, Cl_2CHSCH_3. In addition to the compounds listed above, hydrogen chloride, sulfur dichloride, elemental sulfur, and an unidentified crystalline solid were products of the decomposition. Table I gives the approximate molar composition of samples which had decomposed for varying lengths of time. Heating accelerated the decomposition but irradiation seemed to have no accelerating effect and pmr spectra of irradiated and nonirradiated samples were essentially identical at comparable time intervals.

The decomposition of CH_3SCl_3 is a rapid, self-catalyzed reaction. When a sample of the dry solid, spread out in an inclined test tube, is gently heated through the glass at one edge, the decomposition begins at the point heated and spreads through the mass like fire spreading through a field of dry grass. Condensation of the volatile products and recombination with the liquid residue gave a mixture, the pmr spectrum of which revealed the presence of methyl chloride, chloromethanesulfenyl chloride, methanesulfenyl chloride, dichloromethanesulfenyl chloride, methyldisulfur chloride, methyltrisulfur chloride, methyltetrasulfur chloride, and bischloromethyl disulfide. Hydrogen chloride and sulfur dichloride were also products of the decomposition. Table II shows the approximate relative abundance of the components in decomposition mixtures as determined by integration of their pmr spectra.

TABLE II

DECOMPOSITION PRODUCTS OF METHYLSULFUR TRICHLORIDE

	Mol %		
Compound formed	Dry solid	Dry solid	In CCl_4
$ClCH_2SCl$	55.6	61.0	60.3
CH_3SCl	20.4	14.6	17.2
CH_3S_2Cl	0.0	3.3	0.8
CH_3S_3Cl	8.4	8.9	2.9
CH_3S_4Cl	2.3	2.4	14.4
Cl_2CHSCl	6.8	6.3	
$(ClCH_2S)_2$	4.5	3.5	1.4
CH_3Cl	1.6	0.0	2.9
HCl	+	+	+
SCl_2	?	?	+

At the present time there is no firm basis for formulating a mechanism for these decompositions. Our previous studies of the reaction of methanesulfenyl chloride have emphasized its tendency to react by an ionic mechanism.[3] On the other hand, Grant and Van Wazer[5] explained in terms of free radicals the complicated equilibria and "scrambling of parts" which

(6) H. Brintzinger, K. Pfannstiel, H. Koddebusch, and K. E. Kling, *Chem. Ber.*, **83**, 87 (1950).
(7) E. Schneider, *ibid.*, **84**, 911 (1951).
(8) R. Mayer and H. J. Frey, *Angew. Chem.*, **76**, (20), 861 (1964).
(9) I. B. Douglass, K. R. Brower, and F. T. Martin, *J. Amer. Chem. Soc.*, **74**, 5770 (1952).

result when sulfur chlorides react with methyl sulfide and methyl disulfide but referred to "initial complex formation." Several other recent publications have discussed free-radical reactions of sulfenyl chlorides.[10] One can readily explain the formation of the decomposition products identified in this study in terms of radical reactions. On the other hand, more difficulty is experienced in outlining ionic steps which would yield the products found.

With the assistance of Mr. Robert B. Clarkson in the chemistry laboratory at Princeton University, an attempt was made to determine whether fresh or decomposing samples of CH_3SCl would give an electron spin resonance spectrum which would indicate the presence of free radicals. No such signals were observed, indicating that, if radicals are formed, they react so rapidly that the concentration at any one time is too low to produce an esr signal. Evidence for highly reactive radicals, believed to be $CH_3S\cdot$, was obtained by irradiating, at liquid nitrogen temperature, methyl disulfide adsorbed on Vycor glass. An esr spectrum of the sample showed a strong signal with partially refined hyperfine structure. The hyperfine structure disappeared when deuteriomethyl disulfide was put through the procedure. The $CH_3S\cdot$ signal slowly decayed at liquid nitrogen temperature and completely disappeared when the sample was warmed to room temperature and immediately cooled again to liquid nitrogen temperature. The observed radical, in contrast to the methyl radical, cannot be stabilized on Vycor at room temperature. The failure to observe esr signals during the decomposition of CH_3SCl may possibly be attributed to the inability of the Vycor glass to stabilize a radical intermediate.

In our attempts to confirm the identity of components in the decomposition mixture and to clarify the reactions by which they might be formed, some previously unreported aspects of organosulfur chemistry were observed. When CH_3SCl was allowed to react with sulfur dichloride a complex mixture resulted containing CH_3SCl, CH_3S_2Cl, CH_3S_3Cl, and CH_3S_4Cl. These results along with others reported below are analogous to those reported by Van Wazer and Grant for other systems.[4,5]

The reactions of sulfur dichloride and sulfur monochloride with mercaptans have long been employed to prepare alkyl and aryl trisulfides and tetrasulfides.[11] The present study has shown that in preparing methyl tetrasulfide the order in which the reactants are mixed is important in determining the products formed. Addition of the sulfur monochloride to methyl mercaptan at low temperature gives pure methyl tetrasulfide. Reverse addition, however, of mercaptan to the sulfur monochloride gives a mixture of methylpolysulfur chlorides and methyl polysulfides.

The pmr spectra of a number of organosulfur compounds were examined in an attempt to identify the peaks in the pmr spectrum of the decomposition mixtures. Table III consolidates this data. The δ values for the protons in the methylpolysulfur chlorides do not agree with those previously reported.[4,5] The values for corresponding protons among the chloro derivatives of methyl sulfide appear to be influenced by factors other than simple inductive effects.

TABLE III
PMR CHEMICAL SHIFTS OF SOME ORGANOSULFUR COMPOUNDS

	CH_3S-	$ClCH_2S$-	Cl_2CHS-
CH_3SCH_3	2.08		
$ClCH_2SCH_3$	2.28	4.68	
$ClCH_2SCH_2Cl$		4.86	
Cl_2CHSCH_3	2.47		6.75
Cl_2CHSCH_2Cl		4.86	6.85
$Cl_2CHSCHCl_2$			6.75
Cl_2CSCH_3	2.66		
Cl_2CSCH_2Cl		5.10	
$Cl_2CSCHCl_2$			7.05
CH_3SSCH_3	2.41		
CH_3SSCH_2Cl	2.60	4.78	
$ClCH_2SSCH_2Cl$		4.84	
CH_3SSSCH_3	2.56		
$CH_3SSSSCH_3$	2.66		
CH_3SCl	2.91		
CH_3SSCl	2.75		
CH_3SSSCl	2.65		
$CH_3SSSSCl$	2.51		
$ClCH_2SCl$		5.08	
Cl_2CHSCl			6.83

Experimental Section

Pmr spectra were obtained by the use of a Varian Associates Model A-60 nmr spectrometer. In each case a 10% solution of the compound or mixture to be tested was prepared in Spectro-Grade carbon tetrachloride containing 1% of tetramethylsilane. At frequent intervals the calibration of the instrument was checked with a sealed tube containing a solution of 1% chloroform and 1% tetramethylsilane in carbon tetrachloride.

Decomposition of Methanesulfenyl Chloride (I).—I was prepared according to the method previously described.[3] It was purified by distillation through an 11-in., glass helix packed column under reduced pressure (boiling below 0° at 10 mm) and condensed in a receiver cooled in Dry Ice. The product, after storing overnight at −78°, showed only a single pmr peak at δ 2.91 downfield from tetramethylsilane.

In first carrying out the decompositions, two 20.64-g (0.25 mol) samples were placed in separate identical Pyrex flasks. Each flask was fitted with a port for removing liquid samples, a manometer to indicate pressure development and an outlet connected through a stopcock to a Dry Ice trap which in turn was connected through a drying tube to a flask containing a measured amount of standard alkali. One flask was illuminated several hours daily with a 274-W General Electric sun lamp and the other was wrapped in black cloth and placed in a dark cupboard. Both flasks were flushed with dry nitrogen at the start of the experiment and were kept at room temperature. At appropriate intervals small samples of the decomposition mixtures were removed with a capillary syringe for pmr analysis.

At the beginning of the experiment the manometer indicated a fairly rapid generation of gas which made it necessary to open the stopcock several times during the first 2 hr. Thereafter it was left open.

After 24 hr the color of the liquid was less red and the pmr spectrum, in addition to the peak at δ 2.91 for CH_3SCl, showed five major peaks at 2.40, 2.55, 2.65, and 2.77 and four minor peaks at 2.47, 2.60, 4.79, and 6.74. All of these peaks persisted to the end of the experiment and no new peaks developed. Table I shows the approximate composition in mole per cent of the liquid withdrawn at the various time intervals.

After 10 days, withdrawn samples were no longer completely

(10) J. F. Harris, Jr., *J. Org. Chem.*, **31**, 931 (1966), and references therein.

(11) A. Schöberl and A. Wagner in "Houben-Weil, Methoden der Organischen Chemie," Vol. 9, 4th ed, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p 87.

miscible with carbon tetrachloride and precipitated a white solid when diluted. After the seventeenth day crystals appeared in the mother liquor. At the end of 38 days 2.79 g of solid had accumulated in the flask exposed to light and 1.53 g in the one kept in the dark. This was the only detectable difference in the two experiments.

The solid was colorless, insoluble in acetone, carbon tetrachloride, ether, and hexane and melted sharply at 74–75°. It reacted in water to give an acidic solution containing chloride ions. On standing in a loosely stoppered test tube the solid slowly liquefied but appeared to be stable indefinitely when excluded from moisture. Analysis indicated a composition which could not be interpreted in terms of definite composition. Some samples of CH_3SCl, allowed to stand undisturbed for as long as 2 months, failed to precipitate any solid.

Identification of Products from CH_3SCl.—The volatile condensate from the cold trap, after being vaporized through an alkaline solution and dried, gave an infrared (ir) spectrum identical with that of authentic methyl chloride. The pmr spectrum showed a single peak at δ 3.00 also identical with that of methyl chloride.

The peaks in the pmr spectrum of the decomposition mixture at δ 2.41, 2.56, and 2.66 were attributed to methyl disulfide, methyl trisulfide, and methyl tetrasulfide. A freshly distilled sample of methyl disulfide showed a single peak at δ 2.41. A sample of methyl trisulfide, prepared by adding sulfur dichloride to liquefied methyl mercaptan, showed a principal peak at δ 2.56. Likewise, a sample of methyl tetrasulfide, prepared by adding sulfur monochloride to liquefied methyl mercaptan at −20° showed a principal peak at δ 2.66. An old sample of methyl tetrasulfide, showing by its pmr spectrum that it contained all the lower methyl polysulfides, was injected into a gas–liquid chromatograph (110°) column packed with 20% Apiezon J on 60/80 mesh Chromosorb W. The retention times for methyl di-, tri-, and tetrasulfides were found to be 0.8, 3.8, and 19.4 min, respectively. A similar amount of the decomposition mixture showed components with identical retention times.

Methyldisulfur chloride, CH_3SSCl, is believed to be the decomposition product responsible for the pmr peak at δ 2.77. An authentic sample of this compound was prepared by the method of Böhme and von Ham[12] through the reaction of sulfuryl chloride with methyl trisulfide. The pmr spectrum of this reaction mixture showed peaks at δ 2.91 for methanesulfenyl chloride and at 2.77 for methyldisulfur chloride.

The four unidentified peaks remaining were considered as possibly resulting from chloro derivatives of dimethyl sulfide or dimethyl disulfide. All of the chloro derivatives of methyl sulfide were prepared by the methods reported by Truce, Birum, and McBee.[13] The properties of all these compounds, except $\alpha,\alpha,\alpha',\alpha'$-tetrachlorodimethyl sulfide, agree well with those reported by the previous workers. The latter compound, in spite of repeated close fractionation through a 4-ft helix-packed column could not be separated from the $\alpha,\alpha,\alpha,\alpha'$-tetrachloro isomer. In the mixtures, however, the pmr spectra of the two compounds could be readily identified. One of the chloro derivatives of dimethyl sulfide, dichloromethyl methyl sulfide (CH_3SCHCl_2), had pmr δ shifts which coincided with two of the minor unknown peaks in the spectrum of the decomposition mixture. The other two minor unidentified peaks are believed to indicate the presence of chloromethyl methyl disulfide. An impure sample of this compound was prepared by the reaction of chloromethanesulfenyl chloride (containing some I) with methyl mercaptan. A pmr spectrum of the reaction product showed a peak at δ 2.41 characteristic of methyl disulfide and two major peaks at 2.60 for CH_3SSCH_2Cl and at 4.79 for CH_3SSCH_2Cl, having peak areas integrating 3:2.

The amount of hydrogen chloride formed during the decomposition, while not determined precisely, was not large. Titration of the alkaline solution in the absorption train described above indicated that only 0.03 equiv of alkali had been neutralized during the decomposition of 0.25 mol of I. Some hydrogen chloride, however, was lost when the system was periodically opened and some remained dissolved in the original decomposition mixture and in the cold trap condensate.

(12) H. Böhme and G. von Ham, *Ann.*, **617**, 62 (1958).

(13) W. E. Truce, G. H. Birum, and E. T. McBee, *J. Amer. Chem. Soc.*, 74, 3594 (1952).

In an effort to identify elemental sulfur and sulfur dichloride among the decomposition products, a portion of a decomposition mixture was treated with phenol, steam distilled, and acetylated. On chromatographing a chloroform solution of the acetylated mixture on silica gel there was obtained a small sample of elemental sulfur with mp 116–117°, unchanged on admixture with flowers of sulfur which had been recrystallized from chloroform. There was also obtained a small quantity of bis(*p*-ce-atoxyphenyl) sulfide with mp 94–94.5°, unchanged on admixture with an authentic sample,[14] prepared by the reaction of sulfur dichloride with phenol followed by acetylation.

Preparation and Decomposition of Methylsulfur Trichloride (II).—A solution of methyl disulfide (4.7 g, 0.05 mol) in 50 ml of anhydrous methylene chloride contained in a large tube was cooled in a Dry Ice–Acetone bath and chlorinated, with frequent shaking, until the red color of methanesulfenyl chloride had disappeared and a greenish yellow color indicated excess chlorine. The solid was then allowed to settle, the supernatant liquid was decanted, and without external cooling the remaining solvent was removed under the reduced pressure of a water pump. The tube containing the fine crystals of CH_3SCl_3 was then connected to a second tube cooled in a Dry Ice–Acetone bath and gently heated to start the decomposition. Occasional cooling of the tube kept the decomposition under control. The liquid residue was finally chilled, combined with the material which had collected in the cold trap, and subjected to pmr analysis. Other preparations were allowed to decompose in the presence of solvent. Table II shows the composition of several decomposition mixtures.

Sulfur dichloride in the reaction product was demonstrated as follows. A carbon tetrachloride solution of the decomposition products from 0.07 mol of CH_3SCl_3 was treated with 5.0 g of freshly distilled phenol and kept at 25° for 1 day. Evaporation of the solution in a rotary evaporator at 50° (14 mm) yielded a gum which was treated with acetyl chloride (10 ml) for 48 hr at 25°. Recrystallization of the gummy product obtained when the residue was poured on ice yielded 100 mg of bis(4-acetoxyphenyl) sulfide with mp 93.5–94° (lit.[14] mp 94°), unchanged on admixture with an authentic sample.

The Reaction of CH_3SCl with Sulfur Dichloride.—Methanesulfenyl chloride (1.0 g, 0.012 mol) was added in one portion to freshly distilled sulfur dichloride (4.5 g, 0.044 mol) contained in a test tube immersed in a 25° bath. An immediate exothermic reaction took place. At various time intervals small samples were removed, diluted to 10% concentration with carbon tetrachloride containing TMS, and analyzed by pmr spectroscopy. Integration of the resulting spectra gave the results shown in Table IV.

TABLE IV

PRODUCTS FROM THE REACTION OF METHANESULFENYL CHLORIDE[a] WITH SULFUR DICHLORIDE[b]

	Products, mol %			
Time	CH_3SCl	CH_3S_2Cl	CH_3S_3Cl	CH_3S_4Cl
30 min	64	16	5	16
2 hr	49	25	10	15
24 hr	30	30	23	17
48 hr	28	22	31	19

[a] 0.012 mol. [b] 0.044 mol.

The Reaction between Methyl Mercaptan and Sulfur Monochloride.—Sulfur monochloride (13.5 g, 0.10 mol) was added dropwise over 40–50 min to a stirred solution of methylmercaptan (9.9 g, 0.206 mol) in 45 ml of carbon disulfide at −20°. After holding the pale yellow solution at −20° for 3 hr and storing for 12 hr at 0°, its pmr spectrum showed a single peak at δ 2.66 corresponding to methyl tetrasulfide.

In a second experiment methyl mercaptan (1.12 g, 0.023 mol) was allowed to vaporize slowly into a solution of sulfur monochloride (3.12 g, 0.023 mol) in 25 ml of carbon tetrachloride containing TMS and held at −30°. After the solution was warmed to room temperature, the pmr spectrum indicated that the major

(14) H. Tassinari, *Gazz. Chim. Ital.*, **17**, 85 (1887).

product was CH_3SSCl along with CH_3SCl, $CH_3S_6CH_3$, $CH_3S_5CH_3$, $CH_3S_4CH_3$, $CH_3S_3CH_3$, and $CH_3S_2CH_3$.

Esr Study of the Decomposition of CH_3SCl.—Preliminary spectra taken on bulk liquid samples at room temperature and at liquid nitrogen temperature gave no esr signals, even when the decomposition was proceeding vigorously. Presuming that the failure to observe the radical intermediate was due to a very short lifetime and low steady-state concentration, it was decided that the reaction be run on Vycor glass, a porous silica glass known to stabilize free radicals, in the hope that the Vycor support would permit the development of a detectable concentration of radical intermediates.

Before attempting to observe a radical intermediate produced by the decomposition of CH_3SCl, a study of the photodissociation products of the parent compound methyl disulfide was made. A small sample of Spectro-Grade methyl disulfide, CH_3SSCH_3, was first degassed by repeatedly freezing the liquid to liquid nitrogen temperature, evacuating the sample, and then allowing the sample to melt under vacuum in a closed vessel. This procedure was repeated until no gas bubbles were observed to evolve in the sample as it melted.

A Vycor glass rod was cleaned in HNO_3, thoroughly washed in water, treated with 30 cm of O_2 at 600° for 15 hr, and evacuated at 500° for 15 hr. Esr spectra of the Vycor glass and sample tube were taken at liquid nitrogen temperature, both before and after 20 min of irradiation with a mercury arc lamp (2537-Å light) at liquid nitrogen temperature, and no signals were observed. Enough CH_3SSCH_3 was then distilled onto the glass to constitute a surface coverage of one-half monolayer. During the distillation process, the Vycor was kept at liquid nitrogen temperature. The sample tube containing the sample then was sealed and allowed to come to room temperature.

Esr spectra of the methyl disulfide on Vycor taken at room temperature and liquid nitrogen temperature disclosed no signals. A sample then was irradiated at room temperature for 10 min intervals with light of 3550-Å wavelengths. No signals were observed even after 1 hr of irradiation. Finally, the sample at liquid nitrogen temperature was irradiated for 10 min with light of 2537-Å wavelength. Esr spectra taken immediately after irradiation and at liquid nitrogen temperature showed a strong signal with partially resolved hyperfine structure. Subsequent spectra at liquid nitrogen temperature showed a slow decay of this signal. Warming to room temperature and immediately cooling again to liquid nitrogen destroyed the signal completely. Two separate runs were made on the preparation and irradiation of methyl disulfide, confirming the reproducibility of the signal observed.

The procedure outlined above was repeated through the distillation of one-half monolayer of CH_3SSCH_3 onto a clean Vycor rod. The sample was allowed to come to room temperature and then cooled to liquid nitrogen temperature. Esr spectra showed no signal present. With the sample at liquid nitrogen temperature on the vacuum line (sealed), a sample of chlorine gas was introduced into the system. The chlorine was frozen into a liquid nitrogen trap and the solid chlorine was evacuated to remove any oxygen present. The chlorine then was warmed to room temperature, and a small amount, less than the amount of methyl disulfide previously adsorbed, was introduced into the sample tube. (Note—an equivalent vapor pressure of 25.3 cm of CH_3SSCH_3 was adsorbed onto the Vycor glass and 20 cm of Cl_2 was introduced in the same way through a volume calibrated cell, resulting in equal volumes of CH_3SSCH_3 at 25.3 cm and Cl_2 at 20 cm being introduced.) The sample then was warmed to Dry Ice–acetone temperature and allowed to stand for 2 hr.

An esr spectrum of the sample taken at liquid nitrogen temperature showed no signal. The sample then was warmed to room temperature for 5 min and cooled to liquid nitrogen temperature; another spectrum was taken. Again no signal was observed. The sample was warmed to room temperature and spectra taken at 20-min intervals for 4 hr. All spectra were observed at liquid nitrogen temperature and several were made at room temperature. No signals were observed. The sample was warmed to 50° for 1 hr and esr spectra were taken. No signals were observed. The sample was allowed to stand at room temperature for 15 hr, after which spectra were taken, then allowed to stand for 48 hr, after which spectra were taken. In no instance were any signals observed over a region of the spectrum between 1.6 gauss and 4 gauss. Over the 3 days in which experiments were performed, the sample was observed to darken in color, from practically colorless at the beginning to dark yellow at the end. At all times, the sample appeared clear and transparent.

The esr signal observed in irradiated methyl disulfide showed an asymmetric signal with four partially resolved hyperfine lines. The intensity ratios of the four lines were approximately 1:3:3:1, giving evidence that the hyperfine field was provided by the three protons on the methyl group. Without detailed consideration of the molecular orbital structure of the proposed radical $CH_3S\cdot$, it is impossible to make a definite assignment. Previous work done on methyl radical, $CH_3\cdot$, on Vycor glass indicates a hyperfine splitting of 23 gauss, and an asymmetry arising from surface effects.[15] Our observed hyperfine splitting of approximately 10 gauss shows that the species responsible for the observed esr signal is not $CH_3\cdot$, but rather some radical whose electron density is concentrated considerably farther from the methyl protons. When the irradiation procedure was repeated using deuteriomethyl disulfide, CD_3SSCD_3, the hyperfine structure of the signal completely disappeared, strengthening the belief that the original signal was due to the $CH_3S\cdot$ radical.

All of the esr spectra cited in this report were made on a Varian X-band spectrometer, using 100-kHz modulation and phase sensitive amplification. The spectrometer has a proven sensitivity to 3×10^{13} absolute number of spins giving a signal-to-noise ratio of 20:1.

Registry No.—I, 5813-48-9; II, 661-38-1.

Acknowledgment.—This work was supported in part by a grant, AP 00383, from the National Center for Air Pollution Control, U. S. Public Health Service.

(15) J. Turkevich and Y. Fujita, *Science*, **152**, 1619 (1966).

The Chemistry of Nitrogen Radicals. IX. Reactions of N-Halocyanamides and N-Halosulfonamides

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The photolytic rearrangement of N-*t*-bntyl-N-halobutanesulfonamides to the corresponding 3-halobutanesulfonamides occurred in ~75% yield; cyclization of the products gave either the sultam (V) by ring closure at nitrogen or an isomeric cyclopropanesulfonamide (IV) by ring closure at the carbon α to the sulfone group. Additions of N-chloro-N-methylcyanamide and N-chloro-N-methylmethanesulfonamide to both conjugated and nonconjugated olefins in 45–75% yield are also reported. Photolytic reactions of N-*t*-butyl-N-chlorocyanamide in the presence of olefins gave carbodiimide derivatives as the principal products.

In recent years an increasingly active study of free-radical reactions of aliphatic N-halo compounds has shown that two types of synthetically important processes can be realized with a variety of N-halamines RN(hal)Y. Depending on the nature of the alkyl group R and the alkyl or electron-withdrawing group Y, either rearrangement of halogen into R or Y or addition of the N-halamine to unsaturated hydrocarbons may occur. Thus, rearrangement of chlorine into the N-alkyl group has been observed in protonated dialkyl-[1] or monoalkyl-N-chloramines,[2] N-chlorocarboxamides,[3] and N-chlorosulfonamides[4] to give the corresponding 4-chloroalkyl isomers. Rearrangement of halogen into the group Y has been reported for N-alkyl-N-halocarboxamides,[5,6] N-chlorocarboximides,[7] and most recently N-alkyl-N-chlorosulfonamides.[8] The addition of N-halo compounds across carbon–carbon double bonds has been carried out with dialkyl-[9–11] and monoalkyl-N-chloramines,[12] N-chlorourethanes,[13] an N,N-dichlorophosphoramidate,[14] N-bromosuccinimide,[15] and an N-chlorosulfonamide.[16] It is the purpose of this report to describe the addition of N-chlorosulfonamides and N-chlorocyanamides to a variety of olefins and to provide considerably more information on the rearrangement of N-halosulfonamides and the conversion of the products into cyclic derivatives than has heretofore[8] been disclosed.

Rearrangement of N-Halosulfonamides.—We have reported previously the rearrangement of N-halocarboxamides and the cyclization of the γ-halocarboxamides thus formed.[5] We now describe the analogous rearrangement of N-halosulfonamides and details of the selective preparation of two types of cyclization products from the rearranged N-halamides. Since the completion of this work, a limited study of N-chlorosulfonamide rearrangements has appeared,[8] which is in agreement with our results.

The preparations of the N-bromo- and N-chlorobutanesulfonamides were straightforward and are summarized in the Experimental Section. The photolytic rearrangements of the N-*t*-butyl compounds were more efficient than those of the N-methyl analogs and proceeded as follows. Irradiation of a 0.4 *M* solution of N-*t*-butyl-N-chlorobutanesulfonamide (**1a**) in a Vycor vessel using an external 100-W uv lamp produced a complete loss of electropositive chlorine in 1 hr in benzene or in 3 hr in carbon tetrachloride. Evaporation of either solution gave a solid, whose nmr spectrum contained the methyl doublet absorption of the γ-chloro isomer **2a** (Scheme I); from the relative areas of this doublet and the *t*-butyl peak, **2a** was found to comprise ~67% of the total N-*t*-butyl compounds present. This is consistent with the report[8b] that **1a** rearranged in benzene to give 62% **2a**, 15% δ-chloro isomer, and 20% parent amide. However, work-up gave ~75% yield of **2a** with no evidence of significant amounts of the δ-chloro isomer.

The Japanese workers[8] apparently did not pursue the chemistry of their rearrangement products except to obtain a very low yield of the sultam of N-*t*-butyl-3-chloropentanesulfonamide on treatment of the compound with alcoholic KOH. In our hands, the analog **2a** afforded a greater yield of either a sultam or a cyclopropane isomer, depending on the base used (Scheme I). The major product from methyllithium in tetrahydrofuran (THF) was 40% N-*t*-butyl-2-methylcyclopropanesulfonamide (**4**), whereas 60% sultam, 2-*t*-butyl-3-methyltetrahydroisothiazole 1,1-dioxide (**5**), resulted from freshly prepared sodium amide in THF.

The rearrangement of the N-bromosulfonamide **1b**

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(13) (a) T. A. Foglia and D. Swern, *ibid.*, **31**, 3625 (1966); (b) T. A. Foglia and D. Swern, *ibid.*, **32**, 75 (1967); (c) T. A. Foglia and D. Swern, *ibid.*, **33**, 766 (1968); (d) K. Schrage, *Tetrahedron*, **23**, 3033 (1967).

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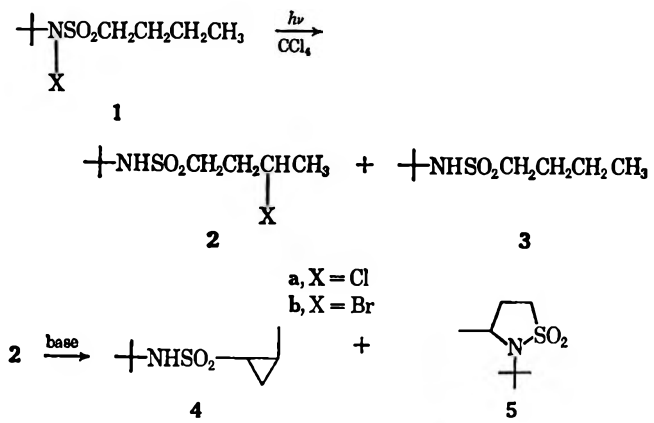
(15) L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **29**, 1290 (1964); W. J. Bailey and J. Bellow, *ibid.*, **20**, 525 (1955).

(16) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963).

in CCl_4 was complete in 45 min and afforded a mixture of **2b** and the parent amide (**3**). Although **2b** could not be separated from **3** by recrystallization, the mixture afforded the same cyclization products as the chloro analog (Scheme I).

SCHEME I



ir (cm^{-1}) 6124 (cyclopropyl), 3240 (NH), 1135 (SO_2); nmr (τ) 4.7 bs (0.88 H, NH), 7.6–8.1 m (1.06 H, SO_2CH), 8.67 s (t-C_4H_9), 8.88 d (CH_3), 8.3–9.1 m (total 14.00 H), 9.10–9.55 m (1.06 H)

ir (cm^{-1}) no NH; nmr (τ) 6.20 m (1.06 H, NCH), 6.6–8.3 m (3.94 H, SO_2CH_3 and CCH_2C), 8.60 s (t-C_4H_9), 8.68 d (CH_3, total both groups 11.65 H)

Compound 2	Base	% yield based on 2			
		2	3	4	5
a	CH_3Li in THF	0	~5	40	~5
b	CH_3Li in THF	0		53	~5
a	$NaNH_2$ in THF	0	5	5	60
b	$NaNH_2$ in THF	0	5	5	55
a	NaOH in CH_3OH	0	10	18	43
a	NaH in xylene	0	70	0	0
a	$AgBF_4$ in CH_2Cl_2	80	0	0	0
a	n-C_4H_9Li in heptane	75	0	0	0

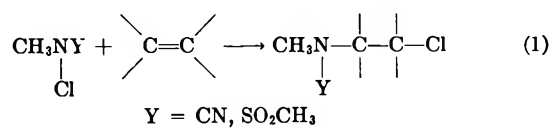
The structures of **4** and **5** were assigned as follows. Preparative glpc gave pure samples of **4** and **5**, which were found to be isomeric from their elemental analyses; neither fractional distillation nor column chromatography on Florisil effected a significant separation. Assignment of the cyclopropane structure to **4** was based on its nmr, ir, and near-ir spectra (Scheme I). The strong NH band also present in the parent amide **3** ruled out the five-membered, nitrogen-containing ring of **5**, and the near-ir band at 1.633 μ implied[17] the presence of a cyclopropyl group. The loss of HCl in forming **4**, shown by the elemental analysis, was further indicative of a cyclic structure for **4**, and the points of ring closure were confirmed from the nmr spectrum. Thus, the doublet methyl-group absorption disclosed the generation of a tertiary γ hydrogen. No peaks occurred between τ 6.8 and 7.0, which showed the absence of the characteristic 2 hydrogen SO_2CH_2 methylene group absorption in **3**, **2a** and **2b**, and **1a** and **1b**, but a single SO_2CH hydrogen was observed at higher field, consistent with its incorporation into a cyclopropane ring. Although three hydrogens absorbed in the cyclopropane region[16] at $\tau > 8.6$, the data do not permit an identification of the highest field hydrogen nor an assignment of the stereochemistry of the two ring substituents.

The isomeric sultam structure **5** was assigned on the basis of spectral data. In particular, the absence of an NH band in the ir spectrum, the presence of a doublet methyl peak in the nmr spectrum, and nmr absorption in the region expected for SO_2CH_2 were definitive. The nmr spectrum was comprised of a multitude of sharp peaks and was very similar to the spectra of the related five-membered ring analogs, 2-t-butylimino-5-methyltetrahydrofuran and the corresponding γ-valerolactone.[5]

Since N-chloro-N-methylvaleramide had previously rearranged to the 4-chloroalkyl isomer, although less efficiently than the N-t-butyl analog,[5] N-chloro-N-methylbutanesulfonamide was prepared and irradiated in benzene. The weight of the doublet CCH_3 absorption relative to the t-butyl peak in the nmr spectrum of the crude product showed the presence of about equal parts of the desired 3-chloroalkyl isomer and other products, but only N-methylbutanesulfonamide could be isolated (30–40% yield) by distillation or column chromatography. Treatment of the rearrangment mixture with either $NaNH_2$ or CH_3Li failed to yield isolable amounts of a cyclization product analogous to **4** or **5**.

Addition of N-Halamides to Olefins.—When we reported the rearrangement of N-halocarboxamides, we noted that both N-t-butyl- and N-methyl-N-chloroacetamide failed to react with olefins to yield an isolable 1:1 adduct.[5] Since the irradiation source was weak (100 W), we repeated the photolyses using styrene as a test olefin and a 450-W Hanovia immersion uv lamp in a Pyrex vessel; small amounts of new amide products were now obtained following chromatography on Florisil, but significant quantities of individual compounds could not be isolated. N-Chloroacetamide itself also failed to give an adduct, either as a heterogeneous mixture in CCl_4 or in CH_2Cl_2 solution.

In dramatic contrast to these results, however, N-chloro-N-methylcyanamide and -sulfonamide gave good to excellent yields of 1:1 adducts with a variety of olefins (eq 1 and Table I). These addition reactions



(1)

appeared to be as facile as those of N-chlorourethans[13] or protonated N-chloramines;[9,12] analogy to these processes suggests that the present reactions were free radical in nature with the amino radical $CH_3\dot{N}Y$ as the chain-carrying species. However, there is reason to doubt that all of these additions did in fact involve *free* amino radicals.

Since a typical free-radical chain process involving alkyl radical intermediates should be inhibited by oxygen, our reactions were repeated in the presence of air. Although the N-chlorosulfonamide reactions were inhibited, better results were obtained with the N-chlorocyanamide in the presence of air than in its absence (Table I). The effect of weak uv irradiation, required in the N-chlorosulfonamide reactions, was

(17) The following ranges have been quoted: 1.624–1.650 μ by P. G. Gassman, *Chem. Ind.* (London), 740 (1962); 1.624–1.640 μ by H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964); and 1.637–1.659 μ by L. Skattebøl, *J. Org. Chem.*, **31**, 2789 (1966).

TABLE I

ADDITIONS OF N-HALAMIDES TO OLEFINS

RN(Cl)Y											
R	Y	*M*	Olefin	*M*	N_2 or air	Temp, °C	*hν*	Time, hr	Adduct[a]	Compd no.	% yield[b]
CH_3	SO_2CH_3	0.16	Butadiene	0.28	N_2	25	+	4.5	$CH_3SO_2N(CH_3)CH_2CH{=}CHCH_2Cl$	6	50
CH_3	SO_2CH_3	0.16	Isobutylene	0.28	N_2	25	+	2.0	$CH_3SO_2N(CH_3)CH_2C(CH_3)_2Cl$	7	70
CH_3	SO_2CH_3	0.16	Styrene	0.28	N_2	25	+[c]	2.5	$CH_3SO_2N(CH_3)CH_2CHClC_6H_5$	8	50
CH_3	SO_2CH_3	0.16	Styrene	0.28	Air	25	+	5.0			None
CH_3	CN	0.24	Butadiene	*d*	Air	10	−	0.9	$NCN(CH_3)CH_2CH{=}CHCH_2Cl$	9	52
CH_3	CN	0.24	Cyclopentadiene	0.53	Air	0	−	0.2	$RN(CN)CH_3$[f]	10	68[g]
$(CH_3)_2CH$	CN	0.29	Cyclopentadiene	0.59	Air	5	−	0.7	$RN(CN)CH(CH_3)_2$[f]	11	58
CH_3	CN	0.24	Isobutylene	0.28	N_2	25	+[g]	0.4	$NCN(CH_3)CH_2C(CH_3)_2Cl$	12	44
CH_3	CN	0.24	Isobutylene	0.28	Air	25	+	0.6	$NCN(CH_3)CH_2C(CH_3)_2Cl$		38
CH_3	CN	0.15	Styrene	0.28	Air	25	+	0.75	$NCN(CH_3)CH_2CHClC_6H_5$	13	76
CH_3	CN	0.19	Styrene	0.31	Air	25	−	1.25	$NCN(CH_3)CH_2CHClC_6H_5$		72

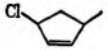
[a] Purified olefinic compounds were *cis–trans* mixtures except for *trans* **6**. [b] Purified compounds. [c] Reaction ceased when irradiation was interrupted but resumed on further irradiation. [d] Not determined. [e] Reaction run in benzene at 30° under air gave 13% **10**. [f] R =  [g] No reaction in the absence of irradiation.

TABLE II

NMR SPECTRA OF N-CHLOROCYANAMIDE AND N-CHLOROSULFONAMIDE ADDUCTS[a]

Compd no.	NCH_3	SO_2CH_3	CH_2Cl	CH_2N	Vinyl H	CCH_2C	CCH_3	C_6H_5
6	—7.20 s, 7.22 s—		5.90 m[b]	6.24 m[b]	4.0–4.5			
	(6.01)		(2.03)	(1.88)	(2.11)			
7	—6.90 s, 7.16 s—			6.62 s			8.35 s	
	(2.88, 3.26)			(1.95)			(5.90)	
8	—7.18 s, 7.27 s—		4.89 t	6.32 d				2.54 s
	(5.92)		(1.00)	(1.92)				(5.15)
9[c]	7.16 s		5.90 m[b]	6.38 m[b]	4.11 m			
	(3.06)		(1.98)	(1.98)	(2.04)			
10[d]	7.18, 7.21		4.8–5.3	5.5–5.9	3.7–4.2 m	6.8–8.2 m		
	(*e*)		—(diffuse; total 1.94)—		(1.97)	(*e*)		
11			4.80–5.35 m	5.40–6.00 m	3.75–4.35 m	6.0–8.2 m[f]	8.69 d, 8.75 d[g]	
			(0.83)	(0.88)	(1.71)	(3.45)	(6.13)	
12	6.94 s			6.74 s			8.36 s	
	(2.85)			(1.87)			(6.26)	
13[h]	7.25 s		4.97 t	6.58 d				2.63 s
	(3.03)		(1.01)	(2.07)				(4.87)

[a] Chemical shifts in τ values relative to tetramethylsilane (TMS); m = multiplet, t = triplet, d = doublet, s = singlet; area count in parentheses; CCl_4 solvent, except $CDCl_3$ for **7** and **8**. [b] Major pattern is a doublet of a doublet with additional splitting. [c] Areas include minor contribution of absorptions due to *cis* isomer (presumably) at τ 4.40 m, 5.2–5.6 m, 6.70 d, and 7.07 s. [d] Areas not measured. [e] Total of 5.08 H in the two groups. [f] Includes isopropyl methine hydrogen. [g] Ratio 4:1 presumably reflects ratio of *cis* to *trans* isomers. [h] Sample from chromatography before distillation; after distillation, new peaks were present at τ 2.85 (C_6H_5), 3.45 and 4.10 (vinyl H?, AB pattern, J = 14 cps), and 7.0 (NCH_3).

TABLE III

PHOTOLYSIS OF *t*-BUTYL-N-CHLOROCYANAMIDE IN THE PRESENCE OF OLEFINS IN CARBON TETRACHLORIDE AT 25° [a]

Olefin	Mol, *t*-BuNClCN/olefin	Sweep gas	Time, min	Work-up[b]	% yield of 1:1 adduct[c]	% yield of **17**	% yield of **18**
Cyclohexene	0.045/0.15	N_2	50	A	22	15	2
	0.045/0.15	Air	50	A	25	7	0
				B	20	6	0
	0.045/0.15	O_2	80	A or B	18	4	0
	0.015/0.15	N_2[d]	30	A	6	14	0
Styrene	0.045/0.11	N_2	45	B	6	32	4
	0.045/0.11	Air	55	B	8	0	14
1-Hexene	0.045/0.11	N_2	60	B	0	21	2
		Air	80	B	0	18	2

[a] Total solution, 300 ml; 15-min preirradiation of cyanamide solution prior to adding olefin to reactor; Hanovia 450-W uv immersion lamp. [b] A, Dimethyl sulfoxide (DMSO)–H_3PO_4–H_2O; B, oxalic acid–ether. [c] After hydrolysis; for structures see text. [d] No preirradiation.

equally ambiguous, since the N-chlorocyanamide additions to the conjugated olefins styrene, butadiene, and cyclopentadiene all proceeded spontaneously in the dark. It is therefore tempting to view these latter reactions as nonradical. However, the addition of N-chloro-N-methylcyanamide to isobutylene did require photolytic initiation, as did the recently reported[18] addition of N-chloro-N-methylethanesulfonamide to 1-hexene. Although normal radical chain processes must have been involved in the light-catalyzed but oxygen-sensitive reactions, molecular addition may have occurred in the others with the development of some free-radical character in the transition state. The latter possibility was discussed previously by Foglia and Swern[13c] regarding additions of N-chlorourethan to olefins.

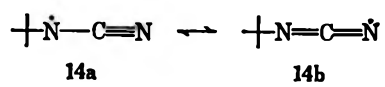
The assignment of structure to the adducts shown in Table I followed from spectral analyses and, where the stability of the compounds permitted, elemental analyses. Only with the unsymmetrical olefins, isobutylene and styrene, did the question of the direction of the N-halamide addition across the double bond arise. Despite the lack of a clear-cut mechanism in the present reactions, we believe by analogy to the many related additions[9–16] that a species with amino radical character added to the double bond and that this was followed by attachment of chlorine to the carbon atom better able to stabilize the resulting radical-like intermediate. This assumption is supported by the following observations.

In the nmr spectra of the isobutylene adducts **7** and **12** (Table II), the methylene singlets (τ 6.62 in **7** and 6.74 in **12**) did not occur at sufficiently high field to rule out the group CH_2Cl, but they were more consistent with the values expected for a methylene group alpha to amide-type nitrogen. However, the presence of the tertiary chloride was strongly implied by the rapid, positive test in acidified, alcoholic silver nitrate observed at 25° with both **7** and **12**.

The nmr spectra of the styrene adducts **3** and **13** (Table II) were also consistent with the structures assigned. The low-field benzylic hydrogen appeared in both compounds as the expected triplet at τ 4.89 in **3** and 4.97 in **13**, whereas the methylene which we assign to NCH_2 appeared as a doublet at 6.32 and 6.58, respectively; all four absorptions had J = 7 cps. The low-field absorption occurred in the region expected for a benzylic methine hydrogen C_6H_5CHCl, but one cannot rule out a benzylic amide group in either adduct on this basis, since the benzylic hydrogen in a carboxamide model compound, α-(benzoylamino)ethylbenzene, absorbed at τ 4.7 in $CDCl_3$. However, the higher-field absorption at 6.3–6.6 seems too high for CH_2Cl attached to a carbon with two electron-withdrawing groups; for example, the methylene absorption in 1,1,2-trichloroethane appears in τ 6.03.[19] The rapid, positive tests obtained with silver nitrate solution at 25° again provided the better evidence for structures containing labile, benzylic chlorine substituents.

When the N-*t*-butyl analogs of both types of N-chloramide were photolyzed in the presence of olefins, the facile additions realized with the N-methyl compounds were not observed. Although interesting results were obtained with the N-chlorocyanamide (see next section), the sulfonamide gave only the parent N-*t*-butylmethanesulfonamide (50–80%) and some chlorinated olefin on reaction in carbon tetrachloride with cyclohexene, norbornene, or styrene. This contrasts with the N-halosulfonamide rearrangements above and with N-halocarboxamide rearrangements,[5] in which the N-*t*-butylamides gave superior results to the N-methyl compounds.

Reactions of N-*t*-Butyl-N-chlorocyanamide.—The reactions of N-*t*-butyl-N-chlorocyanamide (**15**) with olefins (Table III) were considerably more interesting than those of the corresponding sulfonamide. When **15** was irradiated in the presence of cyclohexene under nitrogen, electropositive chlorine was lost and an originally very small band at 2130 cm^{-1} in the ir spectrum of a concentrated sample grew significantly with time. When the reaction was complete, the new band was more intense than the strong NCN band at 2220 cm^{-1} which characterized both *t*-butylcyanamide and its N-chloro derivative **15**. Since the ambident radical species **14** was a possible intermediate in the reaction and the 2130-cm^{-1} band strongly suggested[20]



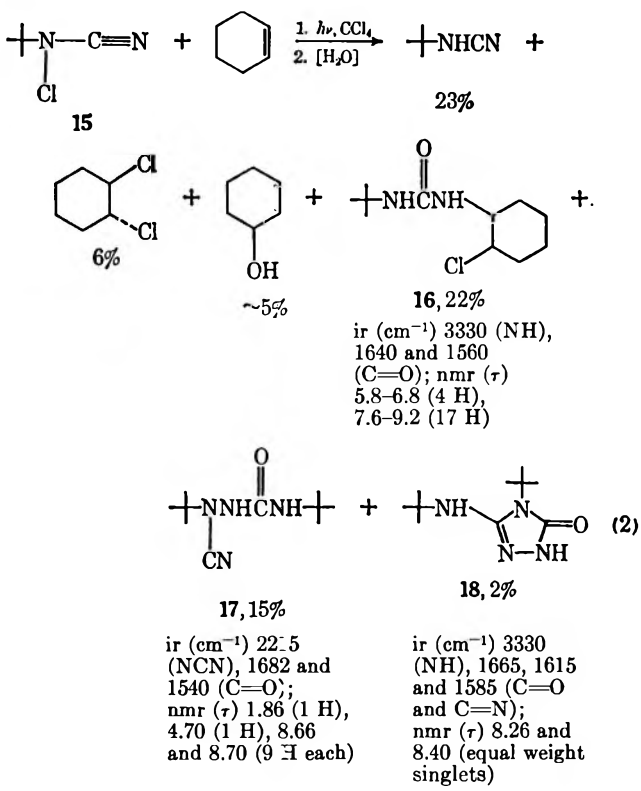
14a **14b**

(18) T. Ohashi, M. Suzie, M. Okahara, and S. Komori, *Tetrahedron Lett.*, 4195 (1968).

(19) Nmr Spectra Catalog, Spectrum No. 2, Varian Associates, 1962.

(20) G. D. Meakins and R. J. Moss, *J. Chem. Soc.*, 993 (1957), quote the range 2140–2125 cm^{-1} for the aliphatic carbodiimide *anti*-symmetric stretching frequency.

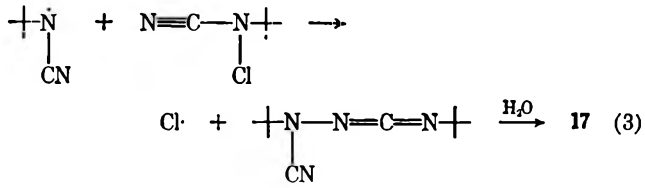
the carbodiimide group –N=C=N–, the reaction solution was concentrated under vacuum and treated with reagents known to hydrolyze diimides to the corresponding ureas. Products were obtained as shown in eq 2; *t*-butylcyanamide was a major product of every reaction studied (Table III), but its yield was not usually determined quantitatively.



(2)

The structures of the adduct **16** and compounds **17** and **18** (or a tautomer of **18**) were deduced from their elemental analyses and the following data. The ir spectrum of **16** contained bands consistent with that of a secondary amide or urea, the nmr spectrum in d_6-DMSO included four low-field hydrogens and an N-*t*-butyl singlet, and a heavy precipitate of silver chloride was obtained from **16** and alcoholic silver nitrate after brief warming. The alternative structure t-$C_4H_9N(R)CONH_2$, in which the other nitrogen is alkylated, was ruled out by the absence of the second NH stretching band characteristic[21] of primary amides and because the NCN group of the required precursor was not expected to hydrolyze; under the conditions used, *t*-butylcyanamide was hydrolytically stable. The chlorine was assumed to reside on the other carbon of the double bond, but the data do not distinguish between a *cis* or *trans* addition in the present case.

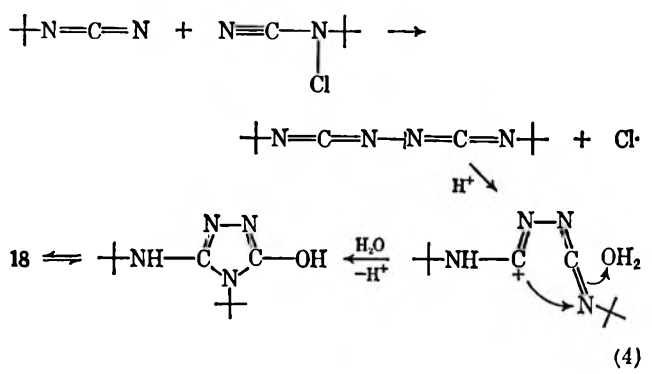
Compounds **17** and **18** were found from their elemental analyses to be isomeric and derived from two molecules of **15**; both melted with the evolution of a gas, presumably nitrogen, and contained basic nitrogen. Only the structures shown appear possible from the spectral data. Compound **17** showed both the NC≡N and secondary amide ir bands, and the d_6-DMSO nmr spectrum contained two 1 H singlets and two *t*-butyl singlets. The N-cyanosemicarbazide **17** is the logical hydrolysis product of a dimer of **14a** with **14b.** However, the precursor of **17** might also have formed by attack of **14a** on the nitrile nitrogen of **15,** followed by (or concurrently with) elimination of a chlorine atom (eq 3). The latter alternative may be the more



(3)

probable, since the yields of **17** sometimes became appreciable (Table III). Since the uv maximum of **15** (286 mμ) falls well below the limit of transparency of the Pyrex reactor (~300 mμ) and is weak (ε 265), a facile photodissociation of **15** and recombination of amide radicals appears improbable. Tailing in **15** to 415 mμ, however, can account for the apparently inefficient photolability observed.

The ir spectrum of compound **18** contained three bands in the double-bond stretching region, and two different *t*-butyl peaks were revealed in the nmr spectrum. NH absorption was present in the ir, although missing from the nmr spectrum in d_6-DMSO, but the molecular weight confirmed a dimeric structure, $(C_4H_9NCN)_2H_2O$. Compound **18** is a reasonable cyclohydration product of a dimer of **14b,** but the bisdiimide precursor could also have formed by an addition–elimination process (eq 4).



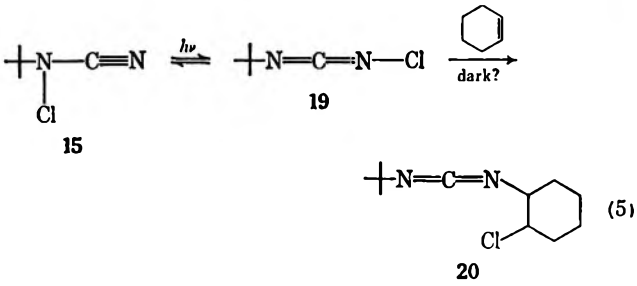
(4)

Several photolyses of **15** were carried out in the presence of cyclohexene in an effort to find the conditions most favorable to the synthesis of the adduct **16.** Irradiation of the chlorocyanamide in CCl_4 for 15 min prior to the introduction of the olefin caused less than 10% loss of active chlorine but a five-fold growth in the minor diimide band originally present; apparently, **15** was isomerizing to the diimide **19** (eq 5). This process is the opposite of the reported photolytic isomerization of carbodiimides RN=C=NR′ to the cyanamides.[22] When the lamp was extinguished and cyclohexene then added, ~25% of the active chlorine disappeared within 5 min, and the reaction was brought to completion by renewed irradiation. This dark reaction suggests that the photolytically produced **19** added spontaneously to cyclohexene

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 206.

(22) J. H. Boyer and P. J. A. Frints, *Tetrahedron Lett.*, 3211 (1968).

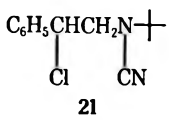
(eq 5). Curiously, a second dark reaction could not be detected, even if only a limited amount (10 mol %) of olefin was added following the first preirradiation. This implies that the isomerization **15** ⇄ **19** was easily inhibited by small amounts of olefins or reaction products.



If the 1:1 adduct **20** did form in a dark reaction, the unexpected failure of air to inhibit adduct formation with cyclohexene or styrene becomes reasonable. However, the yield of **17** was lower in the presence of air in two of the three cases shown in Table III, although the yield of **18**, which we feel must arise by a mechanism closely related to that which gives **17**, was actually increased in the case of styrene. These results will require further study to explain with conviction. Equally puzzling was the result of a reaction carried out with one-third the usual amount of **15** but without preirradiation (Table III); the yield of adduct **16** was severely reduced, but that of **17** was unaffected.

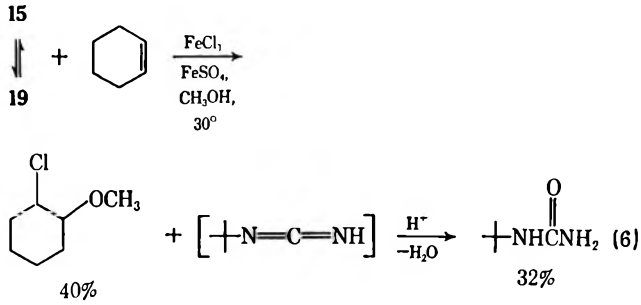
Two further changes in reaction conditions were also without useful effect. Runs made under the conditions of entries 1 or 2 of Table III failed to produce any adduct when the solvent used was benzene (N_2, 60 min), pyridine (air, 40 min), or acetonitrile (air, 40 min), and irradiation under air of a 1:2 mixture of **15** and cyclohexene in the absence of a solvent gave only 9% **16** and no **17** or **18**.

In addition to the three olefins shown in Table III, **15** was also photolyzed in the presence of norbornene, 1,3-cyclooctadiene, cyclopentadiene, methylenecyclohexane, tetramethylethylene, or trimethylvinylsilane. None of these afforded an isolable 1:1 adduct. The adduct (**21**) from styrene (Table III) was assigned the structure shown from a positive silver nitrate test for



labile chlorine and the similarity of its spectral data to those of related compounds.

Finally, it was interesting to find evidence of *t*-butylcarbodiimide itself as a major product of a reaction in methanol between **15** and cyclohexene under conditions known to effect the metal-catalyzed addition of N-chlorodialkylamines to olefins.[10] The products isolated following chromatography on Florisil were 40% 1-chloro-2-methoxycyclohexane, a few per cent 1,2-dichlorocyclohexane, and 32% *t*-butylurea (eq 6). None of the urea was produced when *t*-butylcyanamide was subjected to the conditions of work-up. We therefore believe that the urea arose from *t*-butylcarbodiimide, which is the expected product if **19** were acting as an ionic chlorinating agent similar to N-chlorosuccinimide. About 10% of the urea was also obtained from the photolytic reaction of methylenecyclohexane under nitrogen using either method of diimide hydrolysis.



Experimental Section

Preparation of N-Halamides. N-*t*-Butyl-N-chlorobutanesulfonamide (1a).—The parent sulfonamide (**3**) was prepared from *t*-butylamine and butanesulfonyl chloride (Aldrich Chemical Co.) in benzene: bp 115–120° (0.9 mm), n^{23}D 1.4545 [lit.[8a] bp 155–156° (6 mm), n^{20}D 1.4530]. To 0.20 mol of **3**, 0.3 g of $K_2CO_3 \cdot 1.5H_2O$, and 300 ml of CCl_4 was added dropwise 0.20 mol of *t*-butyl hypochlorite (Frinton Laboratories) and the mixture was heated under reflux for 4 hr. Evaporation of the solvent and distillation through a 600 × 6 mm column packed with a tantalum wire spiral afforded 94% **1a**, bp 86° (0.5 mm), $n^{23.5}$D 1.4698; NH absorption was absent from the ir spectrum of the product (lit.[1] n^{20}D 1.4718).

Anal. Calcd for $C_8H_{18}ClNO_2S$: Cl, 15.57. Found (iodometric titration): Cl, 15.55, 15.58.

N-Bromo-N-*t*-butylbutanesulfonamide (1b).—A 1.1 *M* solution of *t*-butyl hypobromite was prepared as described previously,[5] except that the hypobromite was extracted into one 50-ml and two 25-ml portions of CCl_4, washed with two 20-ml portions each of water and saturated sodium carbonate, and dried over anhydrous potassium carbonate. The sulfonamide **3** (0.08 mol) and 73 ml of the hypobromite solution were stirred in 100 ml of CCl_4 for 90 min to give **1b**, which was then irradiated. After 90 min, no NH absorption was present in an evaporated sample removed from a stirred mixture of 0.08 mol each of **3** and the hypobromite in 100 ml of CCl_4.

When a similar preparation of the crude N-methyl analog was attempted, no loss of NH occurred after 4 hr at room temperature, and only randomly brominated material was produced on heating the sulfonamide–hypobromite mixture under reflux for 3 hr.

N-Chloro-N-methylbutanesulfonamide.—A mixture of 0.2 mol of N-methylbutanesulfonamide, bp 150–155° (0.03 mm), n^{25}D 1.4550, and 0.21 mol of *t*-butyl hypochlorite in 200 ml of CCl_4 was heated under reflux for 2 hr in the presence of 0.5 g of $K_2CO_3 \cdot 1.5H_2O$. The product was obtained in 98% yield: bp 70–73° (0.05 mm), n^{25}D 1.4685.

Anal. Calcd for $C_5H_{12}ClNO_2S$: Cl, 19.10. Found (iodometric titration): Cl, 19.00, 18.98.

N-*t*-Butyl-N-chloromethanesulfonamide.—On chlorination of the parent sulfonamide, mp 39–42° (lit.[23] mp 40–41°), and attempted distillation of the N-chloro derivative at 1 mm, decomposition occurred at a bath temperature of 88°; this N-halamide was therefore used without purification.

N-Chloro-N-methylmethanesulfonamide.—N-Methylmethanesulfonamide, bp 73–79° (0.03 mm), n^{25}D 1.4501 (lit.[24] n^{25}D 1.4493), was chlorinated in the usual manner and distilled: bp 64–65° (1 mm), n^{23}D 1.4737, mp 32–33°, yield 92%.

Anal. Calcd for $C_2H_6ClNO_2S$: Cl, 24.70. Found (iodometric titration): Cl, 24.60, 24.65.

N-*t*-Butyl-N-chlorocyanamide (15).—*t*-Butylcyanamide was used as received from Aldrich Chemical Co. [lit.[26] bp 114–115.5°

(23) V. I. Markov and S. I. Burmistrov, *Zh. Obshch. Khim.*, **33**, 1647 (1963); *Chem. Abstr.*, **59**, 11232*h* (1963).

(24) J. Vaughan and P. Sears, *J. Phys. Chem.*, **62**, 183 (1958).

(25) E. Schmidt, D. Ross, J. Kittl, and H. H. von Diisel, *Ann.*, **612**, 11 (1957).

(14 mm), mp 12–13°]. A solution of 19.6 g (0.20 mol) in 250 ml of CCl_4 was treated with 23 g (0.212 mol) of *t*-butyl hypochlorite and 0.5 g of $K_2CO_3 \cdot 1.5H_2O$ at room temperature for 3 hr. The yellow solution was filtered and evaporated, and the residue was distilled to afford 21.5 g (81%) of **15**: bp 53.5–54° (8 mm), $n^{24}D$ 1.4433, ir 2215 cm^{-1} (NCN) with a weak band at 2080 cm^{-1}.

Anal. Calcd for $C_3H_3ClN_2$: Cl, 26.76. Found (iodometric titration): Cl, 26.54.

N-Chloro-N-methylcyanamide.[26]—A dried solution containing 0.28 mol of cyanogen bromide in 350 ml of anhydrous ether was introduced into a dry flask equipped with a coarse glass-fritted gas dispersion tube projecting to but not below the surface of the liquid. The ether solution was cooled to −30° with mechanical stirring under a nitrogen atmosphere, and methylamine was slowly added through the dispersion tube. When 1.8 mol of amine/mol of cyanogen bromide had been added (2 hr), a precipitate of methylamine hydrobromide was removed by rapid filtration as the filtrate containing methylcyanamide was maintained at −10° or below. It is important that three variables be controlled in order to realize a good yield of methylcyanamide: stringently dry conditions, a reaction temperature of −30° (colder temperatures require excessive reaction times), and a dilution of cyanogen bromide equal to or greater than that indicated.

The cyanamide was chlorinated as follows. The ether solution was concentrated to about one-half its volume in a rotary evaporator at water aspirator pressure but *without* a water bath; this removed any residual methylamine. The resulting solution was diluted with 75 ml of CCl_4 in a reaction flask, cooled to −10°, treated with the theoretical amount of *t*-butyl hypochlorite in 30 ml of CCl_4, and allowed to warm to room temperature over 2 hr. Distillation gave N-chloro-N-methylcyanamide in variable yields of 36–60%: bp 44–46° (30 mm), $n^{24}D$ 1.4393. Occasionally the pot residue decomposed rather suddenly as the distillation neared completion.

Anal. Calcd for $C_2H_3ClN_2$: Cl, 38.06. Found (iodometric titration): Cl, 38.00, 37.95.

N-Chloro-N-isopropylcyanamide.—Ten drops of isopropylamine were added to a dried solution of 30 g of cyanogen bromide in 250 ml of ether at −15°. When a precipitate of the amine hydrobromide appeared, dropwise addition of the remaining 30 g of amine was continued at −15°. The reaction was complete after 45 min. The reaction mixture was then filtered, diluted with CCl_4, and evaporated at 20° to remove ether. The residue was further diluted to 200 ml with CCl_4 and treated with 0.25 mol of *t*-butyl hypochlorite in 50 ml of CCl_4 at 0°. After warming to 25° and stirring for 45 min, the solution was evaporated to a residue which was distilled to give the product in 50% yield: bp 64–65°, $n^{24}D$ 1.4410. The spectral data were as anticipated; a chlorine analysis was not obtained.

Caution. When the amine was added in its entirety to the cyanogen bromide solution at −30°, no reaction occurred as judged by the absence of the precipitate of amine hydrobromide. On warming to −20° after 30 min, still no reaction was evident. However, at −10° the reaction took place with sufficient violence to shatter the reaction vessel and surrounding apparatus.

Rearrangement of N-Chloro-N-*t*-butylbutanesulfonamide (1a).—A solution of 0.08 mol of **1a** in 200 ml of benzene was irradiated at 28–30° for 55 min with a 100-W Hanovia uv lamp; the Vycor vessel was the same as that described previously,[5] and a nitrogen purge of the solution was implemented for 20 min prior to irradiation. On evaporation of the solution a solid was left which was recrystallized from ether–pentane. **N-*t*-Butyl-3-chlorobutanesulfonamide (2a)** was obtained in two fractions: 12.7 g (67%), mp 58–60°, and 2.3 g (12%), mp 47–54°. A further recrystallization afforded **2a** with mp 63–65°. The major impurity was identified as the parent amide **3** on comparison of the appropriate nmr spectra. No evidence of the 4-chloro isomer was found; in particular, no triplet absorption due to the $-CH_2Cl$ group was present in the nmr spectra of the reaction product or recrystallization fractions. The nmr spectrum of **2a** was definitive of the 3-chloro isomer, however: NH, τ 4.90 bs (0.90 H); CHCl, 5.66–6.05 m (0.86 H); SO_2CH_2, 6.84 unsymmetrical quartet (1.94 H); CCH_2C, 7.5–8.3 m (2.07 H); CH_3, 8.42 d (3.24 H), $(CH_3)_3C$, 8.62 s (ratio of area to total of the other 9 H was 0.94).

(26) R. Kitawaki, M. Yamashita, and K. Sugino, *Nippon Kagaku Zasshi*, **78**, 567 (1957); *Chem. Abstr.*, **53**, 5124*g* (1959).

Anal. Calcd for $C_8H_{16}ClNO_2S$: C, 42.19; H, 7.97; Cl, 15.57; N, 6.15; S, 14.08. Found: C, 42.21; H, 7.90; Cl, 15.72; N, 5.94; S, 13.97.

Rearrangement of N-Bromo-N-*t*-butylbutanesulfonamide (1b).—The bromamide was prepared *in situ* as noted above and irradiated in CCl_4 solution; the reaction proceeded identically with that of the N-chloro analog to give a solid, mp 55–65°, after crystallization from ether–pentane (60% yield based on **2b**). Recrystallization gave a sample of **2b**, mp 65–67°, whose nmr spectrum contained the CCH_3 triplet from about 20% of the parent amide **3**; **3** could not be removed by further recrystallization. This mixture, cyclized as described below, contained **2b** in a final yield of 45%. The nmr spectrum of **2b** was similar to that of **2a**: NH, τ 4.72; CHBr, 5.5–6.0; SO_2CH_2, 6.80 unsymmetrical quartet; CCH_2C, ~7.0–8.0; CH_3, 8.22 d; $(CH_3)_3C$, 8.60 s.

2-*t*-Butyl-3-methyltetrahydroisothiazole 1,1-Dioxide (5).—To 0.02 mol of **2a** in 200 ml of dry tetrahydrofuran was added a slurry of 0.02 mol of $NaNH_2$[27] in benzene. The mixture was stirred under reflux for 3 hr in a nitrogen atmosphere, cooled, filtered, and evaporated to a residue which was chromatographed on Florisil. A fraction containing **5** in 60% yield along with 5% **3** and 5% **4** was analyzed by glpc. An analytical sample of **5**, $n^{25}D$ 1.4773, was collected from the product of a similar cyclization of **2b**. The assignment of structure was given in the results section.

Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.23; H, 8.96; N, 7.32; S, 16.76. Found: C, 50.09; H, 9.27; N, 7.21; S, 16.91.

N-*t*-Butyl-2-methylcyclopropanesulfonamide (4).—To 0.02 mol of **2b** in 200 ml of dry tetrahydrofuran was added 0.02 mol of methyllithium as a 2 *M* solution in ether (Lithium Corp. of America). The mixture was stirred at 60° under nitrogen for 4 hr, cooled, evaporated, and treated with ether to precipitate lithium chloride. The concentrated residue had the same ir and nmr spectra as the material obtained when an ether solution of the crude product was washed with water to remove the salt. Both thin layer and gas chromatography showed the presence of **4** and **5**, but **4** predominated by at least fivefold. Short-path distillation [bp 94° (0.12 mm)] did not separate **4** from **5**; the analytical sample of **4**, $n^{24}D$ 1.3106, and the yield were therefore obtained by glpc.

Anal. Calcd for $C_8H_{17}NSO_2$: C, 50.23; H, 8.96; N, 7.32; S, 16.76. Found: C, 50.54; H, 9.48; N, 7.29; S, 16.68.

Other Cyclization Procedures for 2a and 2b (see Scheme I). Sodium Hydroxide in Methanol.[28]—To a mixture of 0.034 mol of **2b** and 0.2 g of N,N-dimethylaniline in 50 ml of anhydrous methanol was added 0.04 mol of NaOH in 50 ml of methanol. The mixture was heated under reflux for 24 hr, cooled, evaporated to one-half the volume, and diluted with ether. This precipitated 3.4 g of NaBr. The filtrate was concentrated and analyzed by glpc (see Scheme I).

Sodium Hydride.—A mixture of 0.02 mol of **2a** and a slight excess of NaH were heated at 130° in xylene for 6 hr. Routine work-up afforded only **3**, identified by ir, nmr, and glpc.

Silver tetrafluoroborate in methylene chloride or acetone, which has been used to cyclize γ-chlorocarboxamides,[29] failed to effect any reaction of **2a** even after heating for 4 hr.

The Addition of N-Halamides to Olefins.—The preparations of adducts **6–13** (Table I) are summarized below; their nmr spectra are summarized in Table II.

N-(4-Chloro-2-butenyl)-N-methylmethanesulfonamide (6).—The reaction vessel was a 300-ml-capacity Pyrex cylinder, ~8 × 30 cm, fitted with a porous glass disk gas inlet near the bottom, a side arm leading to a condenser near the top, and a standard taper joint at the top into which was inserted a Pyrex immersion well with water jacket to accommodate a 450-W Hanovia uv lamp. To this vessel was added 0.044 mol of N-chloro-N-methylmethanesulfonamide and 200 ml of CCl_4. Following a nitrogen gas purge of 20 min, 75 ml of a CCl_4 solution containing 0.08 mol (initially) of butadiene was added. Irradia-

(27) Freshly prepared material (A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1957, p 195) was required; little product resulted on use of commercially available $NaNH_2$.

(28) A. D. Bliss, W. K. Cline, and O. S. Sweeting, *J. Org. Chem.*, **29**, 2412 (1964).

(29) G. L. Schmir and B. A. Cunningham, *J. Amer. Chem. Soc.*, **87**, 5692 (1965).

tion was then carried out for 4.5 hr as agitation was provided by a slow stream of nitrogen rising through the solution. The product was obtained by rotary evaporation of the solution under aspirator vacuum and chromatography on Florisil using methylene chloride and ether as eluents. The adduct 6 was obtained in 72% yield and contained a compound, presumably *cis* 6, which did not survive distillation. The distilled sample, which darkened on standing, was *trans* 6, bp 120–125° (1 mm), $n^{22}D$ 1.4948; its ir and nmr spectra were definitive on comparison with the spectra of the analogous dialkylchloramine adducts,[9a] especially the *trans*-CH=CH doublet at 970 (strong) and 945 (medium) cm^{-1}.

Anal. Calcd for $C_6H_{12}ClNO_2S$: C, 36.45; H, 6.12; Cl, 17.94; N, 7.09; S, 16.22. Found: C, 36.48; H, 6.33; Cl, 18.15; N, 7.09; S, 16.45.

N-(2-Chloro-2-methylpropyl)-N-methylmethanesulfonamide (7).—Crude 7 was obtained similarly in 80% yield from isobutylene except that chromatography was not required. Analytically pure 7, mp 54–55°, resulted after three recrystallizations from hexane.

Anal. Calcd for $C_6H_{14}ClNO_2S$: C, 36.10; H, 7.05; N, 7.02. Found: C, 35.90; H, 7.00; N, 7.26.

N-(2-Chloro-2-phenylethyl)-N-methylmethanesulfonamide (8).—A mixture of 0.044 mol of N-chloro-N-methylmethanesulfonamide and 0.08 mol of freshly distilled styrene (the excess was probably not required) in 280 ml of CCl_4 was purged with nitrogen and irradiated, then stripped to 14 g of a residue which was chromatographed on Florisil. After 3.4 g of a mixture of chlorinated styrenes was eluted with hexane, elution with CH_2Cl_2 and ether gave 6.9 g of a solid, mp 78–81°. Recrystallization from 1:5 CH_2Cl_2–ether gave 8, mp 79.5–81°.

Anal. Calcd for $C_{10}H_{14}ClNO_2S$: C, 48.48; H, 5.70; N, 5.65. Found: C, 48.41; H, 5.72; N, 5.62.

When the reaction was repeated in the presence of a slow stream of oxygen, no amide adduct could be isolated. When the chloramide was stirred with styrene in CCl_4 under nitrogen for 18 hr, no loss of electropositive chlorine occurred, but one-half was lost in 75 min when irradiation was begun. No further loss occurred in a dark period of 2.5 hr; the reaction was completed in 2 hr by renewed irradiation to give 40% 8.

N-(4-Chloro-2-butenyl)-N-methylcyanamide (9).—A solution of 0.06 mol of N-chloro-N-methylcyanamide in 250 ml of CCl_4 at 0° was stirred under gaseous butadiene, which was introduced at a rate sufficient to maintain 15–30°. After 50 min (ambient light only) the reaction was complete, and the mixture was stripped and chromatographed on Florisil. The combined adduct-containing fractions appeared to contain a mixture of both *cis* and *trans* isomers. Distillation was facile but the product decomposed in a few days even at <0°, which prevented a successful elemental analysis; the distillate was predominantly *trans* 9, bp 121–122° (18 mm), $n^{23}D$ 1.4856. The structure of 9 was obvious, as in the case of 6, by comparison of the ir and nmr spectra with those of analogous compounds. An attempt to produce the corresponding acetate from the chloride 9 according to a procedure found useful for the dialkylamino analog[10] was unsuccessful.

3-N-Cyano-N-methylamino-5-chlorocyclopentene (10).—When 0.08 mol of freshly distilled cyclopentadiene was added slowly to 0.036 mol of N-chloro-N-methylcyanamide stirred in 150 ml of CCl_4 in an ice bath, a rapid reaction ensued to give a product which was chromatographed on Florisil and distilled: bp 84.5–86° (0.1 mm), $n^{23}D$ 1.5074. The twin peaks for the NCH_3 group in the nmr spectrum suggest that the product was a *cis–trans* mixture, although the myriad of lines in the total spectrum defied simple analysis. Neither a picrate (from ethanol or acetone[30]) nor a hydrochloride (from ether or pentane) could be prepared.

Anal. Calcd for $C_7H_9ClN_2$: C, 53.68; H, 5.79; Cl, 22.64; N, 17.89. Found: C, 53.70; H, 5.72; Cl, 22.22; N, 17.81.

3-(N-Cyano-N-isopropyl)-5-chlorocyclopentene (11).—A reaction carried out with N-chloro-N-isopropylcyanamide and cyclopentadiene as in the preceding example gave a product that was eluted from Florisil mainly in hexane and the remainder in CH_2Cl_2. Distillation in a semimicroapparatus gave an unstable mixture of *cis* and *trans* 11, bp 86–95° (0.1 mm), $n^{23}D$ 1.4944. The nmr spectrum of 11 consisted of two distinct spectra in relative importance of 4:1; that these corresponded to isomers was evident from the measured areas when similar groups were ascribed to the same type of hydrogen; however, an impurity was also suggested by too great an absorption in the high-field region. A picrate could not be prepared. There seems no reason to doubt, however, that the main component of the product was 11, by analogy with so many similar additions.

N-(2-Chloro-2-methylpropyl)-N-methylcyanamide (12).—Irradiation of 0.06 mol of N-chloro-N-methylcyanamide and 0.07 mol of isobutylene in CCl_4 using the 450-W lamp gave 12 after chromatography on Florisil and distillation: bp 71–72° (0.5 mm), $n^{23}D$ 1.4567. Only 15% 12 was obtained under air on irradiation with a 100-W source after a 2-hr dark period, during which no reaction occurred. A sample of 12 was distilled from CaO without evidence of dehydrohalogenation.

Anal. Calcd for $C_6H_{11}ClN_2$: C, 49.15; H, 7.56; Cl, 24.18; N, 19.11. Found: C, 49.04; H, 7.63; Cl, 24.03; N, 19.11.

N-(2-Chloro-2-phenylethyl)-N-methylcyanamide (13).—The adduct was obtained under an atmosphere of air: bp 120° (0.03 mm), $n^{22}D$ 1.5603; the same yield of 13 was obtained whether or not the solution was irradiated (Table I). Since the nmr spectrum of the distilled product contained some extraneous peaks in the vinyl region which were not present in the sample eluted from Florisil, the contaminant was thought to be a dehydrohalogenation product. However, attempts to induce this reaction failed with the following: sodium hydride, which gave no discrete product; refluxing triethylamine in benzene (no reaction); distillation from molten NaOH (tar); or treatment with methyllithium (tar). Acid-catalyzed reactions were not attempted. The chromatography sample, although providing a definitive nmr spectrum, gave an unsatisfactory elemental analysis.

The Reaction of N-Chloro-N-*t*-butylcyanamide with Cyclohexene (Table III, Entry I).—A solution of 6.0 g of the N-chlorocyanamide in 280 ml of CCl_4 was irradiated with the 450-W uv lamp for 15 min in a slow stream of nitrogen. The lamp was then turned off, 15 ml of cyclohexene was added, and the irradiation was resumed after 5 min. The solution was evaporated under aspirator vacuum at 30° when the titre for electropositive chlorine had reached zero. A residue (10 g) resulted which contained carbodiimide compounds (see results section); these were treated in one of two ways to effect their hydrolysis (Table III). Method A is illustrated here; method B is illustrated in the experiment described below.

The residue was heated with 4 ml of DMSO, 1 ml of H_3PO_4, and 1.5 ml of isopropyl alcohol/g of crude product for 45 min, followed by the addition of 2 ml of water/g of original residue. The mixture was shaken intermittently for 45 min as a precipitate of the urea 16 formed. This procedure is similar to that in which dicyclohexylcarbodiimide, DMSO, and an acid are used in the oxidation of alcohols to carbonyl compounds.[31] The precipitate was collected and washed with 5 ml of chilled 5:1 ether–acetone; the 3.0 g of crude 16 thus obtained was recrystallized using 10 ml of acetone/g to afford 2.3 g of 15 in two crops, mp 151–153°. Several recrystallizations afforded an analytical sample, mp 155–156.5°. The characterization of **N-*t*-butyl-N-2-chlorocyclohexylurea** and of the new compounds described below was discussed in the results section.

Anal. Calcd for $C_{11}H_{21}ClN_2O$: C, 56.76; H, 9.10; N, 12.04. Found: C, 56.45; H, 9.00; N, 12.19.

The filtrate from the collection of crude 15 was poured into 225 ml of water. The combined ether extracts (50 ml, then 5–25-ml portions) of this solution were washed with water and dried. Evaporation under vacuum left 3.2 g of a residue containing N-*t*-butylcyanamide, *trans*-1,2-dichlorocyclohexane, and 2-cyclohexenol (eq 2); the yields were estimated by glpc analysis.

The aqueous phase on separation from the ether extracts was basified with 12 *N* NaOH and immediately extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, concentrated, and evaporated to leave 2.1 g of material that partially crystallized on standing. The crystals (0.70 g) were collected after 1 day at 25° using a small amount of ether diluent: mp 173–175°. Crystallization of 0.4 g from 12 ml of hot benzene on the addition of 1 ml of hot hexane gave **N-*t*-butyl-N'-(N-*t*-butyl-N-cyanoamino)urea (17)**, mp 174–175.5° dec (evolution of a gas).

Anal. Calcd for $C_{10}H_{20}N_4O$: C, 56.58; H, 9.50; N, 26.39. Found: C, 56.34; H, 9.70; N, 26.44.

(30) J. Berger and A. D. Sorensen, *Acta. Chem. Scand.*, **20**, 2002 (1966).

(31) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 4656 (1965); A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966); K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *ibid.*, **87**, 4658 (1965).

The filtrate from the collection of **17** was evaporated. After 1 day, crystals again appeared (0.05 g) and were collected: mp 220–226°. These and similar crystals obtained in other experiments were combined and 0.4 g was recrystallized from 30 ml of ethanol to afford pure **3-*t*-butylamino-4-*t*-butyl-1,2,4(1H)-triazolone (18)**, mp 239–240°.

Anal. Calcd for $C_{10}H_{20}N_4O$: C, 56.58; H, 9.50; N, 26.39; mol wt, 212.3. Found: C, 56.39; H, 9.38; N, 26.23; mol wt, 212.8.

The Reaction of N-Chloro-N-*t*-butylcyanamide with Styrene under Nitrogen.—A reaction was carried out as in the preceding example except that 0.14 mol of styrene was introduced after the preirradiation of the chloramide. The dark reaction with styrene had consumed 27% of the active chlorine in the 10 min before irradiation was again begun. Hydrolysis of 5 g of the 22.5 g of crude products obtained was carried out using method B (Table III), whereby the hydration of carbodiimides with oxalic acid under nonaqueous conditions was performed.[32] To the sample in 30 ml of ether was added oxalic acid in an amount calculated as 1.1 mol/mol of sample, assuming the latter to be comprised entirely of a 1:1 adduct of the chloramide and the olefin. A gas was evolved during the first 2 hr as the mixture was stirred at room temperature and then left without stirring for 48 hr. (When cyclohexene reaction products were hydrolyzed, the adduct urea precipitated in pure form during this time.) The solution was then diluted with ~200 ml of ether, neutralized using saturated $NaHCO_3$ solution, dried, and evaporated. **17** separated on standing: 0.35 g (32%), mp 177–178° dec. The decomposition point of **17** depended on the rate of heating.

After removal of **17**, the residue was chromatographed on alumina. Following the elution of 0.8 g of styrene and chlorinated styrenes with hexane, 0.15 g of material was eluted with CH_2Cl_2. The crystals of **21** which formed in this fraction were washed with pentane and analyzed directly: mp 62.5–64.0°. The nmr spectrum of the product was consistent with its formulation as **N-(2-chloro-2-phenylethyl)-N-*t*-butylcyanamide**: τ 2.67 (C_6H_5), 5.01 (CHCl), 6.62 (doublet of doublets, J = 7.5, 2.0 cps, NCH_2), 8.82 (*t*-butyl). Another compound appeared to be present in trace amounts by the presence of small peaks at τ 2.8, 8.68, 8.75, 9.2, and 9.9. The elemental analysis was nevertheless excellent for **21**, and it is therefore implied that the impurity is an isomer, perhaps the aziridine salt resulting from cyclization.

Anal. Calcd for $C_{12}H_{17}ClN_2$: C, 65.95; H, 7.24; Cl, 14.98; N, 11.83. Found: C, 65.84; H, 7.16; Cl, 14.94; N, 12.16.

A slightly larger amount of **21** was obtained in a similar way when a reaction was run in air (Table III); a sample following chromatography on Florisil gave three times the residue obtained from alumina, but the material gave a mixture of products on distillation. Most significant regarding the reactions of styrene in the presence of air was the elimination of **17** as a product and the isolation of the isomer **18** in unusually enhanced yield, following the oxalic acid treatment (Table III); **18** was eluted from alumina with methanol after the other products had been eluted with less polar solvents.

Iron-Catalyzed Reaction of N-Chloro-N-*t*-butylcyanamide with Cyclohexene in Methanol.—A procedure was approximated which is known to yield adducts of olefins and dialkyl-N-chloramines.[10] To 6.0 g (0.045 mol) of the chloramide and 15 ml (0.15 mol) of cyclohexene in 50 ml of methanol was added 7 g of $FeCl_3 \cdot 6H_2O$ as a slurry in methanol. The temperature of the mixture immediately rose from 5 to 30° and then fell, at which point about two-thirds of the chloramide had reacted. A mixture of 14 g of $FeSO_4 \cdot 7H_2O$ in 80 ml of methanol was then added, but the reaction proceeded only slowly, being complete in 75 min. The reaction mixture was then acidified with 5 N H_2SO_4, diluted fivefold with water, and extracted with ether; the ether was dried and evaporated to give 6 g of a product mixture which was chromatographed on alumina. Elution with hexane and CH_2Cl_2 gave the chloro ether (eq 6), and elution with methanol gave *t*-butylurea, mp 179–180° (lit.[33] mp 179°).

Anal. Calcd for $C_5H_{12}N_2O$: C, 51.70; H, 10.41; N, 24.12. Found: C, 51.55; H, 10.66; N, 24.29.

Registry No.—**2a**, 16339-82-5; **2b**, 19520-00-4; **4**, 19520-01-5; **5**, 19520-02-6; **6**, 19520-03-7; **7**, 19520-04-8; **8**, 19520-05-9; **9**, 19520-06-0; **10** (*cis*), 19519-95-0; **10** (*trans*), 19519-96-1; **11** (*cis*), 19519-97-2; **11** (*trans*), 19519-98-3; **12**, 19541-51-6; **13**, 19520-07-1; **15**, 19520-08-2; **16**, 19520-09-3; **17**, 19520-10-6; **18**, 19520-11-7; N-chloro-N-methylbutanesulfonamide, 16867-16-6; N-chloro-N-methylmethanesulfonamide, 2350-09-6; N-chloro-N-isopropylcyanamide, 19520-14-0; N-*t*-butyl-N-2-chlorocyclohexylurea, 19520-15-1; N-(2-chloro-2-phenylethyl)-N-*t*-butylcyanamide, 19520-16-2.

(32) F. Zetzsche and H. Lindlar, *Chem. Ber.*, **71**, 2095 (1938).

(33) Infrared Spectrum No. 9751, Sadtler Research Laboratories, Philadelphia, Pa.

The Reduction of Oximes, Oxime Ethers, and Oxime Esters with Diborane. A Novel Synthesis of Amines

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Oximes and hydroxylamines are reduced by diborane to the corresponding amines in yields of about 70% if reactions are performed at 105–110°. On the other hand, oxime ethers and oxime esters react with diborane already at 25° to give intermediates which on basic or acidic hydrolysis afford the corresponding primary amines and alcohols in yields of 50–90%.

Previously, it was reported that treatment of aldoximes and ketoximes,[1] as well as nitronate salts,[2] with diborane in tetrahydrofuran at 25° afforded the corresponding N-monosubstituted hydroxylamines in very good yield. We are now reporting that oximes were reduced to amines if the reactions were performed at 105–110° in a diglyme–THF solution. A few representative examples are shown in Table I. It is very likely that these reductions proceeded *via* hydroxylamine intermediates because hydroxylamines themselves were reduced in high yields to amines on treatment with diborane at 105–110° (Table I). The

TABLE I

DIBORANE REDUCTION OF OXIMES AND HYDROXYLAMINES TO AMINES

Compound[a]	Amine[b]	Yield, %
1,3-Diphenyl-2-propanone oxime	1,3-Diphenyl-2-propylamine	74.2
Cyclohexanone oxime	Cyclohexylamine[c]	70.5
p-Nitrobenzaldehyde oxime	*p*-Nitrobenzylamine	72.5
Heptanal oxime	*n*-Heptylamine	72.0
N-Cyclohexylhydroxylamine	Cyclohexylamine[c]	84.4
N-Heptylhydroxylamine	*n*-Heptylamine	62.7

[a] Reductions were carried out at 105–110° for 20 hr in a diglyme–THF mixture. [b] These compounds were identified by their physical data which were in agreement with those reported in the literature. [c] Isolated as the oxalate salt, mp 229–230°. *Anal.* Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.84; H, 7.83; N, 7.37.

temperature effect on the course of the reaction was dramatically indicated in the case of 1,3-diphenyl-2-propanone oxime (**1**). While in a temperature range of 25–65°, **1** was recovered unchanged; at 85–90° it was reduced to N-1,3-diphenyl-2-propylhydroxylamine (**2**) in 77% yield, and at 105–110° the amine, 1,3-diphenyl-2-propylamine (**3**) was obtained as the only product in 74% yield (eq 1).

$$(C_6H_5CH_2)_2C{=}NOH \xrightarrow[85\text{–}90^\circ]{B_2H_6} (C_6H_5CH_2)_2CHNHOH$$
1 **2**

$$\mathbf{1} \xrightarrow[105\text{–}110^\circ]{B_2H_6} (C_6H_5CH_2)_2CHNH_2 \quad (1)$$
3

In the case of the oximes of benzophenone (**4**) and dicyclohexyl ketone (**5**), even at reaction temperatures up to 110° the reduction did not proceed beyond the hydroxylamine stage. Previously,[1] compounds **4** and **5** were recovered unchanged when treated with diborane at temperatures as high as 65°.

Oxime Ethers.—While the reduction of oximes to amines by diborane required high temperatures, oxime ethers underwent the reduction already at room temperature (eq 2).

$$\begin{matrix} R' \\ | \\ RC{=}NOR'' \end{matrix} \xrightarrow[25^\circ]{B_2H_6} \begin{matrix} R' \\ | \\ RCHNH_2 \end{matrix} + R''OH \quad (2)$$

R = alkyl or aryl
R′ = alkyl, aryl or H
R″ = alkyl or benzyl

Reactions were carried out mainly with O-methyl oximes because they were obtained directly in high yield on treating aldehydes and ketones with methoxyamine hydrochloride.[3]

These oxime ethers were also prepared by the reaction of potassium oximates with methyl *p*-toluenesulfonate; however, this procedure gave lower yields (eq 3).

$$R_2C{=}NOH \xrightarrow[2.\ p\text{-}CH_3C_6H_4SO_3CH_3]{1.\ K,\ THF,\ \Delta} R_2C{=}NOCH_3 \quad (3)$$

Reaction Conditions.—By employing O-methyl benzaldehyde oxime (**6**) as a model compound, it was found that the following conditions led to optimum yields: (1) during the addition of the borane–THF solution to the oxime ether the reaction temperature had to be kept below 5° to prevent possible fume-offs; (2) a contact time of 1–2 hr at 65° was found to be sufficient to ensure complete reaction; (3) the yield of amine was, over a wide range, independent of the amount of hydride ion per mole of **6**;[4] and (4) basic or acidic hydrolysis of the reaction mixture gave comparable yields of the amine.

Results

As shown by representative examples in Table II, the reduction of oxime ethers gave good to excellent yields of the corresponding amines. The alkoxy portion of the ethers was reduced to the corresponding alcohol. For instance, O-benzylheptanal oxime (**7**) gave benzyl alcohol and heptylamine in yields of 95.2 and 97.8%, respectively.

The reduction of oxime ethers to amines constitutes an attractive route for the conversion of aldehydes and ketones into amines because it can be carried out at

(1) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965).

(2) H. Feuer, R. S. Bartlett, B. F. Vincent, Jr., and R. S. Anderson, *ibid.* **30**, 2880 (1965).

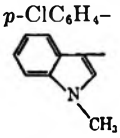
(3) H. M. Fales and T. Luukainen, *Anal. Chem.*, **37**, 955 (1965).

(4) The reduction of **6** with 2.5 and 8.0 equiv of hydride ion gave benzylamine in yields of 91.8 and 91.5%, respectively.

TABLE II

DIBORANE REDUCTION OF OXIME ETHERS TO AMINES[a,b]

$$RC(=NOCH_3)R^1 \xrightarrow[2.\ \text{hydrolysis}]{1.\ BH_3,\ THF} RCHR^1(NH_2) + CH_3OH$$

Amine[c] R	Amine[c] R¹	Registry no.	Mp, °C	Bp (mm) or mp, °C	$n^{20}D$	Yield, %
C_6H_5–	H	100-46-9	196–198[c]	73 (14)	1.5410	92.5
p-$(CH_3)_2NC_6H_4$–	H	19293-58-4	203–205[c]	135–136 (15)	1.5761	87.8
p-$NO_2C_6H_4$–	H	7409-30-5	183–185[c]	110–111 (1.25), 39–40	1.5642	81.7
p-ClC_6H_4–	H	104-86-9	207–209[c]	106–108 (15)	1.5579	84.5
	H	19293-60-8	186–187[d]			71.7
C_6H_5–	C_6H_5–	91-00-9	205–206 dec[c]			65.0
p-$CH_3OC_6H_4$–	p-$CH_3OC_6H_4$–	19293-62-0	188 dec[e]			70.9
C_6H_5–	$-CH_3$	98-84-0	187–189[c]			51.8
Cyclohexyl–	-Cyclohexyl	19293-63-1	157–158[f]	87–89 (0.6)	1.4951	77.2
$CH_3(CH_2)_6$–	H	111-86-4	120–121[c]	57–58 (15)	1.4251	77.5
C_6H_5–	$-CC_6H_5$ (NOCH₃)	19293-64-2	237–240 dec[g]			67.8
C_6H_5–	$-CH_2CC_6H_5$ (NOCH₃)	19293-65-3	241–245 dec[g]	145–146 (0.48)	1.5868	89.7

[a] Reactions were carried out for 2 hr at reflux temperature. [b] Hydride ion (2 equiv) per mole of oxime ether was consumed. [c] Melting point of picrate derivative. [d] Isolated and characterized as the phenylthiourea derivative. [e] Isolated and characterized as the picrate derivative. [f] Isolated and characterized as the phenylthiorurea derivative. [g] Melting point of dipicrate derivative.

room temperature, and has been found to be applicable to a wide variety of compounds. As shown in Table II, oxime ethers containing nitro or chloro groups, and dioxime ethers were reduced, respectively, to the corresponding nitro- or chloroamines and diamines in high yields.

Oxime Esters.—The reduction of oxime esters with diborane also led to amines in high yields, and the acyl portion was reduced to the alcohol. Hydride consumption measurements indicated that twice the amount of hydride was consumed in the reduction of an oxime ester as compared to an oxime ether.

For instance, O-(p-nitrobenzoyl) cyclohexanone oxime gave 68% cyclohexylamine and 80.6% p-nitrobenzyl alcohol (eq 4).[5]

$$RC(=NOCR')R \xrightarrow[25°]{B_2H_6} RCHNH_2 + R'CH_2OH \qquad (4)$$

R = cyclohexyl–
R′ = CH_3 or p-$NO_2C_6H_4$–

Discussion

On the basis of quantitative measurements of hydride consumption and isolation of intermediates which on subsequent hydrolysis gave amines and alcohols, it is proposed that the reduction of oxime ethers with diborane involves essentially three steps (eq 5–7). Although intermediates A, B, and C are presented as monomers they might be polymeric in nature as indicated by the molecular weight determination of the intermediate[6] obtained from **7** and diborane (see Experimental Section).

$$RCH{=}NOR' \longrightarrow \left[\begin{array}{l} H \\ RC{=}NOR' \\ H{-}BH_2 \end{array}\right] \longrightarrow \underset{\underset{A}{BH_2}}{RCH_2NOR'} \qquad (5)$$

$$A \xrightarrow{BH_3} \left[\begin{array}{l} H{-}BH_2 \\ RCH_2N{-}OR' \\ BH_2 \end{array}\right] \longrightarrow \underset{B}{RCH_2\overset{BH_2}{N}H} + \underset{C}{R'OBH_2} \qquad (6)$$

$$B + C \xrightarrow[\Delta]{H^+ \text{ or } OH^-} RCH_2NH_2 + R'OH \qquad (7)$$

The reaction sequence is similar to that suggested for the reduction of oximes,[1] except that it differs in the first step, since no acidic hydrogen is present, and it indicates the formation of cleavage products B and C prior to hydrolysis. This is based on the following observations.

The reaction product of diborane with **7** dissolved in pentane was obtained as an opaque viscous liquid after removal of the solvent *in vacuo*. The nmr spectrum of this intermediate confirmed that reduction of the C=N bond had occurred, because the vinyl proton, present in the starting material **7** which appeared as two triplets[7] was absent.

This intermediate still contained active hydride because on hydrolysis, hydrogen was evolved and on work-up benzyl alcohol and heptylamine were obtained in yields of 38 and 42%, respectively.

Step 1 in the reaction is the actual reduction step wherein the double bond becomes saturated. The

(5) After this work was completed A. Hassner and P. Catsoulacos [*Chem. Commun.*, 590 (1967)] reported that treatment of oxime acetates with diborane afforded amines.

(6) The term intermediate applies to a mixture of components.

(7) J. H. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw Hill Book Co., Inc., New York, N. Y., 1959, p 374.

four-centered attack is in agreement with present views of the addition of borane to multiple linkages.[8] In step 2, electrophilic attack of borane on nitrogen is followed by a hydride shift with the resulting cleavage of the N–O bond to give B and C. Evidence that cleavage had occurred was obtained (1) from hydride consumption measurements, which showed that 2 equiv of hydride ion instead of 1 equiv was consumed prior to hydrolysis; (2) from the mass spectrum of the intermediate, which had peaks at *m/e* 233, 127, and 120 (relative intensity 0.88, 1.32, and 36.72, respectively) in agreement with structures A, B, and C, where R = *n*-heptyl and R¹ = benzyl; (3) from the infrared spectrum, which showed bands at 3200 (NH), 2480 (BH), 1605 (BN), and 1170 cm⁻¹ (OCH_2);[9] and (4) from the elemental analysis and molecular weight determination, which indicated that the intermediate consisted of a mixture, (see Experimental Section).

Step 3 presents the hydrolysis to the final products. In order to obtain maximum yield of product, it was necessary to reflux basic or acidic solutions of the intermediate.

Experimental Section

Apparatus.—Experiments were performed in the setup described previously.[1]

Reagents.—Diborane was generated as described by Brown[10] and solutions of diborane in THF were prepared and standardized.

Aldehydes and ketones of Eastman White Label grade were distilled or recrystallized prior to use. Hydroxylamine and methoxyamine hydrochloride, Eastman White Label grade, were used as received. Methyl *p*-toluenesulfonate was prepared by the method of Ross, *et al.*[11]

Oximes were prepared by methods described in the literature. Tetrahydrofuran was purified by the method of Feuer and Savides.[12]

Equipment.—All infrared spectra were taken with Perkin-Elmer recording spectrophotometers, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on Aerographs A-700 and A-903 using a 4-ft SF-96 on Chromosorb W column. Mass spectra were obtained with a Hitachi RMU-6A mass spectrometer.

High-Temperature Diborane Reductions. Cyclohexylamine. A. Using Cyclohexanone Oxime.—The following experiment is typical of the procedure employed. To 2.26 g (20.0 mmol) of cyclohexanone oxime dissolved in 50 ml of diglyme at 0° was introduced by means of a hypodermic syringe 91.0 mequiv of hydride ion, at such a rate that the temperature did not exceed 10°. Continuing the reaction for 20 hr at 105–110° and then lowering the temperature to 0° was followed by the addition of 10 ml of 20% potassium hydroxide. (*Caution!* The first few drops of base should be added slowly because a considerable exotherm develops.) Then refluxing the reaction mixture for 1 hr, extracting with pentane for 24 hr, adding the combined extracts to a saturated ethereal oxalic acid solution, cooling, and recrystallizing from ethanol gave 2.72 g (70.5%) of **cyclohexylamine oxalate**, mp 229–230°.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.84; H, 7.83; N, 7.37.

B. Using N-Cyclohexylhydroxylamine.[1]—The same procedure as in A was followed. From 0.9445 g (8.20 mmol) of N-cyclohexylhydroxylamine, 50 ml of diglyme, and 75.0 mequiv of hydride ion there was obtained 1.33 g (84.4%) of **cyclohexylamine oxalate**, mp 229–230°.

N-Diphenylmethylhydroxylamine.—The same procedure was followed as in A except that the reaction time was 10 hr and hydrolysis of the reaction mixture was carried out by the addition of 5 ml of water followed by 15 ml of 10% hydrochloric acid.

From 4.0 g (20.3 mmol) of benzophenone oxime, 25 ml of diglyme, and 91.0 mequiv of hydride ion there was obtained 7.5 g (73.1%) of **N-diphenylmethylhydroxylamine oxalate**. The oxalate salt (2.0 g, 4.09 mmol) was neutralized at 25° by adding it to a mixture consisting of 20 g of sodium carbonate, 200 ml of water and 150 ml of ether, and by stirring for 4 hr.

Extracting the aqueous layer with two 200-ml portions of ether, drying the combined extracts (Na_2SO_4), and removing solvent *in vacuo* gave, after sublimation at 50° (0.05 mm), 0.72 g (73.8%) of **N-diphenylmethylhydroxylamine**: mp 80–81°;[13] ir (KBr) 3280 cm⁻¹ (NH and OH); nmr ($CDCl_3$) δ 5.20 [s, 1, $(C_6H_5)_2CH$], 5.58 (s, 2, NHOH), and 7.32 (s, 10, aromatic H).

N-Dicyclohexylmethylhydroxylamine.—The same procedure was followed as in the preparation of N-diphenylmethylhydroxylamine except that hydrolysis was carried out with 10 ml of 20% potassium hydroxide.

From 4.0 g (19.15 mmol) of dicyclohexyl ketone oxime, 50 ml of diglyme, and 135.0 mequiv of hydride ion there was obtained after sublimation at 85° (0.05 mm) of 2.95 g (73.0%) of product: mp 93–94°; ir (KBr) 3290 and 3230 cm⁻¹ (NHOH); nmr ($CDCl_3$) δ 1.50 [m, 22, $(C_6H_{11})_2CH$], 2.40 (s, 1, CHNHOH), and 5.28 (s, 2, NHOH).

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.66; H, 12.06; N, 6.36.

N-1,3-Diphenyl-2-propylhydroxylamine.—The same procedure was followed as in the preparation of N-diphenylmethylhydroxylamine except that the reaction mixture was refluxed for 20 hr at 85–90° using dioxane as solvent. Also after acidic hydrolysis the reaction mixture was basified to pH 10 at 5° with 20% potassium hydroxide and then extracted with pentane and the extracts added to a saturated ethereal oxalic acid solution.

From 7.0 g (31.0 mmol) of 1,3-diphenyl-2-propanone oxime, 50 ml of dioxane, and 130.0 mequiv of hydride ion there was obtained after sublimation at 70° (0.01 mm) 5.50 g (78.1%) of product: mp 95.5–97°; ir (KBr) 3160 cm⁻¹ (NHOH); nmr ($CDCl_3$) δ 2.80 [m, 4, $(C_6H_5CH_2)_2CH$], 3.20 [m, 1, $(C_6H_5CH_2)_2CH$], 6.03 (s, 2, NHOH), and 7.20 (s, 10, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.41; H, 7.35; N, 6.17.

Similarly, this compound was obtained in 62% yield when diglyme was substituted for dioxane as the solvent.

Preparation of O-Methyl Oximes. Method A.—The following experiment is typical of the procedure employed. A solution of 5.0 g (0.0313 mol) of N-methylindole-3-carboxaldehyde and 2.7 g (0.0324 mol) of methoxyamine hydrochloride in 100 ml of pyridine and 100 ml of absolute ethanol was refluxed for 24 hr.

Removing solvents *in vacuo*, adding 100 ml of water to the residue, cooling, and recrystallizing from ethanol–water (1:1) gave 5.3 g (89.3%) of **O-methyl N-methylindole-3-carboxaldehyde oxime**: mp 78–80°; ir (KBr) 1618 (C=N) and 1053 cm⁻¹ ($NOCH_3$); nmr ($CDCl_3$) δ 3.69 (s, 3, NCH_3), 4.02 (s, 3, $NOCH_3$), 7.30 (m, 4, aromatic H), 8.29 (m, 1, C=CH), and 8.50 (s, 1, HC=N).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.36; N, 14.79.

O,O′-Dimethyl 1,3-Diphenyl-1,3-propanedione Dioxime.—From 10.0 g (0.0446 mol) of 1,3-diphenyl-1,3-propanedione and 8.35 g (0.10 mol) of methoxyamine hydrochloride there was obtained after recrystallization from ethanol–water (4:1) at −78° 10.5 g (83.4%) of product: mp 58–59°; ir (KBr) 1595 (C=N) and 1048 cm⁻¹ ($NOCH_3$); nmr ($CDCl_3$) δ 3.94 [s, 6, $(NOCH_3)_2$], 4.23 (s, 2, $-CH_2-$), and 7.30 (m, 10, aromatic H).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.45; H, 6.46; N, 10.10.

O-Benzyl Heptanal Oxime.—The same procedure was followed as in method A except that only absolute ethanol was used as solvent.

From 10.0 g (0.0878 mol) of heptanal and 10.8 g (0.0879 mol) of benzyloxyamine[14] there was obtained 17.5 g (91.3%) of

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product: bp 100–104° (0.4 mm); n^{20}D 1.5068; ir (neat) 1653 (C=N) and 1026 cm^{-1} ($NOCH_2$); nmr ($CDCl_3$) δ 0.85 (t, 3, CH_2CH_3), 1.21 [m, 8, $(CH_2)_4$], 2.25 (m, 2, CH_2CH_2CH=N), 5.20 (d, 2, $C_6H_5CH_2O$), 6.67 and 7.35 (m, 5, aromatic H).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.65; H, 9.35; N, 6.31.

O-Methyl 4,4′-Dimethoxybenzophenone Oxime. Method B.—The following experiment is typical of the procedure employed. Into a dry 1-l. three-necked flask equipped with a Hershberg stirrer, condenser provided with a drying tube, and pressure-equalizing addition funnel were placed 20 g (0.0778 mol) of 4,4′-dimethoxybenzophenone oxime and 200 ml of THF. To the stirred solution was added 3.03 g (0.0775 g-atom) of potassium. The reaction mixture was refluxed (*Caution!* Heating must be carried out slowly because of a possible exotherm), and after 3 hr 14.9 g (0.080 mol) of methyl *p*-toluenesulfonate in 100 ml of THF was added dropwise.

Refluxing the reaction mixture an additional 3 hr, filtering, and removing THF *in vacuo* gave after two recrystallizations from ethanol–water (1:1) 12.9 g (61.2%) of product: mp 82–83°; ir (melt) 1612 (C=N) and 1058 cm^{-1} ($NOCH_3$); nmr ($CDCl_3$) δ 3.78 [s, 6, $(OCH_3)_2$], 3.93 (s, 3, $NOCH_3$), and 6.85 and 7.35 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.00; H, 6.43; N, 5.39.

O-Methyl Dicyclohexyl Ketone Oxime.—From 15.0 g (0.0719 mol) of dicyclohexyl ketone oxime, 2.8 g (0.0719 g-atom) of potassium, and 13.4 g (0.0720 mol) of methyl *p*-toluenesulfonate there was obtained 10.7 g (66.8%) of product: bp 76° (0.2 mm); n^{20}D 1.4939; ir (neat) 1620 (C=N) and 1061 cm^{-1} ($NOCH_3$); nmr ($CDCl_3$) δ 1.60 [m, 22, $(C_6H_{11})_2$] and 3.72 (s, 3, $NOCH_3$).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.34; H, 11.03; N, 6.01.

O-Methyl *p*-Dimethylaminobenzaldehyde Oxime.—From 25.0 g (0.152 mol) of *p*-dimethylaminobenzaldehyde oxime, 6.0 g (0.153 g-atom) of potassium, and 28.4 g (0.153 mol) of methyl *p*-toluenesulfonate there was obtained 17.0 g (62.8%) of product: mp 64–65°; ir (KBr) 1621 (C=N) and 1055 cm^{-1} ($NOCH_3$); nmr (DMSO-d_6) δ 2.90 [s, 6, $(CH_3)_2N$], 3.70 (s, 3, $NOCH_3$), 6.65 and 7.38 (q, 4, aromatic H), and 7.95 (s, 1, HC=N).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.22; H, 7.76; N, 15.44.

Reaction of Diborane with Oxime Ethers.—The following experiment is typical of the procedure employed. To 3.7125 g (27.5 mmol) of O-methyl benzaldehyde oxime dissolved in 20 ml of THF at 0° was introduced by means of a hypodermic syringe 84.4 mequiv of hydride ion at such a rate that the temperature did not exceed 10°. After refluxing the reaction mixture for 2 hr and cooling to 0°, 10 ml of water was added cautiously followed by 10 ml of 20% potassium hydroxide. Refluxing the reaction mixture for 1 hr, extracting with pentane for 24 hr, removing the solvent *in vacuo*, and distilling the remaining liquid gave 2.70 g (92.5%) of **benzylamine**: bp 73° (14 mm); n^{20}D 1.5410;[15] ir (neat) 3390 and 3300 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 1.34 (s, 2, NH_2), 3.73 (s, 2, $C_6H_5CH_2$), and 7.23 (s, 5, aromatic H).

Similarly, treating 3.7125 g (27.5 mmol) of O-methyl benzaldehyde oxime with 84.4 mequiv of hydride ion for 2 hr at reflux, hydrolyzing the reaction mixture at 0° with 5 ml of water and then refluxing for 30 min gave 8.92 mmol of hydrogen. Then removing THF *in vacuo*, adding 20 ml of 20% potassium hydroxide at 0° to the residue, and refluxing for 1 hr gave an additional 16.65 mmol of hydrogen. The total amount of hydrogen evolved was 25.57 mmol of hydrogen, indicating that 2.06 equiv of hydride ion per mole of oximino ether was consumed in the reduction.

Bis(*p*-methoxyphenyl)methylamine.—From 5.43 g (20 mmol) of O-methyl 4,4′-dimethoxybenzophenone oxime and 118 mequiv of hydride ion there was obtained crude product which was converted into the picrate derivative[16] (6.70 g, 70.9%), mp 188° dec.

Anal. Calcd for $C_{21}H_{20}N_4O_9$: C, 53.39; H, 4.27; N, 11.86. Found: C, 53.25; H, 4.58; N, 11.81.

Dicyclohexylmethylamine.—From 12.0 g (53.8 mmol) of O-methyl dicyclohexyl ketone oxime and 254.2 mequiv of hydride ion there was obtained 8.1 g (77.2%) of product: bp 87–89° (0.6 mm); n^{20}D 1.4951. The **phenylthiourea** of dicyclohexylmethylamine was prepared,[16] mp 157–158°.

Anal. Calcd for $C_{20}H_{30}N_2S$: C, 72.69; H, 9.46; N, 8.51; S, 9.40. Found: C, 72.44; H, 9.30; N, 8.40; S, 9.47.

3-Methylamino-1-methylindole.—From 2.17 g (11.5 mmol) of O-methyl N-methylindole-3-carboxaldehyde oxime and 91.0 mequiv of hydride ion there was obtained crude product. It was converted into the **phenylurea derivative,** mp 186–187°, by treatment with phenyl isocyanate.[16]

Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.93; H, 6.24; N, 14.91.

1,3-Diphenyl-1,3-propanediamine.—From 4.23 g (15.0 mmol) of O,O′-dimethyl 1,3-diphenyl-1,3-propanedione dioxime and 97.5 mequiv of hydride ion there was obtained 3.05 g (89.7%) of product: bp 145–146° (0.48 mm); n^{20}D 1.5868.[17] The dipicrate derivative was prepared,[16] mp 241–245° dec.

Anal. Calcd for $C_{27}H_{24}N_8O_{14}$: C, 47.37; H, 3.53; N, 16.37. Found: C, 47.52; H, 3.72; N, 16.32.

Preparation of O-Benzyl Heptanal Oxime–Diborane Adduct (Isolation of Intermediates).—To a mixture of 2.20 g (10 mmol) of analytically pure O-benzyl heptanal oxime and 100 ml of Phillip's pure grade pentane (99 mol % minimum) was introduced at 0° approximately 1428 mmol of gaseous diborane over a 2-hr period. The reaction mixture was held at ambient temperatures for 4 hr. Removing pentane and excess diborane *in vacuo* and heating the residue at 55° (0.5 mm) for 3 days afforded 2.30 g of a viscous opaque liquid: ir (neat) 3200 (NH), 2480 (BH), 1605 (BN), and 1170 cm^{-1} (OCH_2); nmr ($CDCl_3$) δ 0.88 (t, 3, CH_2CH_3), 1.30 [m, 10, $(CH_2)_5$], 2.95 (m, 2, CH_2CH_2N), 3.88 (s, 1, NH), 4.78 (s, 2, $C_6H_5CH_2$), and 7.44 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (relative intensity) 233 (0.875), 232 (0.435), 149 (10.01), 127 (1.32), 126 (3.93), 120 (36.7), 119 (1.83), 107 (23.6), 106 (50.6), 91 (100.0), 90 (43.6), 79 (26.9), 77 (53.8), 70 (15.3), 65 (21.0), 57 (14.8), 56 (14.8), 55 (19.2), 51 (27.2), 50 (12.6), 43 (18.8), 29 (10.2), 28 (17.9), and 27 (11.1).

Anal. Calcd for $C_{14}H_{24}NOB$ (A): C, 72.12; H, 10.39; N, 6.05; B, 4.64; mol wt, 233.15. Found: C, 67.82, 67.59; H, 9.62, 9.75; N, 4.82, 4.87; B, 5.75, 5.68; mol wt, 266, 267 (in benzene).

Anal. Calcd for $C_7H_{18}NB$ (B): C, 66.15; H, 14.28; N, 11.01; B, 8.56; mol wt, 127.10.

Anal. Calcd for C_7H_9BO (C): C, 70.09; H, 7.56; B, 9.04; mol wt, 119.96.

Refluxing an aliquot (0.3379 g) of the O-benzyl heptanal oxime–diborane adduct with 20% potassium hydroxide evolved 6.15 mmol of hydrogen, and on work-up *n*-heptylamine and benzyl alcohol were obtained in yields of 42 and 38%, respectively.

Reduction of O-(*p*-Nitrobenzoyl) Cyclohexanone Oxime.—The following experiment is typical of the procedure employed to reduce oxime esters. To 2.8021 g (10.7 mmol) of O-(*p*-nitrobenzoyl) cyclohexanone oxime[18] was introduced by means of a hypodermic syringe 84.4 mequiv of hydride ion. Continuing the reaction at ambient temperatures for 20 hr, cooling the reaction mixture to 5°, adding 5 ml of water cautiously, removing excess THF *in vacuo*, refluxing the residue with 20 ml of 10% hydrochloric acid, extracting the reaction mixture with ether for 24 hr, and removing the ether *in vacuo* gave on recrystallization from ethanol–water (1:8) 1.20 g (80.6%) of ***p*-nitrobenzyl alcohol,** mp 92–93°.[19]

Basifying the aqueous layer with 20 ml of 20% potassium hydroxide, extracting with ether for 24 hr, and removing the ether *in vacuo* gave an oil which solidified on standing. The solid was cyclohexylamine carbonate: nmr (DMSO-d_6) δ 1.50 [s, 10, $(CH_2)_5$], 2.85 (m, 1, $CHNH_3$), and 6.15 (s, 3, NH_3). Dissolving the carbonate in hot water, adding a saturated ethanolic picric acid solution, and cooling gave 2.39 g (67.4%) of **cyclohexylamine picrate,** mp 156–157°.[20]

Similarly, treating 2.8021 g (10.7 mmol) of O-(*p*-nitrobenzoyl) cyclohexanone oxime with 84.4 mequiv of hydride ion, continuing the reaction for 20 hr at ambient temperatures, hydrolyzing cautiously at 0° with 5 ml of water and allowing to warm up to room temperature gave 12.84 mmol of hydrogen.

Then removing THF *in vacuo*, adding 20 ml of 10% hydro-

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chloric acid at 0° to the residue and refluxing for 1 hr gave an additional 20.96 mmol of hydrogen. The total amount of hydrogen evolved was 33.80 mmol, indicating that 4.58 equiv of hydride per mole of oxime ester was consumed in the reduction.

Reduction of O-Acetyl Cyclohexanone Oxime.—From 3.15 g (20.3 mmol) of O-acetyl cyclohexanone oxime[21] and 135.5 mequiv of hydride ion there was obtained 1.2420 g (62.0%) of **cyclohexylamine** and 0.8640 g (94%) of **ethanol** as determined by glpc analysis.

Registry No.—Diborane, 19287-88-8; cyclohexylamine oxalate, 19293-66-4; N-dicyclohexylmethylhydroxylamine, 19293-67-5; N-1,3-diphenyl-2-propylhydroxylamine, 19293-68-6; O-methyl N-methylindole-3-carboxaldehyde oxime, 19293-69-7; O,O'-dimethyl 1,3-diphenyl-1,3-propanedione dioxime, 19293-70-0; O-benzyl heptanal oxime, 19293-71-1; O-methyl 4,4'-dimethoxybenzophenone oxime, 19293-72-2; O-methyl dicyclohexyl ketone oxime, 19293-73-3; O-methyl *p*-dimethylaminobenzaldehyde oxime, 19293-74-4; bis(*p*-methoxyphenyl)methylamine (picrate), 19293-75-5; dicyclohexylmethylamine, 7560-83-0; dicyclohexylmethylamine (phenylthiourea derivative), 19293-50-6; 3-methylamino-1-methylindole (phenylurea derivative), 19293-51-7; 1,3-diphenyl-1,3-propanediamine, 19293-52-8; 1,3-diphenyl-1,3-propanediamine (dipicrate derivative), 19293-53-9.

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Electrochemical Dealkylation of Aliphatic Amines

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The anodic oxidation of tertiary aliphatic amines in nonaqueous systems has been studied, using tri-*n*-propylamine in acetonitrile as a model. The reaction causes dealkylation to produce secondary amine and aldehyde. The reaction product contains unreactive tertiary and secondary amine salts in a 2:1 ratio. When water is rigorously excluded, elemental nitrogen is a major product. The investigation included 12 amines; effect of unsymmetrical substitution on the dealkylation was studied. Solvents used were tetrahydrofuran, dimethyl sulfoxide, water, ethanol–water, methanol, and 1,2-dimethoxyethane.

The electrochemical reactions of aliphatic amines, unlike aromatic amines, have received relatively little attention. Dapo and Mann[1] examined the oxidation of triethylamine in dimethyl sulfoxide and reported an 80% recovery of triethylammonium salt. Russell[2] proposed that, on oxidation in acetonitrile, it undergoes a one-electron reaction to produce the cation radical which was thought to abstract a hydrogen atom from either the solvent or water to form triethylammonium salt and cyanomethylene or hydroxyl radicals.

An examination of the cyclic voltammetric oxidation of a series of aliphatic amines showed that, although the reactions in every case appeared to be irreversible one-step oxidations, substituent inductive effects could be correlated with voltammetric peak potentials for secondary and tertiary amines.[3] This indicates that the primary site of attack is the nitrogen atom and that abstraction of the first electron is the potential-determining step.

In related work, O'Donnell and Mann[4] have studied the anodic oxidation of aliphatic amides and Barnes and Mann[5] have reported on anodic reactions of aliphatic primary amines. Weinberg and Brown[6] and Smith and Mann[7] have examined the anodic methoxylation of tertiary aliphatic amines.

A detailed investigation of the oxidation of amines by chlorine dioxide has been reported by Rosenblatt and coworkers.[8–10] This chemical oxidation causes dealkylation of a tertiary amine to produce secondary amine and the appropriate aldehyde. As a result of kinetics studies involving isotope substitution, it was concluded that the reaction of tertiary amines involves an electron transfer in the rate-determining step.

The same types of products have been obtained on oxidation with N-bromosuccinimide,[11] manganese dioxide,[12] and ozone.[13] In several cases, evidence of the formation of enamines has been found. Leonard and Morrow[14] produced stable cyclic enamines by mercuric acetate oxidation of amines. Buckley, *et al.*,[15] trapped enamines formed from simple amines by reaction with quinones to form stable colored compounds. However, enamines produced from amines with simple straight-chain substituents are insufficiently stable to be isolated. They decompose to the secondary amine and the aldehyde.

The present work has involved examination of the reactions of several tertiary and secondary amines in acetonitrile, dimethyl sulfoxide, tetrahydrofuran, and water. The results indicate that the main reaction, in the presence of at least small amounts of water, involves

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dealkylation of the starting material to produce secondary amine, aldehyde, and protons.

Results

Constant potential electrolyses have been carried out in acetonitrile–sodium perchlorate solutions at platinum and graphite anodes over a range of potentials from 0.35 to 2.10 V *vs.* the silver reference electrode. Current-time behavior was observed; the number of coulombs of charge passed was measured and reaction products were examined. Tripropylamine was chosen as the initial subject of investigation; on the basis of these results, other amines and other solvents have been studied.

Tripropylamine reaction mixtures which had not been rigorously dried showed continuous decrease of current with time in approximately exponential decay at all potentials. Coulometric n values, the number of faradays of charge per mole of amine taken, amounted to 0.999 ± 0.001 at 1.90 V. This value was not affected by oxygen in the reaction mixture. At potentials of 1.00 V or less, the n value amounted to 0.976, significantly smaller than the value obtained at higher potentials. With oxygen present at low potentials, a considerable decrease in the n value, to around 0.82, was noted.

Results from oxidation of tripropylamine in acetonitrile, without rigorous exclusion of water, *i.e.*, the number of moles of water at least equal to the initial number of moles of amine, are presented in Table I. Products include tripropylammonium ions, dipropylammonium ions, and propionaldehyde. On the average, 93% of the nitrogen in the starting material was accounted for, and in some cases, with a graphite anode, this was as high as 98%. Except when oxygen is present, there is no indication that change of potential affects the yields. When oxygen was present, with either platinum or graphite anodes, N,N-dipropylformamide was recovered in varying yields amounting to a maximum of 17 mol % of the initial amine at 0° in an oxygen-saturated solution. With large amounts of water, yields of various products were unreproducible.

Most experiments were carried out with sodium perchlorate as the supporting electrolyte. However, the following were also used: silver nitrate, calcium perchlorate, magnesium perchlorate, tetraethylammonium perchlorate, lead perchlorate, potassium perchlorate, and tetramethylammonium tetrafluoroborate. Results were substantially independent of the identity of the supporting electrolyte except that no reaction at all occurred with lead perchlorate and with magnesium perchlorate. Platinum anodes were used in most of the work; however, substitution of spectrographic graphite anodes made no difference except in the recoveries of propionaldehyde, which were consistently higher with graphite than with platinum anodes.

To study the role of water in this reaction, careful precautions were taken to achieve water concentrations at the level of 5 mol % of starting amine or less. The results, presented in Table II, were quite different from those obtained with moderate amounts of water present. Specifically, yields of tripropylammonium ions, dipropylammonium ions, and propionaldehyde were reduced to approximately 65, 10, and 5%, respectively. About 25% of the original amine nitrogen was recovered as nitrogen gas. A significant and variable yield of nonvolatile, presumably polymeric material, was formed.

In addition to tripropylamine, a number of other tertiary amines was examined. The results, presented in Table III, are generally comparable with those obtained for tripropylamine. The exceptions are trimethylamine, for which no dealkylation was observed, and triallylamine, which formed an insoluble deposit on the anode that prevented the reaction from going to completion.

In addition to acetonitrile, methanol, water, dimethyl

TABLE I

PRODUCTS OF OXIDATION OF TRIPROPYLAMINE IN ACETONITRILE

Potential[a]	n	% Pr_3NH^+[b]	% $Pr_2NH_2^+$[b]	% EtCHO[b]	O_2 present	Anode
1.00	0.82	65	15		Yes	Pt
1.90	0.999	70	Present[c]		Yes	Pt
0.50	0.976	70	22	15	No[d]	Pt
0.55	0.965	74	22		No	Pt
0.55[e]	0.973	68	20		No	Pt
0.55[f]	0.980	72	22		No	Pt
0.55[g]	0.960	71	22		No	Pt
0.80	0.85	71	26	27	Yes	Graphite
1.00[h]	0.97	77	33	15	Yes	Pt
1.00[h]	1.05	87	10	15	Yes	Pt
1.00[h]	0.80	54	53	48	Yes	Pt
1.00[i]	0.68				Yes	Pt
1.00[j]	0				Yes	Pt
1.00[k]	0.81, 0.77				Yes	Pt
1.20[l]	0				Yes	Pt
1.00[m]	0.85				Yes	Pt
1.00[n]	0.83, 0.90				Yes	Pt
0.60[o]	0.98	70	17	c	No	Pt
0.40	0.85	58	26	27	Yes[p]	Graphite
0.50	0.84				Yes[q]	Graphite

[a] Volts *vs.* $Ag/AgNO_3$ (0.10 *M*). [b] Mole per cent of starting amine. [c] Qualitatively detected by glpc. [d] Solutions degassed. [e] Reaction at 0°. [f] Reaction at 25°. [g] Reaction at 50°. [h] Solvent, 10% water. [i] $Ca(ClO_4)_2$ (0.10 *M*). [j] $Mg(ClO_4)_2$ (0.10 *M*). [k] Et_4NClO_4. [l] $Pb(ClO_4)_2$ (0.10 *M*). [m] $KClO_4$ (0.05 *M*). [n] $AgNO_3$ (0.2 *M*). [o] Me_4NBF_4. [p] $HCONPr_2$ (2%). [q] $HCONPr_2$ (5%).

TABLE II

TRIPROPYLAMINE OXIDATION PRODUCTS IN DRY ACETONITRILE

Potential	n	% Pr_3NH^+ [b]	% $Pr_2NH_2^+$ [b]	% EtCHO[b]	% H_2O[b]	% N_2[b]	Anode
0.50	0.86	65	11		0.7		Pt
1.25	0.82	61	13	7	0.7		Pt
0.80	0.96				5.1	25	Pt
0.80	1.00				[c]	9	Pt
0.80	0.91				c		Graphite

[a] Volts *vs.* $Ag/AgNO_3$ (0.10 *M*). [b] Mole per cent of starting amine. [c] Less than 5%.

TABLE III

OXIDATION PRODUCTS OF OTHER AMINES IN ACETONITRILE

Compound	Potential[a]	n	% tertiary[b]	% secondary[b]	% aldehyde[b]
Dicyclohexylethylamine	1.00	0.97	38	22,[c] 2.5[d]	[e]
Cyclohexyldiethylamine	1.00	0.76	50	22,[d] 1[f]	[e]
	1.00[g]		37	9,[d] 1[f]	6[h]
Tribenzylamine	1.31	0.94	69	25	36
Tri-*n*-butylamine	1.20	0.95	62	20	16
Trimethylamine	0.70		98	0	0
	0.80		100	0	0
	1.00[i]		56	0	0
Allyldiethylamine	1.00	0.87	57	18[f]	
N-Methyldibenzylamine	0.90	0.87	60	24	34[j]
N,N-Dimethylbenzylamine	0.80	0.65[k]	51	11,[l] 11[m]	16[n]
Ethyldiisopropylamine	0.85	0.89	62	22[o]	[p]
Di-*n*-propylamine	1.40[i]	0.89		70[q]	
	1.30	0.88		61	0
	1.30	0.90		68	0

[a] Volts *vs.* $AgNO_3$ (0.10 *M*). [b] Mole per cent of starting amine. [c] Dicyclohexylamine. [d] Cyclohexylethylamine. [e] Acetaldehyde present. [f] Diethylamine. [g] Approximately same number of moles of water and amine. [h] Acetaldehyde. [i] Water content 5 mol % of amine. [j] Benzaldehyde. [k] Precipitate formed when sample added. [l] Methylbenzylamine. [m] Dimethylamine, estimated from benzaldehyde recovery. [n] Benzaldehyde and formaldehyde present. [o] Diisopropylamine. [p] Acetaldehyde present, acetone absent. [q] N_2 (22%) recovered; $PrNH_2$ shown to be present.

TABLE IV

PRODUCTS FROM REACTIONS IN SOLVENTS OTHER THAN ACETONITRILE

Compound	Solvent	Potential, V	n	% tertiary[a]	% secondary[a]	% aldehyde[c]
Tripropylamine	30% EtOH–H_2O[b]	1.00[c]	0.85	72	18	
	Tetrahydrofuran[b]	1.00[d]	0.69	70	10	10
	Dimethyl sulfoxide[b]	0.80[e]	0.95	80	0	
Triethylamine	Water[f]	0.88[g]	0.93	50	35	20
	Water[f]	1.00[g]	0.98	47	27	28
	Water[f]	1.00[g]		54	40	44
N-Methyldibenzylamine	Methanol[b]	0.50[h]		61	18[i]	[j]
Tripropylamine	Dimethoxyethane[b,k]	0.80[l]	1.06	65	10[m]	
Triallylamine	Water		0.93	93		

[a] Mole per cent of starting amine. [b] Pt anode. [c] Aqueous sce. [d] $Ag/AgNO_3$ (0.10 *M*)–MeCN/$NaClO_4$ (0.05 *M*)–THF. [e] $Ag/AgNO_3$ (0.10 *M*)–MeCN/$NaClO_4$ (0.25 *M*)–DMSO. [f] Graphite anode. [g] $Ag/AgNO_3$ (0.10 *M*)–MeCN/$NaClO_4$ (0.25 *M*)–H_2O. [h] $Ag/AgNO_3$ (0.10 *M*)–MeOH. [i] Dibenzylamine plus a small yield of N-methylbenzylamine. [j] Small amount of benzaldehyde present. [k] Water content 5 mol % of starting amine. [l] $Ag/AgClO_4$ (0.005 *M*)–DME. [m] Also recovered 24% N_2.

sulfoxide, and dimethoxyethane were used as solvents. Results are presented in Table IV. In general, the products of amine oxidation are not greatly affected by changes in solvent. One point of difference was that there appeared to be no dealkylation when the reaction was run in dimethyl sulfoxide. Reactions run in water showed widely varying yields from one experiment to the next.

The behavior of dipropylamine was investigated in acetonitrile, both with and without precautions concerning water content. In either case, the *n* value was 0.90 and about 70% of starting amine was recovered as dipropylammonium ion. In dry electrolyses, nitrogen gas and propylamine were also detected. They were produced in variable amounts. Probably the water content, the exact potential setting used, and the duration of the experiment caused the variations noted.

Discussion

General Reaction Scheme.—In considering a reaction scheme for the model compound, salient points from the experimental results that must be accommodated include involvement of the nitrogen atom in the initial electron transfer, which is rate determining; formation of secondary amine, aldehyde, and protons; and the coulometric *n* of 0.97 electrons per molecule of amine taken. The steps outlined in eq 1–6 are suggested. These provide for an initial transfer of one electron to the anode to form a cation radical **1** which is probably very short lived, losing a proton to leave the neutral radical **2**. This can either undergo

$$(C_3H_7)_3N \xrightarrow{-e^-} \underset{\mathbf{1}}{(C_3H_7)_3N\cdot^+} \qquad (1)$$

$$1 \xrightarrow{-H^+} (C_3H_7)_2\ddot{N}\dot{C}HC_2H_5 \quad \mathbf{2} \qquad (2)$$

$$\mathbf{2} \xrightarrow{-e^-} (C_3H_7)_2\ddot{N}\overset{+}{C}HC_2H_5 \longleftrightarrow (C_3H_7)_2\overset{+}{N}{=}CHC_2H_5 \quad \mathbf{3} \qquad (3)$$

$$\mathbf{2} \longrightarrow (C_3H_7)_3N + (C_3H_7)_2\ddot{N}CH{=}CHCH_3 \quad \mathbf{4} \qquad (4)$$

$$\mathbf{3} + H_2O \longrightarrow (C_3H_7)_2NH + C_2H_5CHO + H^+ \qquad (5)$$

$$\mathbf{4} + H_2O \longrightarrow (C_3H_7)_2NH + C_2H_5CHO \qquad (6)$$

further anodic oxidation in step 3 or can disproportionate in step 4. The possibility of **2** undergoing dimerization or reaction with the solvent or with water was considered. The data in Table I show that about 90% of the starting amine has been recovered as protonated secondary and tertiary amines, making it impossible for dimerization to be an important process when some water is present. No evidence of dimerized products was found, even in small amounts. The role of water is discussed below. Both reaction paths, disproportionation or direct oxidation of radical **2**, give the same coulometric results and produce the same products.

Since the amines are the strongest bases in the system, they are protonated as the reaction proceeds. It is possible that the secondary amine is protonated as it is formed; another possibility is that it may undergo further reaction at the anode before being protonated. If it is protonated as it is formed, the over-all reaction is given in eq 7. This makes n equal to 1.000 and

$$2(C_3H_7)_3N + H_2O \xrightarrow{-2e^-} (C_3H_7)_2NH_2^+ + C_2H_5CHO + (C_3H_7)_3NH^+ \qquad (7)$$

gives 50 mol % each of tripropylammonium salt, dipropylammonium salt, and propionaldehyde, which is not in accordance with experimental results. If it is assumed that a substantial amount of the secondary amine undergoes oxidation before being protonated, as an extreme, all of the protons produced in the initial dealkylation steps would be accepted by unreacted tertiary amine. The over-all reaction would then be that shown in eq 8. According to the stoichiometry of

$$3(C_3H_7)_3N + H_2O \xrightarrow{-2e^-} (C_3H_7)_2NH + C_2H_5CHO + 2(C_3H_7)_3NH^+ \qquad (8)$$

eq 8, the yield of tripropylammonium salt is 67 mol % of the starting amine and neutral dipropylamine is a product. However, it has been ascertained that the recovery of electrolyzed dipropylamine is incomplete, amounting to 70%, with an n value of 0.90 under both wet and dry conditions. If these results are used empirically to modify the stoichiometry of eq 8, the expected recoveries will be 67% tripropylammonium ion, 33% propionaldehyde, and 23% dipropylammonium ion, with an n value of 0.97. Actual experimental results follow: n, 0.97; tripropylammonium salt, 67–72%; dipropylammonium salt, 20–22%; aldehyde, 15%. The experimental values for n and for amine salt recoveries agree reasonably well with the predicted values; that for propionaldehyde is low. This is discussed below.

As an indication that dipropylamine may be undergoing oxidation, as suggested above, the ultraviolet (uv) absorption spectrum of the tripropylamine reaction mixture shows a peak at 320 mμ. A peak at the same wavelength, but five to ten times as intense is observed when dipropylamine is electrolyzed. It is possible that this may be caused by a relatively small yield of a condensation product in the dipropylamine reaction.

Two reactions which, if competitive with the main scheme, would cause reduction of the secondary amine yield and increase in the tertiary amine yield are shown in eq 9 and 10.

$$1 + H_2O \longrightarrow (C_3H_7)_3NH^+ + OH\cdot \qquad (9)$$

$$1 + CH_3CN \longrightarrow (C_3H_7)_3NH^+ + \cdot CH_2CN \qquad (10)$$

The possibility that reaction 9 acts as a major source of protons to such an extent that the mechanism consists of steps 1, 2, and 9 in parallel with steps 1, 2, and 3 was considered. This would involve formation of significant amounts of hydroxyl radicals which presumably would form hydrogen peroxide. It was ascertained that these concentrations of hydrogen peroxide could be detected by cyclic voltammetry and were in fact absent at the end of an electrolysis. Oxygen gas, though detectable in much smaller quantities than would be produced by this scheme, was entirely absent. Similarly, there was no indication of tripropylamine oxide in significant quantities. However, we cannot exclude the possibility that this reaction occurred to a small extent. Reaction 10 like reaction 9 could be a major source of protons; however, it would lead to products characteristic of cyanomethylene radicals. In the anodic oxidation of amides,[4] succinonitrile was produced and attributed to dimerization of cyanomethylene radicals. It was sought in the products of all amine reactions examined, but was found only in the case of triallylamine oxidation. To achieve a significant reaction of triallylamine, it was necessary to operate at such high potentials that the solvent and perchlorate may have been involved in the reaction. If cyanomethylene radicals dimerize head to tail, the resulting ketenimine would be expected to be found ultimately as an amide. With oxygen excluded, no amide could be detected by infrared (ir) spectroscopy.

When yields derived from the reaction scheme are compared with experimental results, the major discrepancy is in the aldehyde recovery. Several factors may be operating. Although aldehyde in acetonitrile is unreactive at a platinum anode, the yields have been consistently smaller at platinum than at graphite. This may be caused by an electrocatalytic oxidation of aldehyde in the presence of small amounts of water. Such an oxidation would have no effect on the coulometric results, since the process of generating platinum oxide to react with aldehyde also produces protons which would make an equivalent amount of starting amine unreactive. In addition to electrocatalytic reaction of aldehyde, it is probable that condensation in the basic reaction solution occurs. We suggest that both these factors are important.

Throughout the discussion, it has been assumed that a sufficient supply of water was available to react as indicated and that it did in fact serve as the source of oxygen in the dealkylation. Other possible oxygen sources are dissolved oxygen and the perchlorate-supporting electrolyte. To determine the effect of

dissolved oxygen, reactions were run with oxygen gas deliberately introduced. The result was a decrease in the value of n to 0.75 and a decrease in the recovery of tripropylammonium salt. N,N-Dipropylformamide was isolated from these reaction mixtures. This is presumed to be the result of reaction of oxygen with **2**, the product of step 2. Both manganese dioxide[12] and ozone[13] have been found to produce N,N-dialkylformamides from tertiary amines. An amino alcohol, indicated in eq 11 with tri-*n*-butylamine, was a suggested

$$(C_4H_9)_3N \xrightarrow[MnO_2]{O_2 \text{ or}} (C_4H_9)_2NCH(OH)C_3H_7 \longrightarrow HCON(C_4H_9)_2 + C_2H_5CHO \quad (11)$$

intermediate. With dissolved oxygen excluded in electrochemical reactions, no formamide is formed, but dealkylation, leading to aldehyde, does take place. Oxygen was routinely excluded from most reactions run in the course of this work. The possibility that perchlorate serves as an oxygen source was checked by substituting tetramethylammonium tetrafluoroborate for sodium perchlorate. The reaction products were not significantly changed, showing that perchlorate is not involved and indicating that water, the only reasonable remaining source of oxygen, is responsible.

The influence of water was investigated by performing reactions in systems on which extraordinary precautions were taken to exclude water. It was possible to reduce the amount of water in a reaction mixture to less than 5 mol % of starting amine. When this was done, it had a very noticeable effect on the reaction. Yields of tripropylammonium salt, dipropylammonium salt, and aldehyde were reduced. A significant fraction of amine nitrogen was recovered as gaseous nitrogen. Unlike "wet" reactions, a significant and variable fraction of the hydrocarbon portion of starting amine was recovered as a nonvolatile, presumably polymeric, material.

We interpret this to indicate that water is involved in reactions from which it is not rigorously excluded, that, if it were quantitatively excluded, a different reaction would occur. Recovery of reduced yields of secondary amine and very much reduced yields of aldehyde is thought to indicate that reactions 5 and 6 are being substantially blocked by the limited availability of water.

Although no exhaustive study of the dry reaction has been undertaken, some observations will be offered. The reaction in the absence of water caused degradation to form elemental nitrogen and a polymeric material, which suggests that a complex fragmentation process may take place. The possibility that the solvent might be involved was investigated by performing the reaction in rigorously dry dimethoxyethane. The results, given in Table IV, were quite similar to those obtained in acetonitrile, indicating that amine, rather than the solvent, is the probable source of nitrogen when the reaction is run in acetonitrile.

In the absence of water, it is difficult to suggest a plausible dealkylation mechanism, especially one that yields elemental nitrogen. Presumably, reactions 1–4 would be unaffected by removal of water. However, if this occurs, **3** would probably not be subject to further reaction, but would be present in the reaction products until the cell was opened, after which the remaining step of reaction 5 would occur. Examination of the products shows that this is not the case. With water excluded, reactions 1, 2, and 4 would produce **4**. The enamine, a weaker base than the corresponding saturated compound, would be oxidized, although probably at a smaller rate than that of the saturated amine. The product of this reaction apparently is subject to fragmentation, possibly resulting in formation of radical intermediates with the unshared electron on the nitrogen atom. Dimerization of this radical would produce a substituted hydrazine, which could be expected to be degraded to elemental nitrogen by anodic oxidation.[16]

Unsymmetrical Amines.—Results of oxidation of trialkylamines, presented in Table III, are generally similar to those for tripropylamine; however, examination of the products of oxidation of unsymmetrically substituted amines shows that dealkylation is not a random process. Cyclohexyldiethylamine, dicyclohexylethylamine, and ethyldisopropylamine lose mainly the ethyl group. N,N-Dimethylbenzylamine and N-methyldibenzylamine lose more of the benzyl groups than would be expected on a statistical basis. Allyldiethylamine loses mainly the allyl group.

Considering the reaction scheme presented, the N-methylbenzylamines would react through steps similar to 1, 2, 3, and 5, since an enamine is impossible. It is reasonable to expect that the benzyl group would be lost in preference to the methyl group, because the greater stability of the benzylic radical would tend to cause its formation to be favored. The same argument can be applied to the case of allyldiethylamine. In these examples, experimental results are in accord with the expected stabilities of the radicals.

This is not true, however, for the examples involving cyclohexyl or isopropyl groups. Preferential loss of these groups because of the greater stability of the corresponding tertiary radical, compared with a secondary radical, would be expected, but the reverse is observed. In these cases, the additional possibility of reaction *via* the enamine in steps 1, 2, 4, and 6 exists; on the basis of information presently available, a definite distinction cannot be made. From the voltammetric data,[3] it would appear that step 1 is rate determining. Therefore it is possible that sequences involving either steps 2 and 3 or steps 2 and 4 could occur so rapidly as to constitute a concerted process. In that event, it is possible that formation of the more stable tertiary radical, corresponding to **2** in eq 2, in a concerted process involving its disproportionation, results in a slower over-all rate for the sequence than when the less stable secondary radical is formed. The higher rate of the sequence involving the less stable radical would lead to the observed product. A similar rationale can be offered for the sequence 2–3, if it is postulated that the less stable radical would be oxidized more readily than the more stable radical. The observed products might also be accounted for by postulating that, for a concerted process involving steps 2 and 3, the necessity for planarity at the iminium group would favor its formation in the ethyl group rather than in the cyclohexyl or the isopropyl groups.

In considering the two proposed schemes, oxidation of

(16) D. M. King and A. J. Bard, *J. Amer. Chem. Soc.*, **87**, 419 (1965).

the radical (steps 1, 2, 3, and 5) and disproportionation to the enamine (steps 1, 2, 4, and 6), it is interesting to note that one compound examined, trimethylamine, although oxidized at the anode, did not undergo dealkylation. Trimethylamine is also one of the compounds for which enamine formation is impossible. Other compounds studied, the benzylmethylamines, are similarly incapable of forming enamines, but did undergo dealkylation. However, these compounds can react *via* the notably stable benzyl radical intermediate. This suggests that enamine formation is involved in dealkylation of simple aliphatic amines.

Experimental Section

Experimental Apparatus.—Electrolyses were performed with a conventional electronic potentiostat; current was integrated with a gas coulometer. H-type electrolysis cells fitted with ground joints to permit exclusion of atmospheric contamination were used. Unless otherwise noted, the reference electrode was a silver wire in contact with a 0.10 *M* $AgNO_3$ solution in acetonitrile which made contact, *via* an asbestos fiber sealed into Pyrex, with a solution of the supporting electrolyte in a guard tube which was similarly in contact with the solution in the anode compartment. Potentials are expressed relative to the reference electrode actually used, in all cases.

Reagents.—Tripropylamine was treated with benzoyl chloride, distilled under reduced pressure and stored over NaOH. No impurities were initially detectable by glpc. At the end of the work, this sample still assayed more than 98% pure. Other amines were the best grade available, generally with less than 2% impurities.

Acetonitrile was prepared by the procedure previously described.[17] Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride immediately before use and were protected from atmospheric contamination. Reagent grade dimethyl sulfoxide was distilled under reduced pressure.

Sodium perchlorate was recrystallized from ethanol–water, dried under vacuum at 150°, and stored under vacuum over P_2O_5. Other reagents were reagent grade, generally used as received.

(17) J. F. O'Donnell, J. T. Ayres, and C. K. Mann, *Anal. Chem.*, **37**, 1161 (1965).

Electrolysis Procedure.—Supporting electrolyte and solvent were mixed in a reservoir fitted with joints to attach to the electrolysis cell and with tubulation to attach to a vacuum line. Solutions were degassed by, typically, three sequences of freezing and pumping with a mechanical pump. They were stored under an atmosphere of purified nitrogen or helium. Electrolysis cells were filled from the reservoir without contact with the atmosphere. Preelectrolysis was run at a potential about 0.1 V more anodic than that used for the reaction. Preelectrolysis typically involved less than 1% of the coulombs taken by the subsequent reaction. Electrolyses were carried on until no further decrease in current was noted. This required from 1 to 3 hr; residual currents were typically 0.2–0.5% of starting currents.

Reactant was introduced by syringe after preelectrolysis and samples of solutions and head space were similarly taken for analysis. Reaction currents were often recorded automatically. Reaction concentrations were generally in the range of 5–50 m*M*; supporting electrolyte concentration was in the range of 0.10–0.25 *M*.

Removal of Water.—Acetonitrile was dried by percolation through a 0.5 in. × 1 m bed of 3A molecular sieves directly into the solvent reservoir. All glassware was baked at 150° under vacuum prior to use. Supporting electrolyte was transferred to the reservoir, after which it was evacuated and held at 200° for several hours. By this process, water assays of the anode solution when the reaction was being run would reliably be down to 0.25 m*M*. Water assay in acetonitrile was done by glpc on Porapak Q at 175°.

Product Analyses.—Amines were generally determined by shaking the reaction mixture with NaOH and chromatographing as previously described.[18] Succinonitrile and N,N-dipropylformamide were similarly chromatographed. In all cases, unknowns were compared with valid samples. In some cases, uv absorption spectra of the volatile fraction of reaction products was used as a means of quantitative analysis for aldehydes. Nuclear magnetic resonance spectra were taken in CCl_4, CD_3CN, or $CDCl_3$ solutions, or neat, using a Varian A-60 spectrometer.

Registry No.—Tripropylamine, 102-69-2.

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(18) J. F. O'Donnell and C. K. Mann, *ibid.*, **36**, 2097 (1964).

Stable Carbonium Ions. LXXV.[1] Protonated Thiocarboxylic Acids, S-Alkyl Esters, and Their Cleavage in Fluorosulfonic Acid–Antimony Pentafluoride Solution. Thio Analogs of Protonated Carbonic Acid

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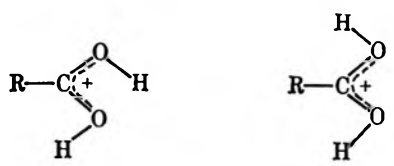
Thiocarboxylic acids were protonated in fluorosulfonic acid–antimony pentafluoride solution. Three isomers of protonated thioacids were found and identified by nmr spectroscopy. The rates of cleavage to oxocarbonium ions and H_3S^+ were compared with the corresponding rates of the oxygen analogs and the results are discussed in terms of the mechanism of the reaction. The protonation of a series of thioacid esters and the rates and mechanism of their cleavage was also investigated. Primary and secondary S-alkyl thioacetates cleave *via* acyl–sulfur fission, whereas alkyl–sulfur fission was found for S-*t*-alkyl thioacetates. Only S-*t*-alkyl thioformates could be cleaved in the acid system yielding *t*-alkylcarbonium ions and protonated thioformic acid. The generation of the sulfur analogs of protonated carbonic acid is also described.

A number of reports have appeared concerning the protonation of carboxylic acids in super acid systems.[3-9] In the case of both formic and acetic acids the existence of two isomers have been shown (I and II), the evidence for the assignments of these structures being based on the coupling constants between the methine and hydroxyl protons in protonated formic acid.[8]

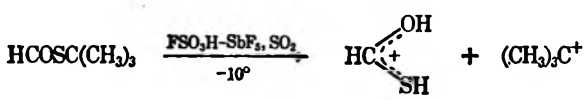


I II

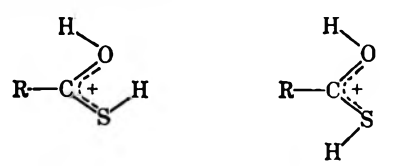
Isomer I is the predominant species in both of these systems, and in protonation of higher homologs isomer II is not found. Our continued interest in cations of this type led us to study the protonation of thiocarboxylic acids. In addition we have compared the rates of cleavage of protonated thioacids and their S-alkyl esters with the rates of cleavage of their oxygen analogs and present data which enables some conclusions to be drawn regarding the mechanism of these cleavage reactions. Owing to the biological importance of thioesters, particularly in enzymatic catalysis, we felt it of particular interest to study the mechanism and cleavage of thio esters.

Results and Discussion

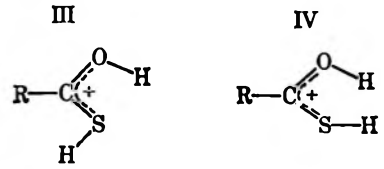
Protonated Thio Acids.—Protonated thioformic acid was generated by cleavage of S-*t*-butyl thioformate (*vide infra*) in 1:1 molar HSO_3F–SbF_5 solution containing an equal volume of SO_2 as diluent. The



100-MHz nmr spectrum at −70° (Figure 1) showed OH absorptions between δ 13.0 and 14.0, SH absorptions between δ 7.0 and 7.4, and methine proton absorptions between δ 10.0 and 10.5. The latter were almost completely obscured by the acid solvent peak at δ 10.25. Analysis of the spectrum was achieved with the aid of double-irradiation experiments and showed the presence of three isomers. The spectral parameters found for the isomers are summarized in Table I. In only one isomer (IV) was coupling between the SH and OH protons found (3.0 Hz). This provides strong evidence that in this isomer both the SH and OH protons are *cis* to the methine proton (IV, R = H) since of the four possible isomers (III–VI, R = H) this is the only one in which a favorable planar W coupling path exists between these protons. Such a configuration is known to lead to coupling constants of the same order of magnitude through both sp^3- and sp^2-hybridized centers.[10] The two *cis* couplings with the methine proton in this isomer are larger than those found in protonated formic acid (3.5 Hz)[8] and have values closer to those for *cis*-HCOH couplings found in protonated aldehydes (8.5–9.0 Hz).[11] The other two isomers each have two vicinal couplings, one small and one large. The larger coupling indicates a *trans* relationship between the methine and hydroxyl or thiol proton and the smaller coupling constant a *cis* relationship. On this basis, the isomers are assigned as shown (R = H), the isomer distribution being 60:30:10 for III, IV, and V, respectively. No evidence for isomer VI was found for protonated thioformic acid.



III IV



V VI

Protonated thioacetic acid, at −60° gave an nmr spectrum (Figure 2) having three methyl peaks at

(1) Part LXXIV: G. A. Olah, D. H. O'Brien, and C. Y. Lui, *J. Amer. Chem. Soc.*, **91**, 701 (1969).

(2) (a) National Institutes of Health Predoctoral Research Investigator, 1967–1968; (b) National Institutes of Health Postdoctoral Research Investigator, 1967–1968.

(3) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **43**, 1045 (1965).

(4) H. Hogeveen, A. F. Bickel, C. W. Hilbers, E. L. Mackor, and C. Maclean, *Chem. Commun.*, 898 (1966).

(5) H. Hageveen, *et al.*, *Rec. Trav. Chim. Pays-Bas*, **86**, 687 (1967).

(6) H. Hogeveen, *ibid.*, **86**, 809 (1967).

(7) M. Brookhart, G. C. Levy, and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1735 (1967).

(8) G. A. Olah and A. M. White, *ibid.*, **89**, 3591 (1967).

(9) G. A. Olah and A. M. White, *ibid.*, **89**, 7072 (1967).

(10) S. Sternhall, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(11) G. A. Olah, D. H. O'Brien, and M. Calin, *J. Amer. Chem. Soc.*, **89**, 3582 (1967).

TABLE I

NMR SPECTRAL PARAMETERS OF PROTONATED THIO ACIDS, $RCOSH_2^+$

Isomer	Rel abundance	Chemical shifts[a] CH₃	CH₂	OH	SH	Coupling constants[b] J_{OH}^3	J_{SH}^3	J^4
R = H[g]								
III	60			13.23	7.33	7.5	13.0	
IV	30			13.47	7.03	8.0	7.5	3.0
V	10			13.86	7.36	16.5	7.0	
R = CH_3[h]								
III	60	3.23[c]		12.97	7.20[d]			
IV	20	3.37		13.17	6.88			3.0
		or						
V	20	3.45		13.45	7.30			
R = CH_3CH_2[i]								
III	70	1.74[e]	3.47[f]	12.65	7.09			
IV	10			12.84	6.86			3.0
V	20			13.43	7.18			

[a] δ in parts per million from external TMS for spectra obtained at −70°. [b] In hertz; J_{OH}^3 and J_{SH}^3 refer to coupling of the methine protons with the OH and SH protons, respectively. J^4 refers to the coupling between the SH and OH protons. [c] Doublet, J = 1 Hz. [d] Quartet, J = 1 Hz. [e] Triplet, J = 7 Hz. [f] Quartet, J = 7 Hz. [g] Registry no.: 19214-46-1. [h] Registry no.: 19214-47-2. [i] Registry no.: 19214-48-3.

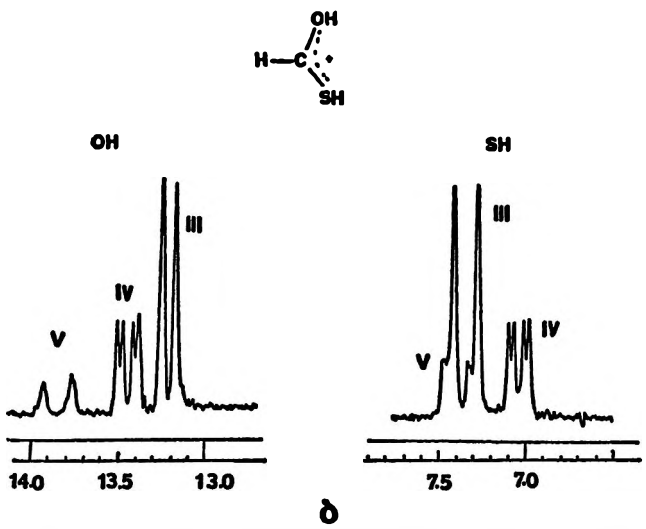


Figure 1.—Nmr spectrum (100 MHz) of protonated thioformic acid in fluorosulfonic acid–antimony pentafluoride–sulfur dioxide solution at −70°. III, IV, and V refer to the isomers assigned in Table I. The region between δ 10.0 and 11.0, where the solvent and methine protons absorb, is not shown.

δ 3.23, 3.37, and 3.45 of relative areas of 3:1:1, indicating, as in the case of thioformic acid, that three isomeric species are present. The pmr spectral parameters are summarized in Table I. The ion having the structure IV is assigned on the basis of the coupling between the SH and OH protons of 3.0 Hz, the reason for this assignment being the same as in the case of the related isomer of protonated thioformic acid. We tentatively assign the other two isomers on the basis of the OH chemical shift and comparison with protonated thioformic acid. With this assignment, isomer III is the most abundant (60%) and IV and V are present in approximately equal amounts (20–20%). One fact appears to contradict the assignment of III and V, and that is the 1-Hz coupling observed between the methyl and the SH protons in the most abundant species. While no corresponding couplings have been observed in protonated acetic acid,[8] protonated aldehydes,[11] and ketones[12] do show a four-bond coupling of about 1 Hz for alkyl groups *cis* to the hydroxyl proton. Using this coupling constant for comparison to assign the isomers is, we feel, less proper than comparison of the chemical shifts, since the π character of the C–O bond in protonated ketones is considerably greater than that of the C–S bond in the present example. As a justification for ignoring this coupling in assigning the spectrum, methyl four-bond coupling through a carbon–carbon double bond is greatest for a *cis* configuration (*cis*-allylic coupling) while for a saturated carbon skeleton a *trans* configuration leads to the largest coupling.[10]

Thiopropionic acid, when protonated in 1:1 HSO_3F–SbF_5–SO_2 solution again shows three isomers. Assigning isomers in an identical manner with that described for protonated thioacetic acid leads to isomer ratios of 70:10:20 for III, IV, and V (R = CH_3CH_2), respectively (see Table I).

Protonated thiobenzoic acid shows only single peaks for the OH and SH protons at δ 12.91 and 6.65. A similar observation was made in the case of protonated benzoic acid and is believed due to a low barrier to rotation about the C–OH bonds[8,9] which cannot be "frozen out" on the nmr time scale in the accessible temperature range studied (−85°).

The isomer ratios observed are relatively independent of the nature of the group R in the series R = H, CH_3, CH_3CH_2, and, furthermore, energetically the three isomers must be very similar. This indicates that steric interaction between the R group and either the proton or lone pairs on sulfur or oxygen is not very significant, although it probably accounts for the reduction in the proportion of isomer IV as the size of R is increased. The preponderance of isomer III over V suggests some hydrogen-bonding interaction between the SH proton on sulfur and the neighboring oxygen in spite of the resultant, unfavorable, four-membered ring. This interaction would be expected to be greater in III than in V since hydrogen bonding to oxygen should be favored over hydrogen bonding to sulfur.

Cleavage of Protonated Thiocarboxylic Acids to Oxocarbonium Ions.—On warming solutions of protonated thio acids in fluorosulfonic acid–antimony pentafluoride

(12) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 3586 (1967).

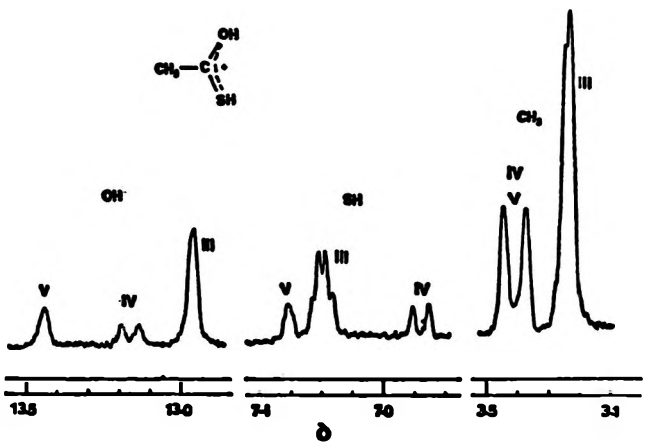
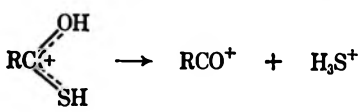


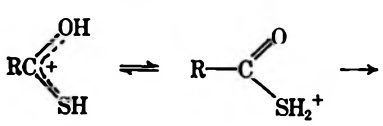
Figure 2.—Nmr spectrum (60 MHz) of protonated thioacetic acid at −60°.

solution to between −10 and 0°, cleavage of the carbon–sulfur bond occurred to give oxocarbonium ions and protonated hydrogen sulfide. Protonated hydrogen



sulfide is unstable under these conditions;[13] however, a small amount of H_3S^+ could be detected in the nmr spectrum as a peak at δ 6.60.

The rates of cleavage of protonated thioacetic and thiopropionic acids to the methyl- and ethyloxocarbonium ions were measured by the method described previously for protonated carboxylic acids[8] and their alkyl esters.[14] The rates were found to be slower than those for the oxygen analogs in both cases by a factor of 50 when compared under the same conditions at 0°.[14] A mechanism which accounts for this rate decrease is one involving a preequilibrium with a sulfur-protonated species (VII).



VII

$$RCO^+ + H_2S \xrightarrow{H^+} H_3S^+$$

Comparing the sulfur and oxygen protonated acids, the concentration of the intermediate VII should be lower in the sulfur case due to the lower basicity of sulfur. The subsequent cleavage of VII should be easier for sulfur owing to the fact that carbon–sulfur bonds are weaker than carbon–oxygen bonds.[15] It has been found, however, that protonated thiols cleave to carbonium ions less easily than do protonated alcohols.[13,16] Since this cleavage is closely related to the present case under discussion this result suggests that the cleavage of VII should be slower for sulfur than for the oxygen analog. This rate difference, in seeming contradiction to the bond strength order, may be due to interaction with a second proton in the transition state of this cleavage reaction, the interaction being greater for oxygen than for sulfur.

$$RSH_2^+ \longrightarrow R^+ + H_2S \xrightarrow{H^+} H_3S^+$$

In an earlier paper we discussed the mechanism of the cleavage of protonated esters and concluded that we could not distinguish between the preequilibrium mechanism and a four-center mechanism.[14] In the present study of the cleavage of protonated thio acids and thio esters the results still do not allow this distinction to be made since the difference between these two mechanisms lies in whether VII and X (see subsequent discussion) is an intermediate or a transition state. While we favor the preequilibrium mechanism, verification of this must await detection of VII; so far, this has not been accomplished.

Protonated S-Alkyl Thio esters.—Details of the nmr spectra obtained for solutions of a series of S-alkyl thioformates and thioacetates in 4:1 molar FSO_3H–SbF_5 diluted with SO_2 [17] are given in Tables II and III. In both series, carbonyl protonation was observed, the OH proton appearing between δ 12.6 and 12.8 (Figure 3).

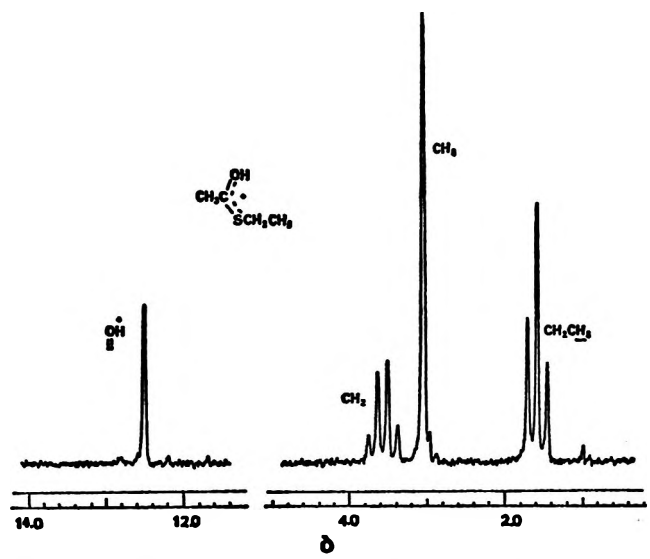
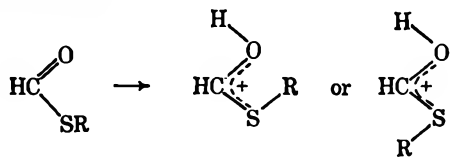


Figure 3.—Nmr spectrum (60 MHz) of protonated S-ethyl thioacetate at −60°.

In the thioformate series, the OH proton appeared as a doublet coupled by 8 Hz to the methine proton, the latter appearing at δ 10.2. Within the limits of the sensitivity of the nmr method, only a single isomeric species could be detected in all the thioesters studied. The magnitude of the coupling observed in the thioformate series shows that the OH and methine proton must have a *cis* relationship to each other and therefore the isomer observed must be either VIII or IX.



VIII IX

(13) G. A. Olah, D. H. O'Brien, and C. U. Pittman, Jr., *ibid.*, **89**, 2996 (1967).

(14) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5494 (1967).

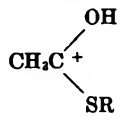
(15) The acid-catalyzed bimolecular hydrolysis of thioacetic acid has been shown to proceed slower than the oxygen analog by a factor of *ca.* 10: J. Hipkin and D. P. N. Satchell, *Tetrahedron*, **21**, 835 (1965).

(16) G. A. Olah, E. Namanworth, and J. Sommer, *J. Amer. Chem. Soc.*, **89**, 3576 (1967).

(17) A 4:1 molar concentration of FSO_3H–SbF_5 was used in preference to the 1:1 molar acid since, in the latter solution, spectra were less well resolved particularly at higher temperatures. The spectra obtained in both acids were (in other respects) identical.

TABLE II

NMR SPECTRAL PARAMETERS FOR PROTONATED THIOACETATES[a] AT −60°

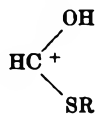


		Nmr			
				R	
R	Registry no.	OH	CH_3 (acetyl)	CH_3	CH_2 and CH
CH_3	19227-67-9	12.75	3.10	3.03	
CH_3CH_2	19214-49-4	12.70	3.12	1.66, t (8.0)	3.65, q
$(CH_3)_2CH$	19214-50-7	12.68	3.05	1.63, d (7.5)	4.46, m
$(CH_3)_3C$	19214-51-8	12.73	3.00	1.80	

[a] Chemical shifts in parts per million from external TMS. Coupling constants in hertz are given in parentheses following the multiplicities: d = doublet, *t* = triplet, q = quartet, m = multiplet.

TABLE III

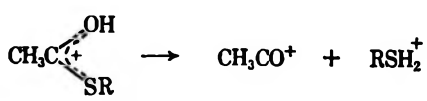
NMR SPECTRAL PARAMETERS FOR PROTONATED THIOFORMATES[a]



			Nmr			
					R	
R	Registry no.	Temp, °C	OH	CH (formyl)	CH_3	CH_2 and CH
$CH_3(CH_2)_2$	19214-52-9	−60	12.78, d (7.7)	10.23, d	1.23, t (7.0)	2.06, m; 3.68, t (7.0)
$(CH_3)_2CH$	19214-53-0	−60	12.75, d (7.7)	10.16, d	1.67, d (7.0)	4.53, m
$(CH_3)_3C$	19214-54-1	−70	12.82, d (8.0)	10.16, d	1.90	

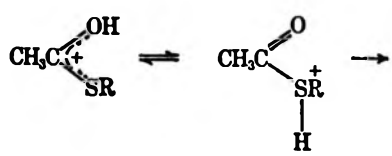
[a] Chemical shifts in parts per million from external TMS. Coupling constants in hertz are given in parentheses following the multiplicities: d = doublet, t = triplet, q = quartet, m = multiplet.

On raising the temperature of solutions of protonated S-alkyl thioacetates to between −20 and 10°, methyl, ethyl, isopropyl, isobutyl, and *sec*-butyl thioacetates underwent acyl–sulfur cleavage giving the methyloxocarbonium ion and the corresponding thiol, the nmr spectra of which have been reported previously[13] (Figure 4).

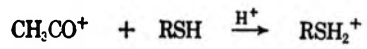


The rates of this reaction were measured by following the disappearance of the nmr signals of the protonated thioacetate and appearance of that of the methyloxocarbonium ion. In all cases the reaction was first order in protonated thioacetate and went to completion. First-order rate constants determined in 4:1 molar FSO_3H–SbF_5 and at 5.5° are reported in Table IV.

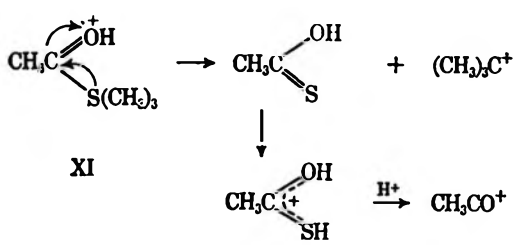
The small increase in the first-order rate constants found in the series, methyl, ethyl, and isopropyl thioacetate is consistent with a mechanism analogous to that proposed for the cleavage of thio acids. Changing the electronic properties of the group R should affect the concentration of the S-protonated intermediate X and the rate of its cleavage in opposite senses, the over-all effect on the observed rate being small.



X



In contrast to the behavior of these thioacetates, *t*-butyl thioacetate underwent alkyl–sulfur cleavage. At −45° the formation of *t*-butyl cation and protonated thioacetic acid could be observed. At higher temperatures, the protonated thioacetic acid undergoes further reaction and *t*-butyl cation and the methyloxocarbonium ion are the observed products.



XI

At 5.5° protonated S-methyl thioacetate reacts at half the rate of protonated methyl acetate, reaction in both cases involving cleavage of the acyl group. The rate of alkyl cleavage of protonated S-*t*-butyl thioacetate, on the other hand, is considerably slower than the corresponding rate for *t*-butyl acetate. The latter reaction

TABLE IV

FIRST-ORDER RATE CONSTANTS FOR THE CLEAVAGE OF THIOACETATES IN 4:1 MOLAR FSO_3H–SbF_5 SOLUTION AT 5.5°

Thioacetate	$K_1 \times 10^4$
S-Methyl	0.63
S-Ethyl	1.46
S-Isopropyl	1.63
S-*t*-Butyl	4.20

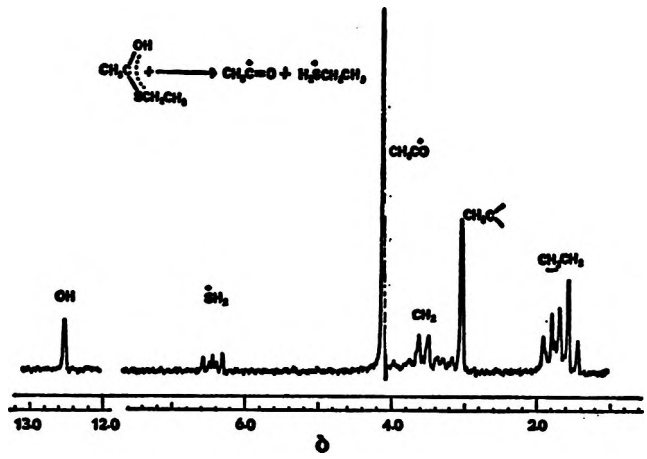
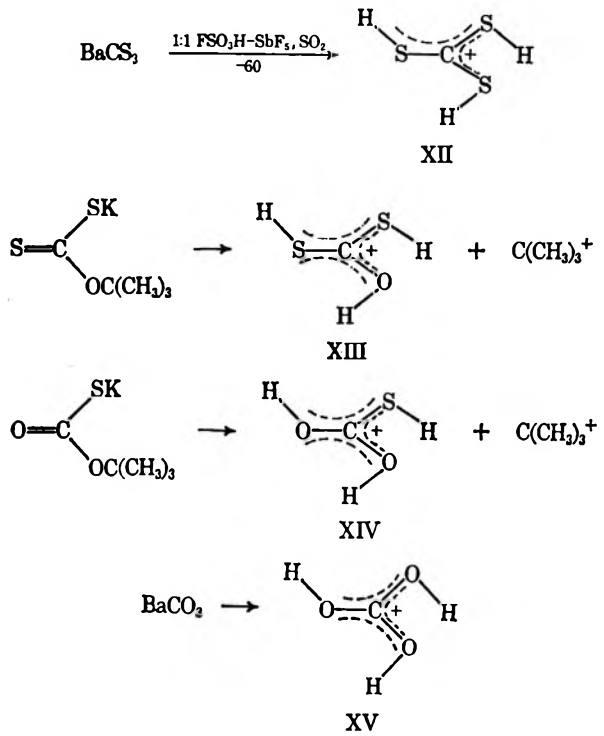


Figure 4.—Nmr spectrum (60 MHz) of protonated S-ethyl thioacetate at −60° after partial acyl–sulfur cleavage at −10°.

occurs immediately on protonation of the ester at −78°, whereas the rate of fission of protonated S-*t*-butyl acetate has a half-life of 15 min at 0°.[14] The considerably enhanced rate of cleavage of protonated *t*-butyl acetate is understandable due to the fact that in the protonated ester a much greater degree of positive charge character is associated with the alkoxy oxygen than is associated with the sulfur in the protonated thio ester. The loss of *t*-butyl cation will thus be greatly facilitated in the case of *t*-butyl acetate compared with the sulfur analog. The result suggests that, whereas the acyl–sulfur cleavage proceeds *via* an S-protonated intermediate X, alkyl–sulfur cleavage occurs directly through the O-protonated species XI, as indicated in the reaction scheme. It is of interest that studies of the acid-catalyzed bimolecular hydrolysis of thioacetates in aqueous acetone[18] have shown that S-*t*-butyl thioacetate, under these conditions, undergoes acyl–sulfur cleavage and, to observe alkyl–sulfur cleavage, the alkyl group has to be a potentially more stable carbonium ion such as triphenylmethyl.

Of the protonated thioformates studied only the *t*-butyl ester underwent cleavage giving the *t*-butyl cation and protonated thioformic acid at −10°. Neither the *n*-butyl or isopropyl esters could be cleaved, even when solutions of the protonated esters were heated to temperatures as high as 100°. This result demonstrates the stability of the methyl oxocarbonium ion compared with the formyl cation.[19]

Thiol Analogs of Protonated Carbonic Acid.—Protonated carbonic acid (trihydroxycarbonium ion) (XV) has been generated in 1:1 FSO_3H–SbF_5 solution at low temperatures.[20] In connection with this present study of the behavior of thiocarboxylic acids and their esters in super acid solutions, we also observed the formation of mono-, di-, and trithiol analogs of protonated carbonic acid. Protonated trithiocarbonic acid (XII) was formed in solutions of barium trithiocarbonate in 1:1 molar FSO_3H–SbF_5– with SO_2 at low temperature (−60°). Protonated dithiocarbonic acid (XIII) was generated under the same conditions from potassium *t*-butylxanthate and protonated thiocarbonic acid (XIV) from O-*t*-butyl S-potassium thiocarbonate.



It was found that generation of XIII and XIV by the routes indicated led mainly to ions XII and XV, XIV being present only to the extent of about 10% at −60°. It proved impossible to generate the ions at a lower temperature owing to the insolubility of the precursors, and the mechanism of this dissociation has not been established. It is possible that the reaction involves transient formation of protonated carbon dioxide, carbonyl sulfide, or carbon disulfide and this possibility is currently being further investigated.

The nmr shifts found for the OH and SH protons in protonated thiocarbonic acids are summarized in Table V. The increased deshielding of both the OH and SH protons as the number of thiol groups in the ion is increased is consistent with the lesser ability of sulfur compared with oxygen to delocalize the positive charge on the central carbon atom.

TABLE V
CHEMICAL SHIFTS OF THE THIOL ANALOGS OF PROTONATED CARBONIC ACID[a]

	Registry no.	OH	SH
$C(OH)_3^+$	19227-68-0	11.55	
$C(OH)_2SH^+$	19214-55-2	11.99	6.73
$C(SH)_2OH^+$	19214-56-3	12.56	7.19
$C(SH)_3^+$	19214-57-4		7.66

[a] In external TMS at −60°. All peaks observed were sharp singlets

Experimental Section

Materials.—The thio acids used were commercially available reagents and were purified before use by repeated fractional distillation under reduced pressure. Thioacetates were prepared by the reaction of the appropriate mercaptan with either acetyl chloride or with acetic anhydride and sodium acetate.[21] The

(18) (a) P. N. Rylander and D. S. Tarbell, *J. Amer. Chem. Soc.*, **72**, 3021 (1950); (b) B. K. Morse and D. S. Tarbell, *ibid.*, **74**, 416 (1952).

(19) Some evidence for the formyl cation, CHO^+, was obtained in SbF_5–SO_2 solution of formyl fluoride at −70° showing a single nmr peak at δ 15.8 The formyl ion is an unstable species, cleaving even at this temperature with evolution of carbon monoxide.

(20) G. A. Olah and A. M. White, *ibid.*, **90**, 1884 (1968).

(21) F. W. Wenzel, Jr., and E. E. Reid, *ibid.*, **59**, 1089 (1937).

thioformate esters were prepared by reaction of formyl fluoride with the appropriate mercaptan in ether solution at 0°.[22] Fluorosulfonic acid and antimony pentafluoride were distilled prior to their use.

Nmr Spectra.—Varian Associates Model A-56/60A and HA 100 nmr spectrometers were used for all spectra. Chemical shifts are reported in parts per million (δ) from external (capillary) tetramethylsilane.

Preparation of Solutions and Kinetic Measurements.—The procedure used for the preparation of solutions of the protonated thioacids and thioesters was identical with that described previously.[14] The same procedure as was used in studies of the cleavage of protonated carboxylic acid esters[14] was used in the present work to determine rate constants for the cleavage reactions studied.

Registry No.—Fluorosulfonic acid, 7789-21-1; antimony pentafluoride, 7783-70-2.

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

(22) G. A. Olah and S. J. Kuhn, *ibid.*, **82**, 2380 (1960).

Organophosphorus Compounds. XI.[1a] ^1H and ^{31}P Nuclear Magnetic Resonance Study of the Protonation of Phosphines

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Symmetrical trialkyl (triaryl) phosphines, as well as diphenylphosphine and phosphine itself were protonated in fluorosulfuric acid. ^1H and ^{31}P nmr spectra of the phosphines and the corresponding phosphonium ions were studied. The one-bond coupling constant, J_{PH}, is inversely related to the bulkiness of the alkyl substituents. J_{PH} and the three-bond coupling constant, J_{HPCH}, are directly related. An empirical correlation of the phosphorus chemical shifts of the protonated phosphines with substituent constants was found.

A long-recognized characteristic of phosphines is their basicity, analogous to the basicity of amines. Although many phosphines have been studied by nuclear magnetic resonance (nmr) spectroscopy,[2] only a few protonated phosphines (which are phosphonium ions containing one or more hydrogen atoms attached directly to phosphorus) have been similarly examined. The trimethylphosphonium ion has been investigated thoroughly.[3] A pmr study of other methylphosphonium ions and the triethylphosphonium ion has been published.[3d] The unsubstituted phosphonium ion (PH_4^+) has only recently been observed spectrally.[4] Phosphorus chemical shifts have also been reported for the tributylphosphonium ion[5a] and the triphenylphosphonium ion.[5b]

We undertook a systematic nmr study of a series of alkyl- (aryl-) phosphines and the protonation of these phosphines in strong acid solution. Eight symmetrically trisubstituted alkyl- (aryl-) phosphines, diphenylphosphine, and phosphine itself (PH_3) were used in our studies. We found that neat fluorosulfuric acid served well both as a proton donor to the phosphines and as a solvent for the phosphonium ions which were formed. ^1H and ^{31}P nmr spectra of the phosphines and their corresponding phosphonium ions in excess fluorosulfuric acid were obtained. We were particularly interested in the effect of protonation on the phosphorus chemical shifts, and in the nmr spectral parameters of the proton which became bonded to the phosphorus atom. We also wanted to investigate the possible empirical correlations of phosphorus shifts in phosphonium ions with substituent constants.

Results

The phosphines and phosphonium ions which were studied, their phosphorus chemical shifts, and nmr spectral parameters of the proton(s) bonded directly to phosphorus are listed in Table I. Except where otherwise noted, the phosphines were examined as neat liquids. Each phosphine (except PH_3), when mixed with a fivefold molar excess of fluorosulfuric acid, yielded a stable solution of the corresponding phosphonium ion. A concentration of 1 mol of PH_3 in 31.5 mol of fluorosulfuric acid was sufficient for obtaining nmr spectra. The excess fluorosulfuric acid appeared in each proton spectrum as a sharp singlet at δ 11.1 to 12.6 (parts per million (ppm) downfield from external tetramethylsilane). The proton(s) attached to phosphorus appeared as widely separated doublets; each component had additional fine structure in those cases where three-bond coupling with other protons was possible. In the 60-MHz proton spectra of the trialkylphosphonium ions, the upfield component of the doublet due to the phosphonium proton was always hidden under peaks due to the alkyl protons. Taking spectra at 100 MHz usually separated this upfield component from the interfering peaks. In the two cases (triisopropylphosphonium ion and tricyclohexylphosphonium ion) where the upfield component remained hidden, the change in position of the downfield component upon switching from 60 to 100 MHz permitted calculation of the proton shift of the phosphonium proton and the one-bond coupling constant, J_{PH}. The trisubstituted phosphines all showed a change in the 24.3 MHz phosphorus spectra from a single broad peak to two widely separated components

(1) (a) Part X: S. J. Kuhn and G. A. Olah, *Can. J. Chem.*, **40**, 1951 (1962); (b) National Institutes of Health Predoctoral Research Fellow, 1968.

(2) Recent summaries of nmr spectra of phosphorus compounds are by (a) G. Mavel in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. I, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Long Island City, N. Y., 1966, Chapter 4; and by (b) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, "P^{31} Nuclear Magnetic Resonance," John Wiley & Sons, Inc., New York, N. Y., 1967.

(3) (a) B. Silver and Z. Luz, *J. Amer. Chem. Soc.*, **83**, 786 (1961); (b) P. Haake, W. B. Miller, and D. A. Tyssee, *ibid.*, **86**, 3577 (1964); (c) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **20**, 449 (1964); (d) H. Dreeskamp, H. Elser, and C. Schumann, *Ber. Bunsenges. Phys. Chem.*, **70**, 751 (1966); (e) K. Moedritzer, L. Maier, and L. C. D. Groenweghe, *J. Chem. Eng. Data*, **7**, 307 (1962).

(4) G. M. Sheldrick, *Trans. Faraday Soc.*, **63**, 1077 (1967).

(5) (a) Reference 2b, p 197; (b) J. E. Lancaster in ref 2b, p 381.

TABLE I

NMR SPECTRAL PARAMETERS OF PHOSPHINES AND PROTONATED PHOSPHINES

No.	Phosphine	Phosphorus shift of phosphine, ppm rel to 85% H_3PO_4	Phosphorus shift of protonated phosphine, ppm	Proton shift of proton(s) bonded to phosphorus, δ	J_{PH}, Hz	J_{HPCH}, Hz
1	PH_3	+238[a]	+101.0	2.28,[b] 6.20[c]	188,[b] 548[c]	
2	$P(CH_3)_3$	+62.2	+3.2	6.36	497	5.6
3	$P(C_2H_5)_3$	+19.2	−22.5	5.97	471	5.3
4	$P(i\text{-}C_3H_7)_3$	−19.3	−44.4	5.58	448	4.2
5	$P(t\text{-}C_4H_9)_3$	−61.9	−58.3	5.46	436	
6	$P(n\text{-}C_4H_9)_3$	+32.6	−13.7	6.01	470	5.1
7	$P(n\text{-}C_8H_{17})_3$	+32.5	−13.0	6.04	465	5.0
8	$P(c\text{-}C_6H_{11})_3$	−11.3[d]	−32.7	5.48	445	3.6
9	$P(C_5H_5)_3$	+5.4[e]	−6.8	8.48	510	
10	$HP(C_6H_5)_2$	+40.7	+21.2	5.14,[f] 7.88[g]	216,[f] 519[g]	

[a] J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Amer. Chem. Soc.*, **78**, 5715 (1956). [b] PH_3 in CCl_4. [c] PH_4^+. [d] In $CHCl_3$. [e] In CCl_4. [f] $(C_6H_5)_2PH$. [g] $(C_6H_5)_2PH_2^+$.

upon protonation. Diphenylphosphine showed the expected change from a doublet to a more widely spaced 1:2:1 triplet upon protonation. The phosphorus spectrum of PH_4^+ was the anticipated 1:4:6:4:1 quintet. Since the proton spectra exhibited stronger and better resolved peaks than the phosphorus spectra, the values given for J_{PH} are taken from the proton spectra. The separation(s) of peaks in the phosphorus spectra of the phosphonium ions was in good agreement with these values of J_{PH}.

Discussion

The magnitude of the one-bond coupling constant, J_{PH}, has been related to the amount of s character in the phosphorus orbital used for bonding to hydrogen.[6] J_{PH} for the phosphonium ion, PH_4^+, is found to be 548 Hz. If replacement of hydrogen by an alkyl (aryl) group results in increased s character in the corresponding phosphorus orbital, this increase would be expected to be at the expense of the s character in the phosphorus bonds to the remaining hydrogen atoms. The values of J_{PH} in the phosphonium ions investigated are indicative of less than 25% s character in the phosphorus bond(s) to hydrogen. Furthermore, an inverse relationship between J_{PH} and the bulkiness of the alkyl substituents is apparent. An increase in the bulkiness of the substituents in the trialkylphosphonium ions would be expected to result in increased mutual repulsions between the substituents. These increased repulsions would be expected to result in larger C–P–C bond angles and increased s character in the phosphorus bonds to the alkyl groups (noting that 109.5° bond angles are associated with sp^3-hybridized bond orbitals and 120° bond angles are associated with sp^2-hybridized bond orbitals). Again, there should be a corresponding decrease in the s character in the phosphorus orbital to the hydrogen atom, accompanied by a decrease in J_{PH}. A direct relationship between J_{PH} and the three-bond coupling constant, J_{HPCH}, is also present.

The possible correlation of phosphorus chemical shifts with additive group contributions has been a subject of interest for several years. Recently, it has been discovered that the phosphorus shifts of many organophosphorus compounds in several classes can be predicted quite accurately by simple linear equations. These equations utilize numerical constants which have been assigned to a number of substituents. The constants, known as σ^P constants, which have been derived for the substituents involved in the phosphonium ions that we have prepared, are listed in Table II. These σ^P constants, which were derived from tertiary phosphines,[7] have general applicability in equations which have been formulated for primary phosphines,[8] secondary phosphines,[9] and quaternary phosphonium ions.[10] We find that such an equation can also be derived for the protonated trialkylphosphines that we have prepared.

TABLE II

SUBSTITUENT CONSTANTS FOR PREDICTING PHOSPHORUS CHEMICAL SHIFTS[a]

Substituent	σ^P
CH_3	0
$n\text{-}C_nH_{2n-1}$ ($n \geq 3$)	10
C_2H_5	14
C_6H_5	18
$c\text{-}C_6H_{11}$	23
$i\text{-}C_3H_7$	27
$t\text{-}C_4H_9$	44

[a] Reference 7.

In Figure 1, the experimental phosphorus shifts of the starting tertiary phosphines and the corresponding phosphonium ions are plotted *vs.* the sums of the constants of the three substituents. The upper line is the one given by the Grim and McFarlane[9] equation for tertiary phosphines (eq 1). The lower line is the

$$\delta^{31}P \text{ (ppm from 85\% } H_3PO_4) = 62 - \sum_{n=1}^{3} \sigma_n{}^P \qquad (1)$$

best least-squares fit to the six phosphonium ion chemical shifts which lie nearest to it. Equation 2 describes this line. We expect that it can be used to

$$\delta^{31}P = 3.2 - 0.56 \sum_{n=1}^{3} \sigma_n{}^P \qquad (2)$$

predict the shifts of other tertiary phosphonium ions.

(6) For a discussion of the possibility of a quantitative relationship, see S. L. Manatt, G. L. Juvinall, R. I. Wagner, and D. D. Elleman, *J. Amer. Chem. Soc.*, **88**, 2689 (1966).

(7) S. O. Grim, W. McFarlane, and E. F. Davidoff, *J. Org. Chem.*, **32**, 781 (1967).

(8) L. Maier, *Helv. Chim. Acta*, **49**, 1718 (1966).

(9) S. O. Grim and W. McFarlane, *Nature*, **208**, 995 (1965).

(10) (a) S. O. Grim, W. McFarlane, E. F. Davidoff, and T. J. Marks, *J. Phys. Chem.*, **70**, 581 (1966); (b) E. Fluck and J. Lorenz, *Z. Naturforsch.*, **22b**, 1095 (1967).

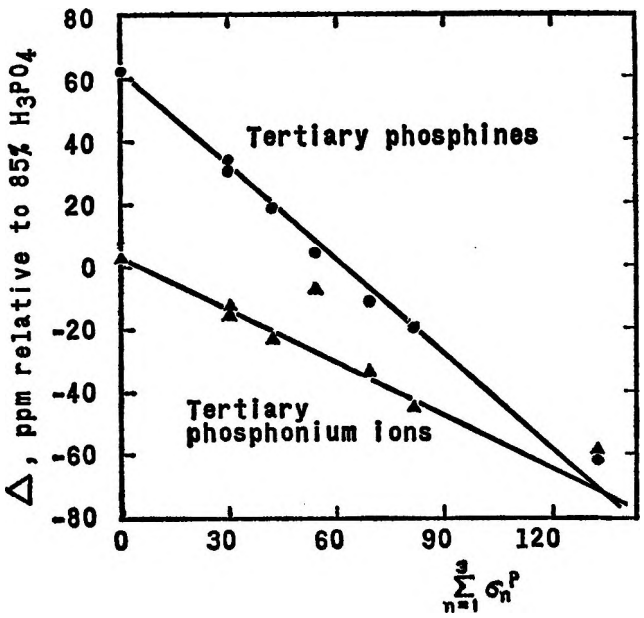

Figure 1.—Experimental phosphorus chemical shifts as functions of substituent constants.

The standard deviation of the six points used in this derivation is 1.7 ppm.

There are three experimental phosphorus shifts in Figure 1 which deviate significantly from predicted values. The phosphorus shift of the triphenylphosphonium ion

$$\left(\sum_{n=1}^{3} \sigma_n{}^{P} = 54\right)$$

is considerably higher than expected. Similar deviations of phenyl-substituted quaternary phosphonium ions were noticed by Grim, *et al.*[10a] They ascribed this behavior to the ability of phenyl groups to act as π-electron donors in phosphonium ions, thereby providing an extra amount of electronic shielding about the phosphorus nucleus.

Figure 1 indicates that, if a phosphine contains substituents with large enough σ^P constants, protonation would lead to an upfield change in the phosphorus shift. Tri-*t*-butylphosphine gives this interesting result—the phosphorus shift moves upfield by 3.6 ppm upon protonation. Furthermore, the shifts of both this phosphine and the corresponding phosphonium ion are somewhat higher than predicted. Van Wazer and Letcher[11] have pointed out, on the basis of quantum mechanical calculations, that the empirical linear equations which have been developed can be used successfully only because bond angles in most alkyl- and aryl-substituted phosphines tend to be the same. We suggest that the mutual repulsions of the alkyl groups in tri-*t*-butylphosphine and the corresponding phosphonium ion are extensive enough to create unusually large bond angles, sufficient to result in deviations from correlation with less crowded molecules.

Experimental Section

Materials.—Trimethylphosphine, triethylphosphine, triisopropylphosphine, tricyclohexylphosphine, and diphenylphosphine were used as obtained from Strem Chemicals, Inc. Commercially available triphenylphosphine was used without further purification. Phosphine was used as obtained from Matheson Co., Inc. Tri-*n*-butylphosphine and tri-*n*-octylphosphine, obtained from Carlisle Chemical Works, Inc., were distilled under reduced pressure before use. Tri-*t*-butylphosphine was prepared according to the procedure of Hoffmann and Schellenbeck.[12] Fluorosulfuric acid was distilled and stored in a Teflon bottle, which was kept in a desiccator until needed.

Nmr Spectra.—Pmr spectra were taken with Varian Associates Models A-60, A-56/60A, and HA-100 nmr spectrometers. Proton chemical shifts are reported in parts per million (δ) from external (capillary) tetramethylsilane. The pmr spectra were integrated, and the peak areas supported the postulated assignments of the various phosphonium ions. Phosphorus nmr spectra were taken with Varian Associates Model HA-60IL nmr spectrometer operating at 24.3 MHz and equipped with a Model V4331A probe. Samples were contained in a 12-mm-o.d. thin-walled polished spinning tube. A 5-mm-o.d. polished tube containing 85% H_3PO_4 as the reference material was inserted in the sample tube and maintained in a concentric position by two specially constructed Teflon inserts. Nearly all of the phosphorus chemical shifts were calculated from frequency sweep spectra taken under conditions of field-frequency stabilization. The phosphorus shifts of trimethylphosphine and PH_4^+ were found from field sweep spectra calibrated by audio frequency side-band modulation. Combinations of field-frequency stabilized and sideband modulated spectra provided the shifts of diphenylphosphine and the diphenylphosphonium ion. Since the peaks in many of the phosphorus spectra were broad and often showed unresolved multibond couplings, the reported phosphorus shifts are probably accurate to about ± 0.5 ppm.

Protonation of Phosphines.—Except in the case of phosphine, itself (PH_3) each phosphine were added dropwise (or otherwise slowly added, with the solid phosphines) to a fivefold molar excess of fluorosulfuric acid with stirring and cooling. Clear yellow solutions quickly formed. In some cases, an ice bath provided sufficient cooling for the exothermic reactions. The protonation of the more reactive phosphines (trimethyl-, triethyl-, triisopropyl-, and tri-*t*-butyl-) was vigorous enough that cooling in a Dry Ice–acetone bath was found to be necessary. The protonation of phosphine was accomplished by condensing PH_3 in a liquid nitrogen cooled tube and adding dropwise a large excess of fluorosulfuric acid. Allowing the tube to warm to room temperature yielded a stable solution of the phosphonium ion.

Registry No.—**1**, 7803-51-2; **1** (protonated), 19287-78-6; **2**, 594-09-2; **2** (protonated), 19287-79-7; **3**, 554-70-1; **3** (protonated), 19287-80-0; **4**, 6476-36-4; **4** (protonated), 19287-81-1; **5**, 13716-12-6; **5** (protonated), 19287-82-2; **6**, 998-40-3; **6** (protonated), 19287-83-3; **7**, 4731-53-7; **7** (protonated), 19287-84-4; **8**, 2622-14-2; **8** (protonated), 19287-85-5; **9**, 603-35-0; **9** (protonated), 19287-86-6; **10**, 829-85-6; **10** (protonated), 19287-87-7.

Acknowledgments.—Support of this work by a grant from the National Institutes of Health and by a Public Health Service Fellowship from the National Institute of General Medical Sciences (to C. W. M.) is gratefully acknowledged.

(11) J. R. Van Wazer and J. H. Letcher in ref 2b, p 212.

(12) H. Hoffmann and P. Schellenbeck, *Chem. Ber.*, **100**, 692 (1967).

Ionic Peroxide Fragmentations[1]

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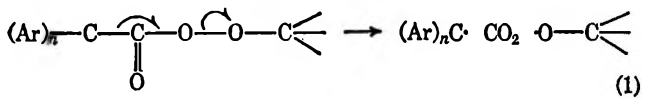
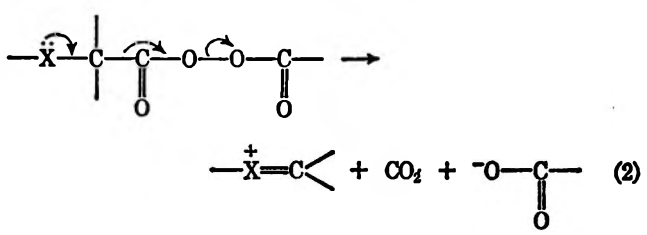
The reaction of α-oxy acids with peroxy acids and N,N′-dicyclohexylcarbodiimide yielded the expected diacyl peroxide only under carefully controlled conditions and then only when the α-oxy group was part of a three-membered ring. The reactions of these peroxides have been studied. Based largely on an examination of products, an ionic fragmentation mechanism has been proposed for their decompositions.

A number of factors influence the ease with which the peroxide bond is broken. For example, location of aryl substituents α to a peroxy ester carbonyl dramatically enhances the rate of homolytic decomposition.[2] This rate acceleration has been attributed to delocalization in the product carbon radical which in turn requires cleavage of both the O–O and C–C bonds in the initial transition state (eq 1). We would like to report



(1)

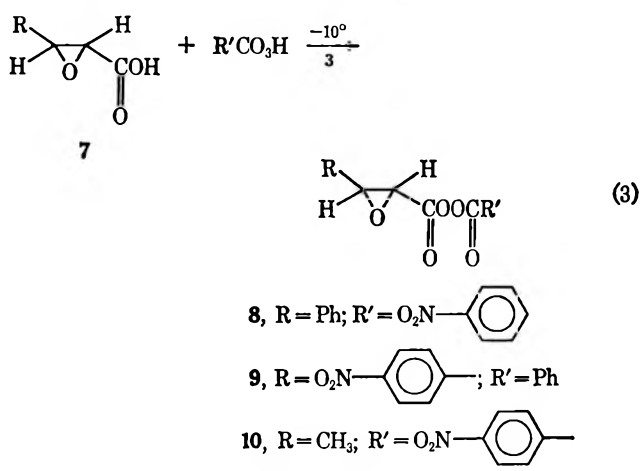
evidence for an ionic concerted cleavage (fragmentation[3]) which is apparently characteristic of certain α-substituted diacylperoxides (eq 2).



(2)

Our attention was directed to these ionic decompositions by the discovery that the reaction of *p*-nitroperbenzoic acid (**1**) and phenoxyacetic acid (**2**) with N,N′-dicyclohexylcarbodiimide (**3**)[4] failed to yield the expected unsymmetrical peroxide (**4**). The only products which could be isolated were **5** and **6** (Scheme I). Although **4** was considered a possible source of these products, all attempts to isolate or detect this peroxide failed.[5] To understand this remarkably facile reaction, it was necessary to find an isolable analog of **4** and examine its breakdown in a controlled manner.

If **4** was in fact the precursor of **5** and **6**, the unshared electrons appeared to represent the most probable locus of its instability. Since constraint of a heteroatom within a three-membered ring has been of previous utility in moderating heteroatom electron release,[6] oxirane analogs of **1** (glycidic acids, **7**) were prepared and allowed to react with peroxy acids and **3** at −10° in carbon tetrachloride. Under carefully controlled conditions, unsymmetrical peroxides **8–10** could be prepared and isolated (eq 3). These compounds differed greatly

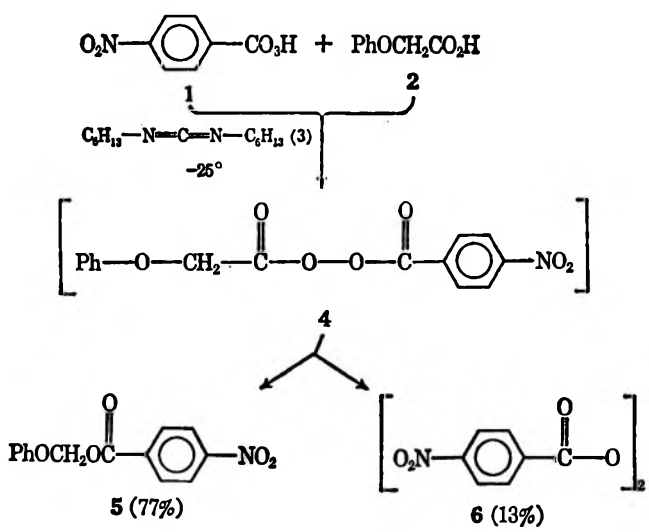


(3)

in their stability. Solid **10**[7] decomposed quickly at room temperature, whereas solid **8** was stable for several days and solid **9** was unchanged after several weeks at room temperature. Inclusion of nitro groups proved necessary to facilitate isolation and purification of these peroxides.

The initial decomposition of peroxide **8** was observed in deuteriochloroform at room temperature. The product was identified as aldehyde **11** (Scheme II). To investigate this reaction further, peroxide **8** was decomposed in methanol. This solvent was selected because of its nucleophilicity in ionic reactions and its hydrogen-donating ability toward radicals. The major products of this reaction were aldehyde (**12**),

SCHEME I



(1) Support of this research by National Science Foundation Grants GP-5531 and GP-8044 is gratefully acknowledged.

(2) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

(3) C. A. Grob, "Theoretical Organic Chemistry," Butterworth and Co. (Publishers) Ltd., London, 1959, p 114.

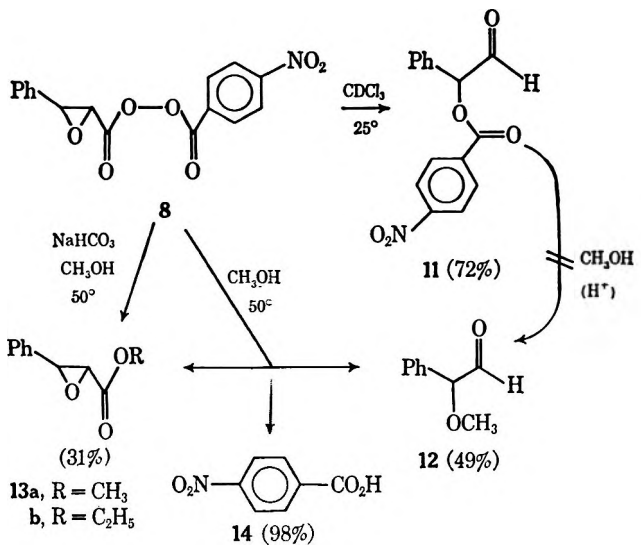
(4) Procedure of F. D. Greene and J. Kazan, *J. Org. Chem.*, **28**, 2168 (1963).

(5) Other methods for the preparation of unsymmetrical peroxides (*cf.* A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961, p 64) gave the same products in lower yields

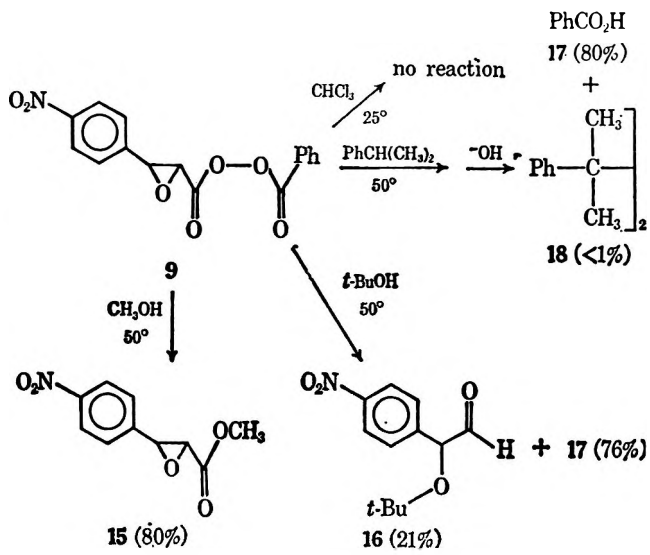
(6) J. A. Deyrup and R. B. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538 (1965).

(7) The great instability of **10** precluded attainment of analytical purity and thus its further study was not attempted.

SCHEME II



SCHEME III



glycidic ester (**13a**), and *p*-nitrobenzoic acid (**14**). Ester **13a** was apparently the result of solvolytic attack by methanol on the glycidyl carbonyl group. This solvolytic attack was enhanced by added base. Added *p*-nitrobenzoic acid, however, did not affect the product distribution.

The formation of **11** and **12** are indicative of the mechanism of this reaction. Although esters are often observed as minor products of radical coupling,[8] there is no obvious manner or precedent for a radical process leading to ether **12**.[9] Failure to observe hydrogen abstraction from methanol or other products of radical coupling also argues against a radical process. The isolation of *p*-nitrobenzoic acid (**14**) in high yield is in agreement with a nonradical path since aroyloxy radicals generally undergo facile decarboxylation (in the absence of efficient scavangers).[10]

Study of the decomposition of peroxide **9** was complicated by its greater stability and the lability of its products. For example, this peroxide failed to decompose in chloroform after 2 days at room temperature, whereas peroxide **8** was totally decomposed under identical conditions.[11,12]

Attempted decomposition of **9** in methanol resulted solely in methanolysis of the peroxide to give ester **15**[13] (Scheme III). To diminish solvent attack on the carbonyl group, a bulkier alcohol, *t*-butyl alcohol, was chosen. In this solvent, aldehyde **16** and benzoic acid were the only identifiable products. The yield of the latter again points to a nonradical process.

Although it is difficult to choose an appropriate standard for comparison, qualitative results indicate that the decomposition of **9** in *t*-butyl alcohol is considerably faster than that of benzoyl peroxide which is known to break (homolytically) only one O–O bond in the rate-determining step. Thus, 80% of the initial amount of benzoyl peroxide failed to react under those conditions which result in the complete decomposition of **9** (in *t*-BuOH).[14] As a final test of the nonradical nature of the decomposition of **9**, this peroxide was decomposed in cumene at 50°. After all of the material had reacted, the mixture was examined. Less than 1% dicumyl (**18**) was detected along with 80% recoverable benzoic acid (after hydrolysis). No other products could be isolated owing to the difficulty of removing the cumene. It can be concluded that at least 99% of the reaction proceeded *via* an ionic route in spite of the relatively nonpolar nature of this solvent. Efficient geminate recombination of radicals would, of course, invalidate the above argument. The ease with which these reaction intermediates can be intercepted by nucleophilic solvents to yield ethers suggests the absence of cage processes in these decompositions.

The elimination from consideration of possible radical processes requires an ionic mechanism and that this ionic reaction be of lower energy than homolytic alternatives. Attempts to construct a detailed mechanistic picture for the ionic decomposition of these peroxides suggested several alternative possibilities. One such possibility concerns the question of whether the oxirane ring opens in a slow step to some intermediate which could undergo rapid decomposition. Routes of this type were excluded *via* suitable controls which tested the stability of the oxirane ring towards nucleophilic ring opening under the reaction conditions. For example, glycidic ester **13b** was *quantitatively* recovered from methanol in the presence of an equimolar amount of *p*-nitrobenzoic acid. Similar complete inertness to ring opening was also observed for a mixture of **15** and benzoic acid in *t*-BuOH.

Another possible route to the observed products is a carboxy inversion process leading to **20** (eq 4) which could subsequently form the observed products.

(8) D. F. DeTar, 17th Organic Symposium, June 1961, as reported in W. P. Pryor, "Free Radicals," McGraw-Hill, Book Co. Inc., New York, N. Y. 1966, p 257; H. Erlenmeyer and W. Shoenauer, *Helv. Chim. Acta*, **19**, 338 (1936).

(9) It was possible to show (see Experimental Section) that **12** was not formed *via* methanolysis of **11**.

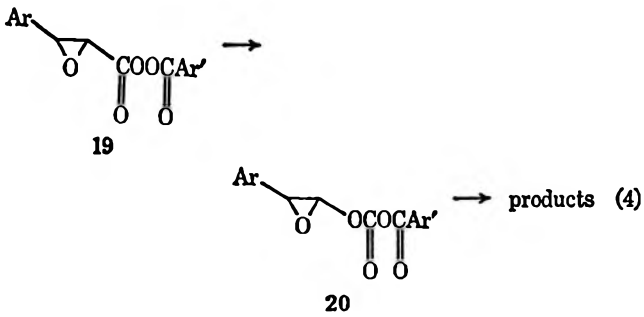
(10) *Cf.* E. Hedaya and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1661 (1967).

(11) At higher temperatures, although decomposition took place, the products were not stable enough to allow isolation.

(12) The greater stability of **8** is in qualitative agreement with an ionic mechanism which involves electron flow from the oxirane ring toward an aryloate leaving group.

(13) The enhanced formation of glycidic ester at the expense of aldehyde from **9** (compared with **8**) supports the formation of **13** by a methanolysis mechanism.

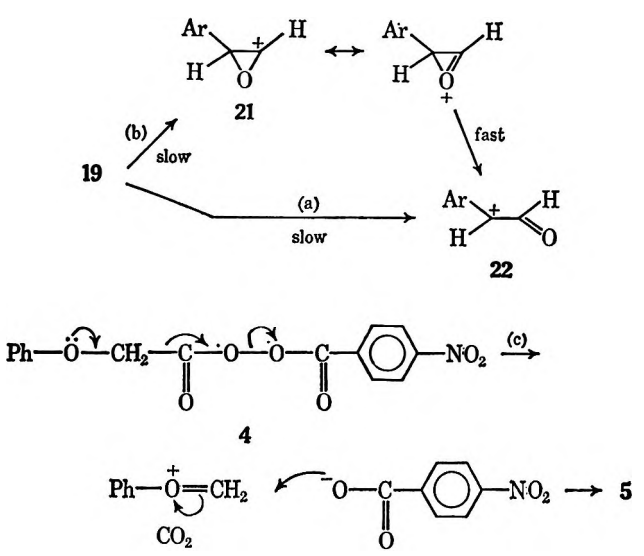
(14) At 83° in *t*-BuOH, benzoyl peroxide required 2 days to react and, after that time, the reaction mixture yielded only 9.9% benzoic acid after base hydrolysis.



Carboxy inversion has ample precedent and constitutes a major path for some diacyl peroxides.[15] It was possible, however, to follow the decomposition of **8** in deuteriochloroform by nmr spectroscopy and in this way ascertain that no detectable amount of **20** was present during or after the reaction. If the carbonate was formed, it must have an exceptionally short lifetime. Although independent preparation of **20** does not seem feasible, existing knowledge concerning carboxy inversion products (carbonates) suggests that **20** should be isolable under our reaction conditions (*i.e.*, room temperature in chloroform).[16-18]

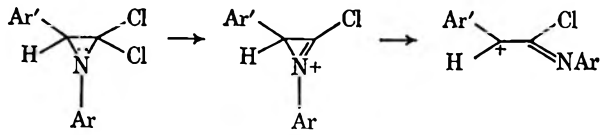
Two paths (Scheme IV) for the decomposition of these peroxides are consistent with the mechanistic

SCHEME IV



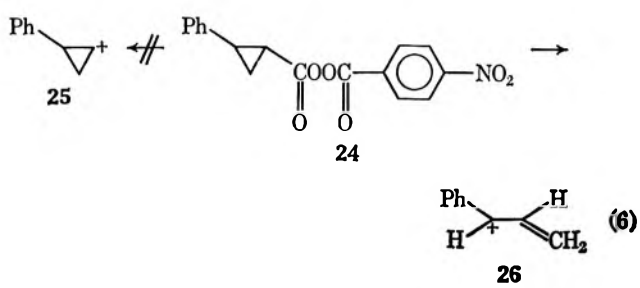
requirements discussed above. Both paths a and b yield carbonium ion **22** which is an obvious and reasonable precursor of the observed ester (**11**) and ethers **12** and **16**. Path a implies direct electrocyclic ring opening, whereas path b is a two-step process in which oxirane carbonium ion **21** serves as an intermediate. By analogy to the first step of path b, path c may be written for the decomposition of the unisolated diacyl peroxide **4**.[19-21]

Direct electrocyclic ring opening has been experimentally verified and theoretically discussed for the reactions of cyclopropanol derivatives.[22] The two step process finds ample precedent in the ring opening reactions of 2-haloaziridines (eq 5).[23] For these



reactions, the intermediacy and properties of **23**,[23] as well as its analogs,[6] have been demonstrated.

In an attempt to distinguish between paths a and b, a homocyclic analog (**24**) of **8** was prepared. The lack of electron-pair stabilization in **25** requires that any heterolytic decomposition of **24** proceed with concerted formation of **26** (eq 6). Since the allylic carbonium ion



26 should be more stable than ketocarbonium ion **22**,[24] we expected that, if **19** yields **22** directly, **24** should be even more reactive.[25] In fact **24** was exceptionally stable and *no* change was detected in **24** after 2 weeks at 50° in $CDCl_3$.[27] We conclude from this experiment that **21** is a discrete intermediate in the decomposition of **19**. In other words, we conclude that electron donation from oxygen (as in the case of nitrogen[6,23]) *followed* by ring opening offers an energetically more favorable route to ionization than the totally concerted process exhibited by the cyclopropane analogs.

In a recent series of papers, McDonald and coworkers have examined the rearrangement of chloroepoxides (**27**) to chloro ketones (**29**).[28] These workers concluded that **28** is produced without intervention of a cyclic

(15) J. E. Leffler, *J. Amer. Chem. Soc.*, **72**, 67 (1950); D. B. Denney, *ibid.*, **78**, 590 (1956); J. E. Leffler and C. D. Petropoulus, *ibid.*, **79**, 3068, (1957).

(16) C. J. Michejda, D. S. Tarbell, and W. H. Saunders, *ibid.*, **84**, 4113 (1962); D. B. Denny and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

(17) It should be pointed out that Greene has also observed ester formation without intervention of carbonate products in the decomposition of certain diacyl peroxides. In contrast to our reactions, however, he apparently observed several simultaneous (including carboxy inversion) decomposition modes.[18]

(18) F. D. Greene, C. C. Chu, H. P. Stein, and F. M. Vane, *J. Amer. Chem. Soc.*, **86**, 2080 (1964).

(19) The *t*-butyl peroxy ester analog of **4** has recently been prepared and a *homolytic* fragmentation process postulated for it and several closely related compounds.[20] The ability of the leaving group to accommodate negative charge thus appears to play a key role in determining the decomposition mode.

(20) C. Ruchardt, H. Bock, and I. Ruthardt, *Angew. Chem. Intern. Ed. Engl.*, **5**, 253 (1966); D. R. Dixon and A. Pajaczkowski, *Chem. Commun.*, 337 (1966).

(21) The formation of **6** could occur directly from the reaction of **1** and **3** or *via* attack by *p*-nitroperbenzoate on **5**.

(22) *Cf.* C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(23) R. E. Brooks, J. O. Edwards, G. Levy, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966).

(24) *E.g.*, J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 169.

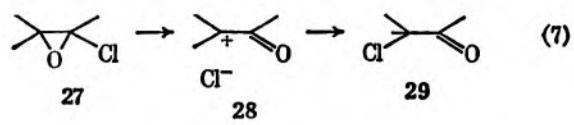
(25) This argument requires that the strain energy of cyclopropane and that of oxirane are essentially the same. Values of 27.5 and 28 kcal (respectively) have been reported.[26]

(26) J. D. Cox, *Tetrahedron*, **19**, 1175 (1963).

(27) In contrast to **8** which had completely reacted within 2 days at 25° in the same solvent.

(28) R. N. McDonald and T. E. Tabor, *J. Amer. Chem. Soc.*, **89**, 6573 (1967), and references therein.

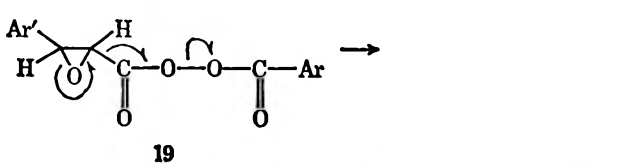
carbonium ion[29] (eq 7). A detailed study of subsituent effects on these reactions is now in progress in hopes of clarifying the mechanism of these ring-opening reactions.



27 28 29 (7)

The failure to observe radical processes deserves some comment. Free-radical substitution α to an ether oxygen has been extensively documented.[30] The oxirane radical itself is known as an intermediate in the free-radical chlorination of epoxides by *t*-BuOCl at 70°.[31] It is interesting to note that, in contrast to the ionic reactions discussed above, the radical chlorination apparently can proceed without ring opening under the reaction conditions. In addition to concerted homolytic O–O rupture, a second free-radical path is also avaliable to **19**. The importance of multiple-bond homolyses which yield delocalized free radicals has already been mentioned and suggested the possibility shown in Scheme V. Although the product radical, **30**,

SCHEME V

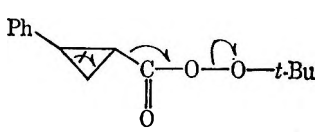


19

Ar'CHCHO + CO_2 + $\cdot O_2CAr$

30

would meet the delocalization requirement, this radical fragmentation is not observed. A similar failure to observe either multiple bond homolysis or ring opening in the free-radical decomposition of **31** and other related cyclopropyl peroxy esters has been described.[32]



31

The ionic character of these peroxide decompositions, in spite of reasonable homolytic alternatives, indicates a considerable driving force for the heterolytic route. Our results suggest that other suitably located electron-rich sites (*i.e.*, those carbon and heteroatom systems which can serve as neighboring groups in solvolytic ionization) might also promote similar ionic fragmentations. In addition to providing new carbonium ion sources, it is also possible that these mild fragmentations in nonpolar solvents could be of degradative, synthetic, and protective utility. Explorations of these possibilities as well as further examination of the chemistry of oxirane carbonium ions are in progress.

(29) R. N. McDonald and P. A. Schwab, *J. Org. Chem.*, **29**, 2459 (1964).
(30) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 479.
(31) C. Walling and P. S. Fredericks, *J. Amer. Chem. Soc.*, **84**, 3326 (1962).
(32) R. D. Swigert, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1964.

Experimental Section[33]

trans-**3-Methylglycidyl *p*-Nitrobenzoyl Peroxide.**—To a cold solution of 100 ml of carbon tetrachloride and 630 mg (6.2 mmol) of *trans*-3-methylglycidic acid[34] was added 1.28 g (6.2 mmol) of N,N′-dicyclohexylcarbodiimide (Aldrich) and 1.13 g (6.2 mmol) of *p*-nitroperbenzoic acid[35] and the mixture was allowed to stir at 0° for 4 hr. The N,N′-dicyclohexylurea (1.2 g, 87%) was filtered and washed with chloroform. The filtrate was evaporated at 0° under reduced pressure to give 1.51 g (92%) of crude product. Some purification (by nmr analysis) was achieved by redissolving the residue in CCl_4 and reevaporation. As solids started to separate, they were filtered, and the center cuts gave a relatively pure sample of white solid: mp 70° (with explosion); ir (Nujol) 1780 and 1810 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.54–8.14 (m, 4, aromatic), 3.64–3.36 (m, 2, CHCH), 1.50 (d, 3, J = 5 Hz, CH_3). The sample starts to decompose noticeably within 1 hr with development of ir absorption at 1700 cm^{-1}.

Potassium *trans*-**3-Phenylglycidate.**—A solution of 5 g of potassium hydroxide in 30 ml of ethanol was added with stirring to a solution of 10 g (52 mmol) of ethyl *trans*-3-phenylglycidate in 20 ml of ethanol at a temperature below 15°. The precipitate was immediately filtered, washed with 30 ml of ethanol, and dried [room temperature (0.5 mm)] yielding 7.2 g (70%) of the salt: nmr (D_2O) δ 7.71 (s, 5, Ph), 4.37 (d, 1, J = 2 Hz, CHCO), 3.94 (d, 1, J = 2 Hz, CHCO), 3.94 (d, 1, J = 2 Hz, CHPh).

trans-**3-Phenylglycidic Acid.**—Potassium *trans*-3-phenylglycidate (3 g, 15 mmol) was dissolved in a minimum amount of water and 140 ml of 0.1 *N* hydrochloric acid was added. The acid solution was extracted five times with 25 ml of chloroform. The solution was dried over sodium sulfate, 25 ml of carbon tetrachloride was added, and the solution was evaporated yielding 2 g (88%) of a white solid: mp 80–84° (lit.[36] mp 83–84°); nmr ($CDCl_3$) δ 7.30 (s, 5, Ph), 4.12 (d, 1, J = 1.5 Hz, CHCO), 3.53 (d, 1, J = 1.5 Hz, CHPh) The acid was used immediately since it decomposes on standing.

p-**Nitrobenzoyl *trans*-3-Phenylglycidyl Peroxide.**—To a cooled (−9°) solution of 175 ml of carbon tetrachloride and 1 g (6.1 mmol) of *trans*-3-phenylglyeidic acid, 1.26 (6.1 mmol) of N,N′-dicyclohexylcarbodiimide (Aldrich) and 1.11 g (6.1 mmol) of *p*-nitroperbenzoic acid (90% active oxygen) were added simultaneously. The mixture was stirred at −9° for 5 hr. The carbon tetrachloride was evaporated, 50 ml of chloroform was added, and the urea was removed by filtration. The chloroform solution was evaporated and the remaining solid was washed with methanol, 1.7 g (85%). The peroxide was recrystallized from chloroform by addition of methanol giving white plates: mp 88° with rapid decomposition; ir (Nujol) 1760 and 1790 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.28 (d, 4, J = 1.7 Hz, NO_2Ph), 7.36 (s, 5, Ph), 4.32 (d, 1, J = 1.5 Hz, CHPh).

Anal. Calcd for $C_{16}H_{11}O_7N$: C, 58.36; H, 3.27; N, 4.25. Found: C, 58.50; H, 3.40; N, 4.18.

2-*p*-Nitrobenzoyloxy-2-phenylacetaldehyde.—*p*-Nitrobenzoyl *trans*-3-phenylglycidyl peroxide was dissolved in deuteriochloroform and allowed to stand at room temperature for 2 days. The deuteriochloroform was then evaporated and the residue was dissolved in carbon tetrachloride: ir (CCl_4) 1750 cm^{-1} (C=O); nmr (CCl_4) δ 9.22 (s, 1, HCO), 7.94 (s, 4, HO_2Ph), 7.14 (s, 5, Ph), 6.00 (s, 1, PhCH). Based on the integrated relative areas of the δ 9.22 or 6.00 singlets *vs.* the 7.14 aryl absorption, the percentage conversion into 2-*p*-nitrobenzoyloxy-2-phenylacetaldehyde was 72%. This reaction product was dissolved in methanol and converted to 2-*p*-nitrobenzoyloxy-2-phenylacetaldehyde 2,4-dinitrophenylhydrazone according to standard procedure.[37] The sparingly soluble orange solid was recrystallized from ethanol–ethyl acetate: mp 187–189°; ir (Nujol) 1710 cm^{-1} (C=O).

(33) All melting points are uncorrected. Chemical shifts of nmr spectra run in organic solvents are reported in parts per million downfield from internal tetramethylsilane (δ). Chemical shifts of nmr spectra run in D_2O are reported in parts per million downfield from a point 4.99 ppm upfield from the DOH peak.
(34) G. Braun, *J. Amer. Chem. Soc.*, **52**, 3185 (1930).
(35) L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962).
(36) W. Dieckman, *Ber.*, **43**, 1035 (1910).
(37) D. Y. Curtin, R. C. Fuson, and R. L. Shriner, "The Systematic Identification of Organic Compounds," 5th ed. John Wiley & Sons, Inc., New York, N. Y., 1964, p 256.

Anal. Calcd for $C_{21}H_{15}O_8N_5$: C, 54.20; H, 3.25; N, 15.05. Found: C, 54.04; H, 3.49; N, 15.10.

Decomposition of *p*-Nitrobenzoyl *trans*-3-Phenylglycidyl Peroxide in Methanol.—To 20 ml of methanol at 50° was added 208 mg (0.63 mmol) of *p*-nitrobenzoyl *trans*-3-phenylglycidyl peroxide. The mixture was allowed to stand at 50° for 20 hr and then the methanol was evaporated. The solids were washed with carbon tetrachloride yielding 104 mg (98%) of *p*-nitrobenzoic acid, mp 240–242° (lit.[38] mp 241.5°). The ir spectrum was identical with that of an authentic sample. The nmr spectrum of the carbon tetrachloride filtrate showed 2-methoxy-2-phenylacetaldehyde (49%) and methyl *trans*-3-phenylglycidate (31%).[39] A small (*ca.* 5% of the total OCH_3 peaks) absorption due to methyl *p*-nitrobenzoate was also detected.

This product identification was confirmed by molecular distillation of the crude reaction mixture at 50–60° (hot air-bath temperature) under vacuum (0.5 mm). In this manner, two fractions were obtained.

The more volatile (collected at 0°) was nearly pure 2-methoxy-2-phenylacetaldehyde: ir (neat) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 9.32 (d, 1, J = 2 Hz, CHO), 7.18 (s, 5, Ph), 4.34 (d, 1, J = 2 Hz, PhCH), 3.36 (s, 3, CH_3). Traces of impurity could not be removed by distillation on this scale and thus structure proof was accomplished *via* oxidation of the aldehyde to 2-methoxy-2-phenylacetic acid. For this purpose, a solution of 105 mg (0.36 mmol) of potassium dichromate in 3.6 ml of aqueous sulfuric acid was added to 152 mg (1 mmol) of the distilled 2-methoxy-2-phenylacetaldehyde. The suspension was stirred on a steam bath for 5 min, cooled, and extracted with ethyl ether. The ether was evaporated and the resulting oil was dissolved in benzene and dried over magnesium sulfate. The oil from benzene evaporation crystallized on standing at room temperature. The acid was recrystallized from petroleum ether yielding 95 mg (57%) of transparent crystals: mp 69–70° (lit.[40] mp 68°); ir (Nujol) 1745 cm^{-1} (C=O); nmr (CCl_4) δ 11.6 (s, 1, OH), 7.30 (s, 4, Ph), 4.46 (s, 1, CH), 3.36 (s, 3, OCH_3).

The less volatile fraction consisted of methyl *trans*-3-phenylglycidate in addition to smaller amounts of the aldehyde and methyl *p*-nitrobenzoate. The absorption pattern of the major component was characteristic and identical with that of the product formed from the decomposition of this peroxide in methanol in the presence of sodium bicarbonate.

Decomposition of *p*-Nitrobenzoyl *trans*-3-Phenylglycidyl Peroxide in Methanol in the Presence of *p*-Nitrobenzoic Acid.—A mixture of 166 mg (0.51 mmol) of the above peroxide, 84 mg (0.51 mmol) of *p*-nitrobenzoic acid, and 15 ml of methanol was heated at 50° for 24 hr. The methanol was removed and the residue was taken up in CCl_4. The resultant nmr spectrum was almost identical with that of the product obtained without added acid. No detectable change was observed in the aldehyde/ester ratio.

Decomposition of *p*-Nitrobenzoyl *trans*-3-Phenylglycidyl Peroxide in Methanol in the Presence of Sodium Bicarbonate.—A mixture of 279 mg (0.82 mmol) of *p*-nitrobenzoyl *trans*-3-phenylglycidyl peroxide, 10 ml of methanol, and a twofold excess of sodium bicarbonate was allowed to stand at 50° for 24 hr. The methanol was evaporated and the solid was washed with carbon tetrachloride. The solid was identified as *p*-nitrobenzoic acid by its mp 240–242° (lit.[38] mp 241.5°) and its ir spectrum which was superimposable on that of an authentic sample. Evaporation of the CCl_4 yielded an oil. Analysis of this oil by nmr spectroscopy indicated the presence of methyl 3-phenylglycidate [nmr (CCl_4) δ 7.26 (s, 5, Ph), 3.98 (d, 1, J = 1.5 Hz, CHCO), 3.76 (s, 3, CH_3), 3.32 (d, 1, J = 1.5 Hz, CHPh)] and methyl *p*-nitrobenzoate (1.7:1). No other products were present. This oil was dissolved in ethanol and an excess of potassium hydroxide was added at 0°. After 7 min, the precipitate was filtered and dried at room temperature under vacuum for 3 hr. The nmr spectrum (D_2O) of this material was superimposable on that previously described for potassium *trans*-3-phenylglycidate.

Reaction of 2-*p*-Nitrobenzoyloxy-2-phenylacetaldehyde in Methanol.—A sample of *p*-nitrobenzoyl *trans*-3-phenylglycidyl peroxide was allowed to decompose in deuteriochloroform at room temperature for 2 days. The deuteriochloroform was evaporated. The nmr spectrum showed 2-*p*-nitrobenzoyloxy-2-phenylacetaldehyde. The oil, which contained some *p*-nitrobenzoic acid, was dissolved in methanol and the solution was allowed to stand at 50° overnight. After evaporation of the methanol, neither 2-*p*-nitrobenzoyloxy-2-phenylacetaldehyde nor 2-methoxy-2-phenylacetaldehyde was observed in the complex nmr spectrum.

Methyl *trans*-3-*p*-Nitrophenylglycidate.—In a flame-dried apparatus flushed with nitrogen, a mixture of 15.1 g (0.1 *m*) of *p*-nitrobenzaldehyde and 17.4 g (0.16 *m*) methyl α-chloroacetate in 50 ml of 1,2-dimethoxyethane was cooled in a salt–ice bath and 18.2 g (0.16 *m*) powdered potassium *t*-butoxide added over 1 hr. The dark mixture was allowed to stir at that temperature for 2 hr, then slowly brought to room temperature, and stirred overnight. Dilute hydrochloric acid was added to neutralize the base and 300 ml of water added. The gummy residue was filtered and washed with 300 ml ethyl ether to yield a tan solid. The solid was recrystallized from ethanol yielding 7.1 g (31.8%) of long pale yellow needles: mp 139–140.5°; ir (Nujol) 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.3–7.4 (m, 4, NO_2Ph), 4.24 (d, 1, J = 2 Hz, $CHNO_2Ph$), 3.87 (s, 3, OCH_3), 3.51 (d, 1, J = 2 Hz, CHCO).

Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.60; H, 3.94; N, 6.14.

***trans*-3-*p*-Nitrophenylglycidic Acid.**—An excess of potassium hydroxide was added to a mixture of 5 g (22.4 mmol) of methyl *trans*-3-*p*-nitrophenylglycidate in 10 ml of water at 0°. Enough ethanol was added to dissolve the ester. After a few minutes, the solution was acidified with excess hydrochloric acid and the ethanol was evaporated. The acid precipitated out of water and was recrystallized from ethanol yielding 4.6 g (96%) of pale yellow platelets: mp 186–188° (lit.[41] mp 186–188°); ir (Nujol) 1700 cm^{-1} (C=O).

Benzoyl *trans*-3-*p*-Nitrophenylglycidyl Peroxide.—To a cooled solution of 150 ml of carbon tetrachloride and 2 g (14 mmol) of *trans*-*p*-nitrophenylglycidic acid, 1.95 g (14 mmol) of N,N'-dicyclohexylcarbodiimide and 1.31 g (14 mmol) of perbenzoic acid were added simultaneously. The mixture was stirred at salt–ice bath temperature for 5 hr. The carbon tetrachloride was evaporated, 50 ml of chloroform was added, and the N,N'-dicyclohexylurea was removed by filtration. The chloroform filtrate was evaporated and the residual solid was recrystallized from chloroform by addition of methanol, yielding 1.45 g (30%) of peroxide: mp 108–108.5° with vigorous decomposition; ir (Nujol) 1760 and 1800 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.40–7.48 (m, 9, aromatic), 4.44 (d, 1, J = 1.5 Hz, CHCO), 3.77 (d, 1, J = 1.5 Hz, CHPh).

Anal. Calcd for $C_{16}H_{11}O_7N$: C, 58.36; H, 3.37; N, 4.25. Found: C, 58.40; H, 3.44; N, 4.23.

Decomposition of Benzoyl *trans*-3-*p*-Nitrophenylglycidyl Peroxide in Methanol.—A mixture of 0.257 g (0.78 mmol) of benzoyl *trans*-3-*p*-nitrophenylglycidyl peroxide and 10 ml of methanol was allowed to stand at 50° for 3 days. The methanol was evaporated and the solids were washed with carbon tetrachloride. The solid (127 mg, 80%) was identified as methyl *trans*-3-*p*-nitrophenylglycidate, mp 138–140°. The ir and nmr spectra were identical with those of the previously prepared sample.

Decomposition of Benzoyl *trans*-3-*p*-Nitrophenylglycidyl Peroxide in *t*-Butyl Alcohol.—A mixture of 255 mg (0.78 mmol) of benzoyl *trans*-3-*p*-nitrophenylglycidyl peroxide and 10 ml of *t*-BuOH was heated at 50° for 3 days. The alcohol was evaporated under vacuum.

The residue was dissolved in $CHCl_3$ and extracted with dilute sodium bicarbonate. Acidification of the aqueous solution and extraction with ether yielded, after drying and solvent removal, a solid. This solid was sublimed to give 72 mg (76%) of benzoic acid, mp 119–122°, which was identified by melting point and ir spectrum. Repetition of this decomposition in *t*-BuOH at 50° in which the entire original reaction residue was hydrolyzed at room temperature with aqueous sodium hydroxide yielded, after repetition of the above isolation procedure, 82% benzoic acid.

(38) "Dictionary of Organic Compounds," 4th ed, J. R. A. Pollock and R. S. Stevens, Ed., Oxford University Press, New York, N. Y., 1965, p 2437.

(39) Since the major products could not be quantitatively isolated, these percentage yields were calculated from the nmr spectrum. The total area of the aryl region was defined as 100%. Five times the integrated area of a single proton divided by the area of the aryl region thus represents the percentage yield of a given component.

(40) A. McKenzie, *J. Chem. Soc.*, **75**, 753 (1899).

(41) E. Kleucker *Ber.*, **55**, 1634 (1922).

The nmr spectrum of the neutral material revealed a major product which was assigned as 2-*t*-butoxy-2-*p*-nitrophenylacetaldehyde: nmr (CCl_4) δ 9.30 (d, 1, J = 2 Hz, CHCO), 8.2–7.2 (m, aromatic), 4.82 (d, 1, J = 2 Hz, CHPh), 1.26 (s, 9, C_4H_9). The structure was assigned on the basis of the nmr spectrum which is analogous to the that of 2-methoxy-2-phenylacetaldehyde. This aldehyde was formed in 20% yield. A second decomposition under the same conditions gave a yield of 22%.[42] Equal-intensity singlets present in several runs at δ 9.58 and 6.16 can tentatively be assigned (by analogy) to 2-benzoyloxy-2-*p*-nitrophenylacetaldehyde.

Attempts at isolating the 2-*t*-butoxy-2-phenylacetaldehyde by crystallization, chromatography, or distillation were unsuccessful. For this reason, several chemical transformations of the reaction mixture were explored.

The residue (191 mg) from the decomposition of 0.675 mmol of benzoyl 3-*p*-nitrophenylglycidyl peroxide was stirred at steam-bath temperature for 10 min in 10% sulfuric acid solution containing 105 mg of potassium dichromate. Only *p*-nitrobenzoic acid 43 mg (38%) was recovered in the acid fraction. The reaction was run at room temperature overnight and again yielded the identical acid. Oxidation was attempted at room temperature in a water–acetone system with excess silver oxide, but *p*-nitrobenzoic acid was again the sole product.

The residue from the decomposition of 304 mg (0.92 mmol) of benzoyl *trans*-3-*p*-nitrophenylglycidyl peroxide in *t*-BuOH was dissolved in 3 ml of ethanol and added to a solution 350 mg (9.2 mmol) of sodium borohydride in 20 ml of ethanol. The solution was allowed to stir overnight. About 20 ml of water was added and the solution was heated on the steam bath for 5 min. After cooling, the ethanol was evaporated and the product extracted into chloroform. The components were separated by thick layer chromatography on alumina with chloroform. The 2-*t*-butoxy-2-*p*-nitrophenylethanol was collected at R_F 0.6 as an oil: nmr (CCl_4) δ 8.2–7.4 (m, 4, aromatic), 4.6 (*t*, 1, J = 7 Hz, $CHCH_2OH$), 3.4 (broad *t*, 2, CH_2OH), 2.0 (broad t, 1, OH), 1.17 (s, 9, OC_4H_9). This oil could not be crystallized and was, therefore, converted into a phenylurethan derivative according to a standard procedure.[43] A white solid was obtained from CCl_4–petroleum ether (bp 00–00°): mp 69–71°; nmr (CCl_4) δ 8.3–7.0 (m, aromatic), 4.74 (t, 1, J = 7 Hz, $CHCH_2$), 4.00 (d, 2, J = 6 Hz, $CHCH_2$), 1.13 (s, 9, OC_4H_9); mass spectrum (70 eV) *m/e* (rel intensity) 358 (2.2), 328 (0.6), 208 (0.4), 119 (57.5), 117 (53.3), 57 (100) (expected: 358). Difficulties in obtaining and purifying this material did not permit obtaining a sample of analytical purity.

Decomposition of Benzoyl Peroxide in *t*-Butyl Alcohol.—A mixture of 500 mg (2.1 mmol) of benzoyl peroxide and 10 ml of *t*-BuOH was allowed to stand at 50° for 3 days. The alcohol was evaporated. The melting point and ir spectrum of the remaining white solid (416 mg, 83%) were identical with those of the starting material.

A mixture of 550 mg (2.3 mmol) of benzoyl peroxide and 15 ml of *t*-BuOH was refluxed for 2 days. The alcohol was evaporated and the product was hydrolyzed in aqueous sodium hydroxide at room temperature overnight. The basic solution was washed with chloroform and acidified with hydrochloric acid and the product was extracted into chloroform. The chloroform was evaporated and the residue was sublimed at 50° under vacuum to yield 54 mg (9.9%) of a white solid, mp 96–115°. The ir spectrum showed benzoic acid.

Decomposition of Benzoyl 3-*p*-Nitrophenylglycidyl Peroxide in Cumene.—Cumene was shaken with concentrated sulfuric acid until the acid remained colorless. It was washed three times with aqueous sodium bicarbonate solution and four times with water, dried over magnesium sulfate, and passed through activated silica. The cumene was then refluxed over sodium under nitrogen for 24 hr and distilled under nitrogen through a 40-cm, helices-packed, vacuum-jacketed column at a reflux ratio of 10:1. Cumene was collected at 152° (760 mm) and stored in the dark under nitrogen.

A sample of 101 mg (0.307 mmol) of benzoyl *trans*-3-*p*-nitrophenylglycidyl peroxide in about 10 ml of cumene was degassed and sealed under nitrogen. It was allowed to stand at 50° for 4 days in the dark. The sample was brought to exactly 10 ml and examined by gas chromatography. Comparison with an authentic equimolar solution of dicumyl showed the peroxide decomposition mixture to contain no detectable dicumyl. After distillation of cumene, the reaction mixture was hydrolyzed and the acidic products were sublimed to give 80% of benzoic acid, mp 120–122°.

Stability of Substituted Oxiranes toward Acid-Catalyzed Decomposition in Alcohol. A.—A solution of 121 mg (0.63 mmol) of ethyl *trans*-3-phenylglycidate and 105 mg (0.63 mmol) of *p*-nitrobenzoic acid in 20 ml of methanol was allowed to stand at 50° for 20 hr and the methanol was evaporated. The residue was separated into its components by extraction of the ester with carbon tetrachloride. The nmr spectra and weights of the two fractions revealed that the original materials had been recovered in quantitative yield.

B.—A mixture of 95 mg (0.73 mmol) of benzoic acid and 174 mg of (0.78 mmol) methyl *trans*-3-*p*-nitrophenylglycidate in 10 ml of *t*-BuOH was heated at 50° for 3 days. The mixture was then cooled and evaporated to give 269 mg of residue which was identified by nmr spectroscopy as an equimolar mixture of two starting materials.

Phenoxymethyl *p*-Nitrobenzoate.—A solution of 732 mg (4 mmol) *p*-nitroperbenzoic acid and 760 mg (5 mmol) phenoxyacetic acid in 40 ml each of CH_2Cl_2 and Et_2O was cooled to −25°. A cooled solution of N,N′-dicyclohexydicarbodiimide in 10 ml of CH_2Cl_2 was added rapidly with stirring. The urea began to precipitate within 45 sec. After 24 hr at −25°, the reaction was filtered and the filtrate was washed with water and 10% Na_2CO_3. After the mixture was dried, the solvents were evaporated. The residue was extracted with hot cyclohexane which yielded 840 mg (77%) of phenoxymethyl *p*-nitrobenzoate: mp 101–101.5°; ir ($CHCl_3$) 1773 cm^{-1} (C=O); nmr $CDCl_3$ δ 6.7–8.25 (m, 9, aromatic), 6.0 (s, 2, OCH_2O); mass spectrum (70 eV) *m/e* (rel intensity) 273 (13), 243 (3), 150 (100), 120 (13), 104 (32).

Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.55; H, 4.06. Found: C, 61.64; H, 4.17.

The cyclohexane-insoluble residue was extracted with chloroform. Evaporation of the chloroform gave 900 mg of material which was spectrally identified as 4,4′-dinitrobenzoyl peroxide. The yield of phenoxymethyl *p*-nitrobenzoate based on available peracid was 90%.

***p*-Nitrobenzoyl *trans*-2-Phenylcyclopropylcarboxoyl Peroxide.**—*p*-Nitroperbenzoic acid (100 g, 0.55 mmol) and N,N′-dicyclohexylcarbodiimide (1.00 g, 0.62 mmol) were added simultaneously to a cooled solution of *trans*-2-phenylcyclopropanecarboxylic acid (1.27 g, 0.62 mmol) in 150 ml of carbon tetrachloride. The mixture was allowed to stir at ice-bath temperature for 5 hr. The carbon tetrachloride was evaporated, 50 ml of chloroform was added and the N,N′-dicyclohexyl urea was removed by filtration. The chloroform was evaporated and the residual solid was recrystallized from chloroform by addition of ethanol yielding 1.03 g (57%) of the peroxide. The analytical sample was prepared by dissolving a sample partially in chloroform, filtering, eluting the solution through a 2-cm column of 20% deactivated alumina with chloroform, and recrystallizing the peroxide twice by addition of ethanol with about 50% loss of material. The sample was dried at room temperature under vacuum (0.2 mm) for 12 hr: mp 114–116° with evolution of gas; ir (Nujol) 1760 with a shoulder at 1780 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.1–8.34 (m, aromatic), 2.52–2.9 (m, 1, CHPh), 1.4–2.23 (m, 3, ring protons).

Anal. Calcd for $C_{17}H_{13}O_6N$: C, 62.38; H, 4.00; N, 4.28. Found: C, 62.17; H, 4.06; N, 4.13.

Decomposition of *p*-Nitrobenzoyl *trans*-2-Phenylcyclopropylcarboxyl Peroxide.—A saturated solution (about 10%) of *p*-nitrobenzoyl *trans*-2-phenylcyclopropylcarboxyl peroxide in deuterated chloroform failed to show any change in the nmr spectrum after standing at 50° for 2 weeks.

Registry No.—*trans*-3-Methylglycidyl *p*-nitrobenzoyl peroxide, 19190-77-3; potassium *trans*-3-phenylglycidate, 19190-78-4; *trans*-3-phenylglycidic acid, 1566-68-3; *p*-nitrobenzoyl *trans*-3-phenylglycidyl peroxide, 19190-79-5; 2-*p*-nitrobenzoyloxy-2-phenylacetaldehyde hydrazone, 19202-49-4; 2-methoxy-2-phenylacetaldehyde, 19190-53-5; methyl *trans*-3-phenylglycidate, 19190-80-8; methyl *trans*-3-*p*-

(42) The same method of calculating yields was used as previously described.[34] In this case, however, the integrated area of a single proton was multiplied by four.

(43) Reference 37, p 229.

nitrophenylglycidate, 19202-48-3; benzoyl *trans*-3-*p*-nitrophenylglycidyl peroxide, 19190-81-9; 2-*t*-butoxy-2-*p*-nitrophenylacetaldehyde, 19202-50-7; 2-*t*-butoxy-2-*p*-nitrophenylethanol, 19190-54-6; 2-*t*-butoxy-2-*p*-nitrophenylethanol phenylurethan derivative, 19190-55-7; phenoxymethyl *p*-nitrobenzoate, 19190-56-8; *p*-nitrobenzoyl *trans*-2-phenylcyclopropylcarboxoyl peroxide, 19202-51-8.

Synthesis of Perfluoroalkyl Vinyl Ether Acids and Derivatives

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Contribution No. 189 from E. I. du Pont de Nemours and Company, Elastomer Chemicals Department, Experimental Station, Wilmington, Delaware 19898

Received April 18, 1968

Potassium salts of certain perfluorodicarboxylic acids have been found to undergo a monodecarboxylation to yield perfluoroalkyl vinyl ether acid salts in low yield. Various carboxyl derivatives were prepared.

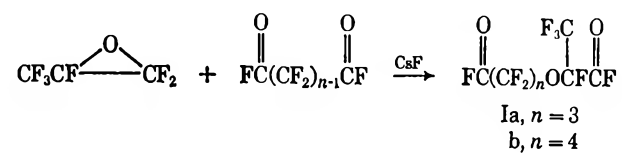
Although alkyl trifluorovinyl ethers, $ROCF{=}CF_2$, in which R is a hydrocarbon alkyl group can be prepared by the reaction of an alkali metal alkoxide with tetrafluoroethylene (TFE), this procedure generally fails when an alkali metal perfluoroalkoxide is used. An exception is the reaction of potassium perfluoroisopropoxide with fluorinated cyclobutene to give the vinyl ether.[2] In most cases the fluoroalkoxide anion prefers to lose fluoride ion rather than react with the fluoroolefin. The most convenient preparation of perfluoroalkyl vinyl ethers is by pyrolysis of certain fluorinated ether acid salts *via* the following reaction.

$$R_FOCF(CF_3)CO_2M \xrightarrow{\Delta} R_FOCF{=}CF_2$$[3]

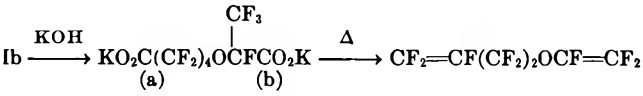
This general procedure has now been refined so that a selective pyrolysis of only one of the carboxyl groups to certain perfluoroalkyldicarboxylic acid salts can be carried out. Thus the reaction can now be used of prepare, although in low over-all yield, functionally substituted perfluoroalkyl vinyl ethers, a new class of compounds. The vinyl ether esters and nitriles can be copolymerized with other fluorinated monomers such as TFE and vinylidene fluoride and other perfluoroalkyl vinyl ethers.

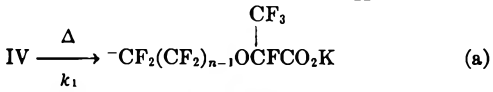
The type of dicarboxylic acid salt used is illustrated in IV, in which the rate of pyrolysis of the carboxyl group on the more substituted α-carbon (b) is faster than the rate of pyrolysis of the other end (a). Pyrolyses of this nature in the perfluorocarbon series are thought to proceed through a carbanion intermediate. The carbanion resulting from pyrolysis at (b) should be more stable due to the delocalizing ability of the α-CF_3 group. A fluorine α to a carbanion is known to have much less delocalizing ability than a fluorine β to the negative charge[4] due to an inductive effect through space.[5]

Compound I is easily prepared by the reaction of hexafluoropropylene epoxide (HFPO)[6] with a diacid fluoride to give the unsymmetrical adduct.[7] This reaction, carried out at $-30°$ in diglyme with cesium fluoride catalyst, involves initial reaction of cesium fluoride with a carbonyl group to give a perfluoroalkoxide, which then attacks the electrophilic center carbon of HFPO to produce I in about 70% yield.

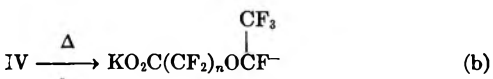


Ia, $n=3$
b, $n=4$





(a)



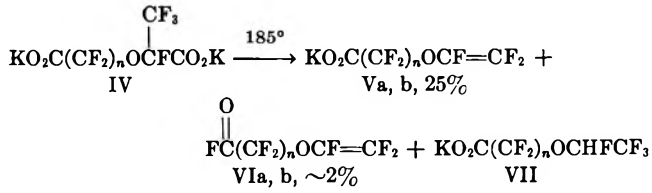
(b)

$k_2 > k_1$

Evidence of such a difference in the rate of pyrolysis came from the discovery of small amounts of monodecarboxylated product in the pyrolysis of the potassium salt IVb during preparation of the diene II. This product was isolated as the vinyl ether acid, perfluoro-6-oxa-7-octenoic acid (III). The normal temperature

$$CF_2{=}CFO(CF_2)_4CO_2H$$
III

for complete pyrolysis of IVb to the diene II[8] is 200–225°. Infrared and glpc analyses of the product from complete pyrolysis also give evidence of smaller amounts of the internal olefin $CF_3CF{=}CFCF_2OCF{=}CF_2$, which is produced by double-bond migration. For mono-



IV Va, b, 25%

VIa, b, ~2% VII

(1) Address correspondence to the author at the Stanford Research Institute, South Pasadena, Calif. 91030.

(2) R. W. Anderson, N. L. Madison, and C. I. Merrill, Abstracts, Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967, p 64.

(3) C. G. Fritz and S. Selman, U. S. Patent 3,291,843 (1966).

(4) S. Andreades, *J. Amer. Chem. Soc.*, **86**, 2003 (1964).

(5) A. Streitwieser, Jr., and D. Holtz, *ibid.*, **89**, 692 (1967); A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *ibid.*, **89**, 693 (1967).

(6) For a synthesis of HFPO see British Patent 904,877 (1962); *Chem. Eng. News*, **45**, (33), 18 (1967).

(7) C. G. Fritz and E. P. Moore, U. S. Patent 3,250,807 (1966).

(8) Compound II was first synthesized by this method by Dr. Charles G. Fritz, Plastics Department, E. I. duPont de Nemours & Co., Inc.

decarboxylation a lower temperature was called for. Pyrolysis of IVb at 185–200° gave the monodecarboxylated potassium salt Vb as the major product and in about 15–25% conversion. The pyrolysis was carried out under vacuum and the major product, being nonvolatile, remained behind in the reaction flask. The reaction can be halted when the volatile materials due to double decarboxylation (II) begin to collect in a cold trap connected to the pyrolysis flask.

A volatile by-product of this reaction is the vinyl ether acid fluoride VI, which is produced in low yield. Formation of acid fluorides and anhydrides has been previously reported during pyrolysis of fluorinated acid salts.[9] A more common by-product is the hydro ether VII, which arises from reaction of the carbanion (b) with traces of water of hydration in the potassium salt. Preparation of the dipotassium salt by neutralization of the dibasic acid with aqueous potassium hydroxide invariably gave a 2–5% conversion to the hydrocompound along the vinyl ether even after prolonged drying of the potassium salt (2–3 days under vacuum at up to 120°). Some pyrolysis may have occurred during the drying operation to give the hydro compound. To avoid contamination of the product by the hydro compound, it was necessary to prepare the dipotassium salt IV from the dimethyl ester by saponification with anhydrous potassium hydroxide in anhydrous methanol. Removal of the methanol solvent under vacuum could be done at a lower temperature and was more efficient than removal of water. Less than 1% of hydro compound was produced on pyrolysis after this procedure.

Although the pyrolysis of the dipotassium salt gave a low yield (18–25%) of the vinyl ether potassium salt, it was found that pyrolysis of the half-neutralized dibasic acid (VIII) at 185° gave a 70% conversion to monodecarboxylated product, about 70% of which was the hydro ether potassium salt and about 30% was the vinyl ether.

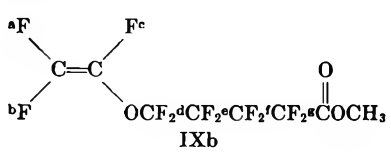
$$[O_2C(CF_2)_4OCF(CF_3)CO_2]^{2-}H^+K^+ \xrightarrow{185^\circ}$$
VIII

$$KO_2(CF_2)_4OCHFCF_3 + KO_2(CF_2)_4OCF{=}CF_2$$
50% 20%

$$\text{K salts} \xrightarrow[H^+]{MeOH}$$

$$CF_2{=}CFO(CF_2)_4\overset{O}{\overset{\|}{C}}OCH_3 + CF_3CHFO(CF_2)_4\overset{O}{\overset{\|}{C}}OCH_3$$
IXb XII

The vinyl ether acid salts were converted to their methyl esters for distillation and identified by ^{19}F nmr and by their infrared spectra. The infrared spectrum shows the vinyl ether unsaturation at 5.42 μ as a medium intensity band and the ester carbonyl at 5.6 μ. Fluorine nmr at 56.4 MHz showed the vinylic fluorine (a) of methyl perfluoro-6-oxa-7-octenoate (IXb) to



IXb

be two doublets centered at 117 ppm (referred to $CFCl_3$) with J_{ab} = 83 Hz and J_{ac} = 66 Hz. The fluorine at b occurs as four triplets at 124.6 ppm but is partly hidden by the CF_2 group at f with J_{bc} equal to 116 Hz and J_{bd} equal to 6 Hz. The fluorine at c was expected to be farther downfield due to the very electrophilic character of the CF_2O group and it occurs at 138.2 ppm as four triplets with J_{cd} = 6 Hz.

Other work done in these laboratories and elsewhere[10] has shown that the center for nucleophilic attack on the vinyl ether double bond is the terminal carbon. Thus the carbon next to oxygen has more delocalizing ability and fluorine c should be found far downfield. These absorptions are typical of all the perfluoroalkyl vinyl ethers that have been prepared to date. The CF_2O group of IXb occurs at 86.8 ppm, the CF_2 group e at 127 ppm, the CF_2 at f occurs at 125 ppm, and the CF_2 next to the carbonyl at 111 ppm. A number of derivatives of the pyrolysis products were prepared. The amide is easily prepared from the vinyl ether ester by reaction with ammonia. Addition of a stoichiometric amount of ammonia will give only the vinyl ether amide.

Addition of excess ammonia will presumably result in addition of ammonia across the vinyl ether double bond, loss of HF, and production of an amide nitrile.

$$H_2N\overset{O}{\overset{\|}{C}}(CF_2)_nOCF{=}CF_2 \xrightarrow{NH_3} H_2N\overset{O}{\overset{\|}{C}}(CF_2)_nOCHFCF_2NH_2 \xrightarrow{-HF} H_2N\overset{O}{\overset{\|}{C}}(CF_2)_nOCHFC{\equiv}N$$

Reaction of the vinyl ether with a secondary amine gives an adduct which is hydrolytically unstable and is converted to an amide on contact with water.[8]

$$R_fOCF{=}CF_2 + R_2NH \longrightarrow R_fOCHFCF_2NR_2 \xrightarrow{H_2O} R_fOCHF\overset{O}{\overset{\|}{C}}NR_2$$

The vinyl ether nitrile can be prepared in good yield in the conventional manner by reaction of the amide with phosphorus pentoxide at 160°.[11] The infrared spectrum of the nitrile XI shows the nitrile group at 4.4 μ and the double bond at 5.42 μ. The over-all

$$CF_2{=}CFO(CF_2)_n\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow{NH_3} CF_2{=}CFO(CF_2)_n\overset{O}{\overset{\|}{C}}NH_2$$
Xa, n = 3
b, n = 4

$$X \xrightarrow{P_2O_5} CF_2{=}CFO(CF_2)_nC{\equiv}N$$
XIa, b

yield of XIb beginning with perfluoroglutaryl fluoride was only about 6%.

Perfluorinated vinyl ethers are stable compounds with no known toxic properties. However, exposure to ultraviolet light will cause isomerization to the acid fluoride which then undergoes homolytic cleavage of

$$R_fOCF{=}CF_2 \xrightarrow{uv} R_fCF_2\overset{O}{\overset{\|}{C}}F \xrightarrow{uv} R_fCF_2CF_2R_f$$

(9) J. D. La Zerte, L. J. Hals, T. S. Reid, and G. H. Smith, *J. Amer. Chem. Soc.*, **75**, 4525 (1953).

(10) A. V. Tumanova, *et al.*, *Zh. Obshch. Khim.*, **35**, 399 (1965); *Chem. Abstr.* **62**, 13148e (1965).

(11) The nitrile XIb was prepared by Dr. Almut F. Breazeale, Elastomer Chemicals Department, E. I. du Pont de Nemours & Co., Inc.

the CF_2–COF bond to form products of radical coupling.[12]

Experimental Section

All ^{19}F nmr spectra were taken with a Varian Associates A-56/60 spectrometer at 56.4 MHz using $CFCl_3$ as an internal standard. Infrared spectra were taken with a Perkin-Elmer Infracord spectrophotometer. Melting and boiling points are uncorrected. Perfluoroglutaryl chloride and perfluorosuccinic acid were obtained from Peninsular Chemresearch, Inc. Perfluorosuccinyl chloride was prepared from the potassium salt by reaction with PCl_5. Hexafluoropropylene epoxide (HFPO) was obtained from Plastics Department, E I. du Pont de Nemours & Co. It is also available from Peninsular Chemresearch.

Preparation of Starting Materials.—Perfluoroglutaryl and succinyl fluorides were prepared from the corresponding acid chlorides by reaction with sodium fluoride in tetramethylene sulfone.[12] A typical example is as follows. Into a 2-l. three-neck flask fitted with mechanical stirrer, dropping funnel, and take-off condenser attached to a short Vigreux column were added 500 ml of tetramethylene sulfone and 200 g (5.3 mol) of sodium fluoride and warmed to 60°. Perfluoroglutaryl chloride (400 g, 1.44 mol) was added at such a rate as to maintain the head temperature at 50° or less. The perfluoroglutaryl fluoride was distilled, bp 47–49°, 315 g (90%). The yield of perfluorosuccinyl fluoride (bp 18–19°) was 80%.

Perfluoro-2-methyl-3-oxaoctanedioyl Fluoride (Ib).—A dry 1-l. three-neck flask, fitted with a mechanical stirrer and with fittings wired down to contain 5–10 psig, was charged with 427 g of perfluoroglutaryl fluoride under dry nitrogen, 150 ml of diglyme, and 30 g of cesium fluoride. The vessel and contents were cooled to −30° in a Dry Ice–acetone bath and evacuated to about 25 mm. The mixture was stirred vigorously and 335 g of hexafluoropropylene epoxide (HFPO) was condensed into the flask. The temperature was gradually raised to maintain pressure between 0 and 5 psig for about 8 hr until at room temperature no excess pressure remained in the flask. Distillation of the reaction mixture at 1 atm under dry nitrogen yielded perfluoro-2-methyl-3-oxaoctanedioyl fluoride, bp 108°, in 75% yield based on the perfluoroglutaryl fluoride; nmr of **Ib**: −21.6 (1 F, C-COF), −23.8 (1 F, O-C-COF), the CF_2O group forms an AB system at 80.5 and 87.5 (J = 148 Hz), 84.5 (3 F, CF_3), 120 (2 F, O=CCF_2), 125 (2 F, O=$CCCF_2$), 127 (2 F, O=$CCCCF_2$), 146 ppm (1 F, OCF).

A more convenient procedure is to maintain the reaction flask at or above room temperature and at 1 atm of pressure and to lead the HFPO into the flask from a stainless steel cylinder at a rate sufficient to maintain a good reflux from a condenser kept at Dry Ice temperature. The reaction is somewhat exothermic and was cooled in a water bath to keep the temperature down to an arbitrary 50–55°. The advantage of this method is a shorter reaction time (~2 hr).

Perfluoro-2-methyl-3-oxaheptanedioyl Fluoride (Ia).—The adduct was prepared in good yield by condensing 270 g (1.62 mol) of HFPO in an evacuated and dry 1-l. three-neck flask kept at −30° and containing 315 g (1.62 mol) of perfluorosuccinyl fluoride, 50 ml of diglyme, and 10 g of cesium fluoride. The HFPO was added over a 1.5-hr period and the contents were stirred vigorously with a mechanical stirrer. Pressure inside the flask was kept between −10 and +5 psig for about 18 hr. Glpc analysis showed very little starting material and one product peak. The fluorocarbon layer was distilled to give 453.5 g (1.26 mol) of perfluoro-2-methyl-3-oxaheptanedioyl fluoride, bp 86° (80%).

The dipotassium salt IVa was prepared from the diacid fluoride by the addition of KOH in excess water. Phenolphthalein was used to determine the end point. Thorough drying of the salt under vacuum at 100° for 2–3 days was required before pyrolysis.

Dipotassium Perfluoro-2-methyl-3-oxaoctanedioate (IVb). A. IVb from the Acid.—A two- or threefold excess of water was cautiously added to the warm (about 50°) diacid fluoride Ib in a polypropylene beaker. Some of the HF which was formed and excess water were removed under vacuum. The acid was dissolved in water and neutralized to the phenolphthalein end point with aqueous potassium hydroxide. The salt was then dried thoroughly on a rotovac under vacuum at about 100° for several days. It was ground into a fine powder several times during the drying process.

B. From the Ester.—Into an open polyethylene bottle under an atmosphere of dry nitrogen was charged 443 g of perfluoro-2-methyl-3-oxaoctanedioyl fluoride. The bottle and contents were warmed to about 50° and 50 ml of methanol was added slowly and cautiously with occasional stirring in 0.5 hr. The bottle and contents were warmed on a steam bath for several hours at atmospheric pressure to remove excess HF, then stored overnight over sodium fluoride. The liquid was distilled on an 18-in. spinning band column at reduced pressure to yield 462 g of dimethyl perfluoro-2-methyl-3-oxaoctanedioate, bp 112° (1.5 mm). The dimethyl ester was then mixed with an approximately equal volume of methanol, and several drops of phenolphthalein solution and methanolic anhydrous KOH were added to the ester at a rate sufficient to maintain a temperature of 40–50° until the phenolphthalein end point was reached. Solvent was removed by heating *in vacuo* at 50–65° for 1 week. The hydroscopic salt was ground several times during the drying period into a finer mesh and stored as a fine powder under dry nitrogen in preparation for pyrolysis.

Potassium Perfluoro-6-oxa-7-octenoate (Vb). A. Pyrolysis of Dipotassium Perfluoro-2-methyl-3-oxaoctanedioate (IVb) Prepared from the Acid.—Pyrolysis of 250 g of the salt was carried out with 40–50-g batches of the finely ground dipotassium salt IVb in a 250-ml three-neck flask under vacuum. The flask was connected in series to a Dry Ice trap and liquid nitrogen trap and the vacuum pump. The flask was then immersed in a silicone oil bath preheated to 195°. The powder was frequently agitated to prevent caking on the bottom of the flask. At this temperature, CO_2 evolution could be observed by its solidification in the liquid nitrogen trap. The temperature was raised slowly until, after 2–4 hr, it stood at 210°. At this point a small amount of liquid began to collect in the Dry Ice trap. This liquid is largely the diene II and results from decarboxylation at both ends of the molecule. Heating was then discontinued.

B. Pyrolysis of IVb Prepared from the Ester.—A sample of 41.5 g of the dipotassium salt IVb prepared under anhydrous conditions from the ester was pyrolyzed in the same manner as described above. However, after immersion of the salt in the oil bath at 190°, the salt fused into a crusty mass. It was cooled and reground into a fine powder. After this, the salt remained as a powder during pyrolysis. The fine powder is necessary to prevent complete pyrolysis and to ensure good heat transfer. Heating was continued at 190–204° for 3.5 hr.

Methyl Perfluoro-6-oxa-7-octenoate (IXb). A.—The brown solid after pyrolysis of 250 g of IVb (prepared from the acid of Ib) was dissolved in water and acidified with concentrated HCl solution to separate the fluorocarbon acid. The water layer was extracted with ether and the ether extract was combined with the acid layer and filtered. The acid was then mixed with excess methanol and sulfuric acid and refluxed for 2 hr. The lower ester layer was separated, dried over anhydrous magnesium sulfate, and distilled into two fractions: 36 g of bp 146–150° and 6 g of by 150–156°. Also approximately 10% of the ester of the unreacted dibasic acid was recovered.[13] The product composition was analyzed using a glpc column of Dow Corning FS 1265 fluid on firebrick at 100°. The first fraction consisted of 80% of IXb and 20% of XII; the second fraction contained 65% of XII. Samples for analysis were obtained from further distillation. Yields were about 18% of IXb and 6% of XII. Infrared of IXb showed 3.4 (w), 5.45 m (C=C), 5.6 s (C=O), 7.0 m, 7.5 s, 7.7 s, 8.5 sb, 9.6 m, 10.5 m, 11.4 m, 12.6 m, 13.3 m, and 14.1 m μ. *Anal.* Calcd for $C_8H_3O_3F_{11}$: C, 26.98; H, 0.84; F, 58.69. Found: C, 27.1; H, 1.0; F, 59.7.

Nmr of XII showed that the OCF_2 group forms an AB system at 86.5 and 88.5 ppm (J = 150 Hz) and peaks at 86.6 (3 F, CF_3), 120 (2 F, CF_2C=O), 125 (2 F, CF_2CC=O), 127 (2 F, $OCCF_2$), 148 ppm (1 F, J_{HF} = 52 Hz, CHF). *Anal.* Calcd for $C_8H_4O_3F_{12}$: C, 25.5; H, 1.1; H, 60.6. Found: C, 24.9; H, 1.3; F, 58.8.

From 575 g of the dipotassium salt pyrolyzed (IVb), 31 g of cold-trap condensate was accumulated. Distillation under a dry nitrogen atmosphere yielded 7.3 g (2.1% conversion) of perfluoro-6-oxa-7-ocetenoyl fluoride (VIb), bp 90–91°, as well as some of the diene, II. Identification was inferred from the infrared and nmr spectra and by reaction with methanol to give an ester with infrared spectrum identical with that of IXb:

(12) J. F. Harris, Jr., *J. Org. Chem.*, **30**, 2182 (1965).

(13) These are over-all yields based on the amount of dipotassium salt pyrolyzed.

infrared, 5.3 (C=O) s, 5.4 (C=C) w, 7.5 s, 7.8 s, 8.4 vsb, 9.0 m, 9.8 m, 11.3 m, 11.7 m, 12.5 m, 13.2 m, and 14.0 m μ; nmr, −21.6 (1 F, COF), 87 (2 F, OCF_2), 117 (2 d, 1 F, J = 86, 66 Hz, CF=CO), 120 (2 F, CF_2C=O), 125 (4 t, 1 F, J = 112, 86, 6 Hz, CF=CO, *trans*), 125 (2 F, $OCCCF_2$), 127 (2 F, $OCCF_2$), 139 ppm (4 t, 1 F, J = 112, 66, 6 Hz, C=CFO).

B.—The brown solid after pyrolysis of 41.5 g of IVb (prepared from the diester under anhydrous conditions) was worked up as described above and distilled to give 7.7 g of vinyl ether ester IXb, bp 144°, 25% conversion, and 8.6 g of unpyrolyzed ester was recovered. Glpc analysis of the product showed only 0.4 area % of the saturated ester XII.

Pyrolysis of Dipotassium Perfluoro-2-methyl-3-oxaheptanedioate (IVa).—The dry potassium salt, prepared from Ia *via* the aqueous procedure described above for IVb, was pyrolyzed in 50–75-g batches in a 500-ml round-bottom flask at a temperature of 190–198° and about 1 mm. The flask was connected to a Dry Ice trap, a manometer, and a pump. Frequent agitation of the finely ground salt was necessary to prevent it from caking too much. Heating was continued for 2–3 hr and about 2–3 g of a yellow liquid collected in the Dry Ice trap during each run. The end of the reaction could be approximated by the amount of liquid collected which is a crude measure of the amount of twice-decarboxylated product forming. At temperatures above 198° the salt melted. In order to decarboxylate one end of the potassium salt and not the other, the pyrolysis must be run at the lowest temperature possible, and at 190° a satisfactory rate of CO_2 evolution was obtained. As the reaction proceeded, the temperature was raised slowly to 198°. Evolution of CO_2 is noticeable due to agitation of the powder by the escaping gas. At 198°, after 2–3 hr, this agitation had diminished: potassium salt pyrolyzed, 460 g (1.06 mol); pyrolysis residue (crude product), 362.4 g; recovered in Dry Ice trap, 37.4 g; estimated CO_2 lost (1.06 mol), 46.6 g; unaccounted loss during pyrolysis, 13 g.

Methyl Perfluoro-5-oxa-6-heptenoate (IXa).—A sample of 317 g of the crude pyrolysis product was taken up in water and concentrated HCl was added. The lower organic acid layer was separated and dried by distilling off a benzene–water azeotrope, and then excess methanol and excess concentrated sulfuric acid were added and refluxed for 7 hr. The product was washed with water and distilled with benzene to dryness. Distillation under reduced pressure gave 41 g (18%) of the vinyl ether ester, bp 61–62° (51 mm) (contained about 10% of the saturated hydro ester), and about 2 g of the saturated ester, $CH_3O_2C(CF_2)_3$-$OCHFCF_3$. Twenty-one per cent of the starting material was recovered as the dimethyl ester and the diacid. Infrared of IXa showed 3.3 w, 5.45 m, 5.6 s, 6.95 m, 7.5 sb, 8.5 vsb, 9.3 m, 10.2 m, 10.9 m, 12.2 m, 12.5 m, 12.9 w, 13.4 m, and 13.9 m μ; nmr, 87 (2 F, OCF_2), 117 (2 d, 1 F, J = 88, 66 Hz, CF=CO), 121 ppm (t, 2 F, CF_2C=O), 124.5 (4 t, 1 F, J = 110, 88, 6 Hz, CF=CO, *trans*), 128 (2 F, $OCCF_2$), 142 ppm (4 t, 1 F, J = 110, 66, 6 Hz, C=CFO).

Anal. Calcd for $C_7H_3O_3F_9$: C, 27.46; H, 0.98; F, 55.87. Found: C, 27.5; H, 1.02; F, 55.9.

From 460 g of dipotassium salt IVa which was pyrolyzed, there was recovered 37.4 g of liquid from the Dry Ice trap which was distilled to give 7.4 g (2.5%) of perfluoro-5-oxa-6-heptenoyl fluoride (VIa), bp 70°. Identification was inferred from the infrared and nmr spectra and by reaction with methanol to give an ester with infrared spectrum identical with IXa: infrared, 5.3 s (C=O), 5.4 m (C=C), 7.4 s, 7.7 s, 8.4 vsb, 8.8 s, 9.4 m, 10.4 m, 10.8 m, 12.3 m, 13.0 m, 13.9 m, and 14.5 m μ; nmr, −21.6 (1 F, COF), 87 (2 F, OCF_2), 117 (2 d, 1 F, J = 88, 66 Hz, CF=CO), 121 (2 F, CF_2C=O), 124 (4 t, 1 F, J = 110, 88, 6 Hz, CF=CO *trans*), 129 (2 F, $OCCF_2$), 139 ppm (4 t, 1 F, J = 110, 66, 6 Hz, C=CFO).

Pyrolysis of the Half-Neutralized Perfluoro-2-methyl-3-oxaoctanedioic Acid (VIII).—The finely powdered salt was pyrolyzed at a bath temperature of 185–190° with frequent agitation to prevent caking as for the dipotassium salt. At 185° a melt formed which immediately gave off CO_2, leaving a solid residue. After about 2 hr, CO_2 evolution had ceased. Preparation of the esters as described above gave a 70% yield of monodecarboxylated esters which consisted of 27% of IXb and 73% of XII.

Perfluoro-5-oxa-6-heptenamide (Xa).—One gram of anhydrous ammonia (0.06 mol) was condensed in a graduated cold trap and allowed to evaporate into a 250-ml three-neck flask containing 35 ml of anhydrous ether and 18.3 g (0.06 mol) of the vinyl ether ester IXa at −30°. The vinyl ether had been purified by distillation to remove the saturated ester. The contents were stirred magnetically and the flask was evacuated before addition of the ammonia. The uptake of ammonia was complete in 5 min and the flask was allowed to warm to room temperature. The solvent was removed under vacuum and a white solid remained. Crystallization from benzene gave 13 g (73%) of white crystals. The melting point of 64.5–65.5° was determined after a second crystallization and sublimation; infrared, 3.0 m, 5.4 m, 5.9 sb μ (C=O).

Anal. Calcd for $C_6H_2F_9O_2N$: C, 24.7; H, 0.7; N, 4.8. Found: C, 24.8; H, 0.9; N, 4.27.

Preparation of the next higher homolog, perfluoro-6-oxa-7-octenamide (Xb), was accomplished in the same manner to give a 75% yield of white solid, mp 89.5–91.5°.

Anal. Calcd for $C_7H_2F_{11}O_2N$: C, 24.6; H, 0.6; N, 4.1; F, 61.3. Found: C, 24.4; H, 0.8; N, 3.8; F, 62.1.

Perfluoro-1-cyano-5-oxa-6-heptene (XIb).—Twelve grams (0.04 mol) of the amide Xb was thoroughly mixed with 8 g (0.056 mol) of phosphorus pentoxide in a drybox and placed in a 300-ml round-bottom flask. A steam-heated reflux condenser was attached in order to keep the amide (mp 90°) from crystallizing high up on the walls of the flask. A Dry Ice trap was attached, the flask was placed in an oil bath previously heated to 140°, and the heat was gradually increased to 160°. After 2 hr, 2 g of fresh P_2O_5 was added and heating was continued for 2 hr more. The flask was swept clean of product by evacuation and the crude nitrile was distilled to give 7.1 g (65%) of vinyl ether nitrile, bp 89–91°. Glpc analysis showed this material to contain 17 area % of the saturated ether nitrile derived from XII and 83% of XIb. Infrared of an 83:17 mixture showed 4.4 m, 5.45 m, and 7.7–8.8 vsb μ; nmr, 87 (2 F, OCF_2), 108 (2 F, $CF_2C{\equiv}N$), 117 (2 d, 1 F, J = 83, 64 Hz, CF=CO), 125 (5 F, 2 multiplets, CF=CO, $OCCF_2CF_2$), 138 ppm (4 t, 1 F, J = 108, 64, 6 Hz, C=CFO).

Anal. Calcd for $C_7F_{11}ON$: C, 26.02; F, 64.69; N, 4.33. Found: C, 26.2; H, 0.3; F, 64.7; N, 4.62.

Registry No.—Ia, 19190-57-9; Ib, 13140-22-2; IXa, 19190-61-5; IXb, 19190-58-0; Xa, 19190-59-1; Xb, 19190-60-4; XIb, 19237-73-1; XII, 19190-62-6; dimethyl perfluoro-2-methyl-3-oxaoctanedioate, 16835-45-3.

Photoacylation. II. Intramolecular Photoacylation of Enolates[1]

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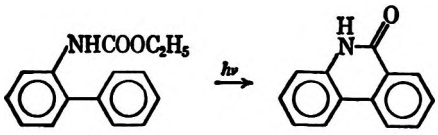
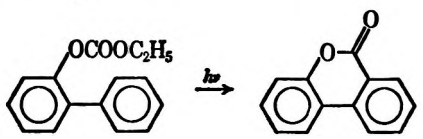
Received October 25, 1968

Under the influence of ultraviolet light, the sodium enolate of diethyl *o*-biphenylylmalonate (**5**) in ethanol undergoes intramolecular photoacylation to give ethyl 9-phenanthrol-10-carboxylate (**6**) in 70% yield. The reaction had been extended to the enolates of phenylethylidenemalonate (**7**) and phenylethylidenecyanoacetate (**8**) systems. They cyclized to give the corresponding naphthol derivatives. The reaction represents a new type of photochemical process of organometallic compounds which may have synthetic applications.

In an earlier communication from this laboratory,[1] we reported that ethyl N-*o*-biphenylylcarbamate (**1**) and ethyl *o*-biphenylylcarbonate (**2**) underwent intermolecular photoacylation to give tricyclic products (reactions 1 and 2). The reaction had been extended to a number of other systems.[3] The pathway of this reaction may be visualized as the photoactivation of the aromatic system followed by the ring closure. In contrast to the Lewis acid catalyzed acylatin of aromatic compounds, the reaction may be carried out in neutral media and under mild conditions. The scope and limitation of this process were examined, and the current report deals with the intramolecular photoacylation of enolates.



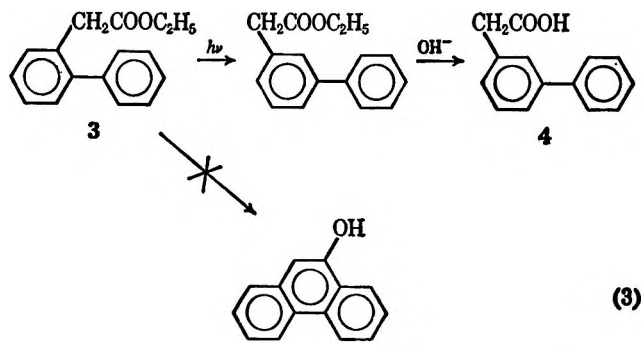
1 (1)



2 (2)

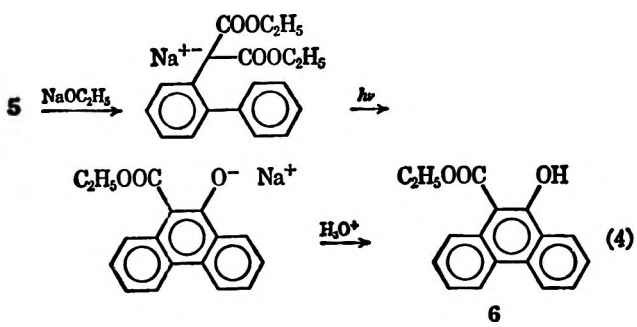
Results and Discussion

In contrast to ethyl *o*-biphenylylcarbamate (**1**) and ethyl *o*-biphenylylcarbonate (**2**), ethyl *o*-biphenylylacetate (**3**) does not undergo intramolecular photoacylation to give a tricyclic product. When a benzene solution of **3** was irradiated with a Hanovia medium-pressure mercury arc, the uv absorption spectrum of the system gradually shifted to longer wavelength, the nmr spectrum underwent no appreciable change except in the aromatic proton region, while the ir spectrum remained essentially unchanged. These results indicated that **3** might be undergoing a molecular rearrangement to give a less-hindered isomeric biphenyl derivative. Chromatography, saponification and recrystallization of the irradiated mixture yielded *m*-biphenylylacetic acid (**4**). Therefore instead of undergoing intramolecular photoacylation, **3** rearranges to give the less-hindered *meta* isomer (reaction 3). Although the mechanism of this rearrangement was not examined in detail, it may well be analogous to the position isomerization of simple substituted benzene derivatives under the influence of light which proceeds *via* a benzvalene derivative as the intermediate.[4]



3 **4** (3)

The photobehavior of **3** suggests that systems containing nonbonding 2p electrons conjugated with the aromatic nucleus are necessary for the intramolecular photoacylation. In compounds **1** and **2**, these electrons derive from the heteroatom, nitrogen or oxygen. The photochemistry of the enolate of diethyl *o*-biphenylylmalonate (**5**), which also possesses nonbonding 2p electrons as carbamate **1** and carbonate **2**, was subsequently examined. When an ethanolic solution of **5** was irradiated in the presence of sodium ethanolate, a facile cyclization occurred (reaction 4). Only a single product was detected by tlc which is less polar and fluoresces more strongly than **5**. Ethyl 9-phenanathrol-10-carboxylate (**6**) was isolated in 70% yield by chromatography, and its structure was established by spectroscopic determinations. The properties of **6** parallel closely to those reported for the corresponding methyl ester.[5] We also found that **5** does not undergo intramolecular photoacylation in the absence of sodium ethanolate, neither does it undergo thermal cyclization below 185°.



6 (4)

The scope of this reaction was extended to the

(1) Paper I: N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, **88**, 5369 (1966).

(2) On leave of absence from the Department of Chemistry, National Taiwan University, Taipei, Taiwan, China.

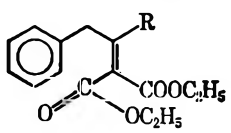
(3) G. R. Lenz and N. C. Yang, *Chem. Commun.*, 1136 (1967); G. R. Lenz, Ph.D. Thesis, University of Chicago, 1967.

(4) L. Kaplan, K. E. Wilzbach, W. G. Brown, and S. S. Yang, *J. Amer. Chem. Soc.*, **87**, 675 (1965), and later papers.

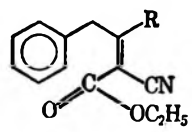
(5) I. M. Hunsberger, R. Ketchum, and H. S. Gutowsky, *ibid.*, **74**, 4839 (1952).

enolates of phenylethylidene malonate (**7**) and phenylethylidene cyanoacetate (**8**) systems. Both ethyl 2-carbethoxy-3-methyl-4-phenyl-2-butenoate (**7a**) and ethyl 2-cyano-3-methyl-4-phenyl-2-butenoate (**8a**) were prepared by the Knoevanagel reaction between phenylacetone and diethyl malonate or ethyl cyanoacetate according to the method of Marion and McRae (reaction 5).[6]

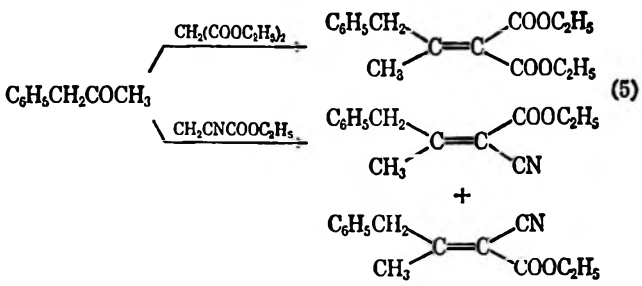
When the same reaction was applied to prepare ethyl 2-carbethoxy-4-phenyl-2-butenoate (**7b**) from phenyl-



7a, R = CH_3
b, R = H



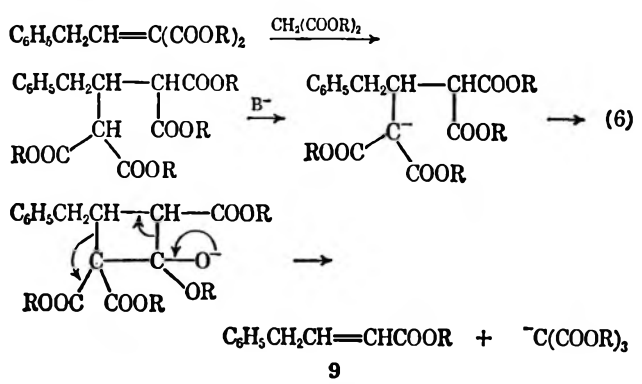
8a, R = CH_3



(5)

acetaldehyde and diethyl malonate, considerable experimental difficulty was encountered. Following a published procedure,[7] only ethyl 4-phenyl-2-butenoate (**9**) was isolated as the product. By modifying the reaction conditions and reducing the reaction time, a mixture of **7b** and **9** was isolated in a relative ratio of 1:4 which could not be separated by repeated distillation or by chromatography. The mixture was used for irradiation without further purification.

A rational explanation for our difficulty in the preparation of **7b** is that **7b** may undergo Michael addition with the excess malonate present in the reaction medium after it is formed. The formation of **9** as the major product in the condensation may be rationalized through the following pathway analogous to the abnormal Michael addition (reaction 6).

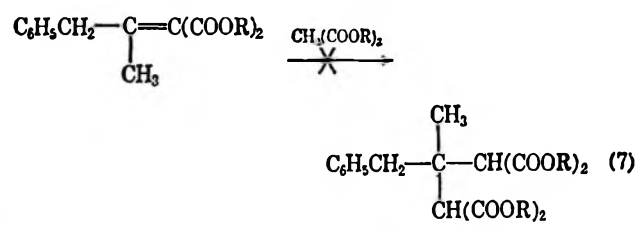


(6)

9

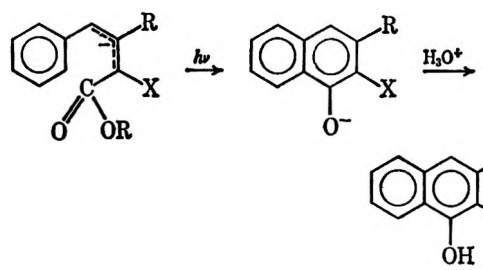
We were unsuccessful in preparing ethyl 2-cyano-4-phenyl-2-butenoate (**8b**) from phenylacetaldehyde and ethyl cyanoacetate following a published procedure.[8] The material obtained showed the absence of any olefinic proton in the nmr spectrum, and we concluded that secondary reaction may have occurred in this condensation.

In contrast to compounds **7b** and **8b**, compounds **7a** and **8a** prepared from phenylacetone will undergo Michael addition much more slowly or not appreciably under the same reaction conditions. In **7a** and **8a**, since the site of addition of a carbanion in the Michael addition is an sp^2 carbon bearing two substituents (C_6H_5– and CH_3–), the product formed would be a highly hindered one with a quarternary carbon atom at position 3 (reaction 7).



(7)

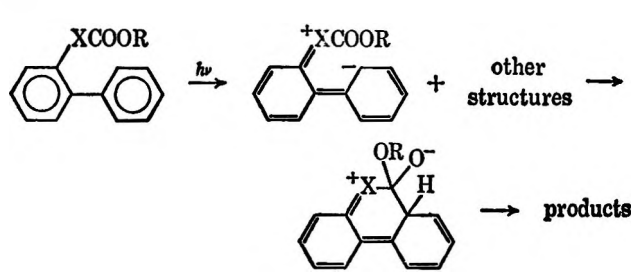
From compounds **7a**, **8a** and **7b**, the enolates undergo intramolecular photoacylation smoothly to give naphthol derivatives **9**, **10** and **11** (reaction 8).



(8)

9, R = CH_3; X = $COOC_2H_5$
10, R = CH_3; X = CN
11, R = H; X = $COOC_2H_5$

The principal transition in the biphenyl system is the L_a transition which exhibits considerable charge-transfer character.[9] When systems containing nonbonding 2p electrons such as carbonions or heteroatoms are conjugated with the biphenyl system, the nonbonding electrons will delocalize into the biphenyl system in the electronic excited state. There will be an increase in electron density at the *o'* positions in the excited state of **1**, **2** and the enolate of **5** which will facilitate the cyclization to give the tricyclic products. The electronic transition in the enolates of **7** and **8** has not been characterized, however, a similar process apparently applies here also.



The photochemistry of organometallic compounds has not been systematically investigated. The princi-

(6) L. Marion and J. A. McRae, *Can. J. Res.*, **18, B**, 265 (1940).
(7) D. Vorländer, *Ann.*, **345**, 245 (1906).
(8) R. P. Linstead and C. T. D. Williams, *J. Chem. Soc.*, 2745 (1962).
(9) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, New York, N. Y., 1962, pp 273–276, 389–407.

pal photochemical reaction of simple organometallic compounds such as organolithium reagents is the formation of radicals.[10] This investigation represents a new photochemical reaction of organometallic compounds which has possible synthetic applications. The investigation is being continued.

Experimental Section

General Procedure.—The light source used was a Hanovia 450-W medium-pressure mercury arc. Irradiations were carried out in an apparatus consisting of two parts, an outer jacket and a dipper well. The dipper well was a water-cooled Hanovia 5-l. flask immersion well made of quartz. The outer jacket was made of Pyrex glass fitted with a fritted nitrogen inlet at the bottom and septum-covered inlet in the midsection for withdrawing aliquots during an irradiation. Different jackets varying in capacity from 150 to 250 ml were used. The solution level was always kept above the top of the mercury arc to prevent pyrolysis. Melting points and boiling points were uncorrected. Mass spectra were recorded with an AEI MS-9 high-resolution mass spectrometer, uv spectra with a Cary 14 spectrometer, and ir spectra with a Perkin-Elmer Infracord or a Beckman IR-7 spectrometer. Nmr spectra were obtained on a Varian A-60 or A-60A spectrometer in CCl_4 or $CDCl_3$ with TMS as an internal standard. Microanalyses were carried out by the Micro-Tech, Inc. of Skokie, Ill., or by Dr. A. Bernhardt of Mülheim, Germany.

Ethyl *o*-biphenylylacetate (3) was prepared by the esterification of the corresponding acid.[11]

Diethyl *o*-biphenylylmalonate (5) was prepared from **3** following the method of Carissimi and coworkers.[11]

Ethyl 2-carbethoxy-3-methyl-4-phenyl-2-butenoate (7a) was also prepared by the method of Marion and McRae.[6] A mixture of phenylacetone (67 g), diethyl malonate (80 ml), aniline–$ZnCl_2$ complex (from 10 ml of aniline and 25 g of freshly dried $ZnCl_2$) and acetic anhydride (60 ml) was heated at 100° for 75 hr. The crude products (34 g) were obtained after the usual work-up and vacuum distillation, bp 140–194° (0.4 mm). Acetanilide (8.3 g) which crystallized upon standing was removed by filtration. The filtrate was fractionally distilled to yield a constant-boiling fraction (20 g), bp 116° (0.05 mm). This fraction was shown to be a mixture by tlc on a Kodak alumina strip developed with ethyl acetate. In addition to the main spot (R_f 0.60), two other impurities (R_f 0.29 and 0.04) were found. A part of this fraction (14.5 g) was chromatographed over basic alumina (200 g, Merck). The second fraction eluted with ethyl acetate showed only a single spot on tlc was concentrated to yield an oily liquid (7.1 g). It was distilled under reduced pressure to give pure **7a** (6.0 g): bp 116° (0.05 mm); ir (neat) 1715 cm^{-1} (conjugated ester C=O); nmr (CCl_4) δ 1.25 (t, 6, J = 7.2 Hz, OCH_2CH_3), 1.92 (s, 3, allylic, CH_3), 3.69 (s, 2, $ArCH_2$), 4.20 (q, 2, J = 7.2 Hz, OCH_2CH_3), 4.23 (q, 2, J = 7.2 Hz, OCH_2CH_3), and 7.25 ppm (s, 5, ArH).

Ethyl 2-cyano-3-methyl-4-phenyl-2-butenoate (8a) was prepared according to the method of Marion and McRae.[6] Phenylacetone (40.2 g), ethyl cyanoacetate (33.9 g), and piperidine (1.5 ml) were stirred at room temperature for 2 days. After the work-up, the mixture was distilled under reduced pressure to yield a fraction boiling at 120–128° (0.05–0.10 mm) (25 g). This fraction was fractionally redistilled to give **8a** (20 g): bp 126° (0.05 mm); ir neat 2220 (CN) and 1720 cm^{-1} (conjugated ester C=O).

The nmr spectrum of **8a** revealed that it was a mixture of two geometrical isomers in a ratio of 4:5: nmr (CCl_4) δ 1.31 (t, 3, J = 7.1 Hz, OCH_2CH_3), 2.10 and 2.21 (s, 3, allylic, CH_3), 3.82 and 4.17 (s, 2, $ArCH_2$), 4.21 and 4.25 (q, 2, J = 7.1 Hz, OCH_2CH_3), and 7.18 and 7.20 ppm (s, 5, ArH). Assuming the ester function is a more effective deshielding group than the nitrile function, the major isomer was assigned the structure with the 3-methyl group *cis* to the ester group on the basis of nmr.

Condensation of Phenylacetaldehyde with Diethyl Malonate.—The method of Vorländer[7] was followed exactly in an attempted preparation of ethyl 2-carbethoxy-4-phenyl-2-butenoate (**7b**). To a mixture of phenylacetaldehyde (25 g) and diethyl malonate (68 g) maintained at 5°, diethylamine (2 ml) was added with stirring. Additional diethylamine was added daily over a period of 7 days (total 5 g) while the stirring continued. After the usual work-up, a portion of the reaction mixture (4.5 g) was distilled to yield a fraction (130 mg), bp 127–130° (0.6 mm). The ir and nmr spectra of this fraction indicated that it was essentially pure ethyl 4-phenyl-2-butenoate (**9**) instead of the desired product. The procedure was then modified. To a mixture of phenylacetaldehyde (25 g) and diethyl malonate (68 g) and glacial acetic acid (3 ml) maintained at 5°, diethylamine (7.5 ml) was added slowly and the stirring was continued at room temperature for 16 hr. The reaction mixture was fractionally distilled under reduced pressure three times to yield a fraction (5.46 g), bp 124–126° (0.05 mm). On the basis of the ratio of olefinic protons to other protons in the nmr, the mixture was shown to be a mixture of **9** and **7a** in a relative ratio of 4:1. The purity of this fraction was not improved either by column chromatography or by further distillation under reduced pressure.

Condensation of Phenylacetaldehyde with Ethyl Cyanoacetate.—The condensation was attempted according to the method of Linstead and Williams.[8] From phenylacetaldehyde (18 g), ethyl cyanoacetate (17.4 g) and diethylamine (1.5 ml), a fraction (7.3 g) boiling at 120–140° (0.15 mm) was obtained after the work-up and distillation under reduced pressure. The fraction was redistilled to yield a mobile mass (4.1 g), bp 124° (0.05 mm). The nmr spectrum of these fractions showed the absence of any olefinic proton, and we concluded that no desired product was formed in this reaction.

Irradiation of Ethyl *o*-Biphenylylacetate (3).—Ethyl *o*-biphenylylacetate (0.30 g) in 100 ml of benzene was irradiated under nitrogen for 16 hr. The ir spectrum of the crude mixture was virtually the same as that of the starting material but the uv spectrum showed a significant red shift to 248 mμ (log ϵ = 4.04) and the nmr spectrum showed a different aromatic resonance pattern and the ethoxyl group protons were shifted slightly downfield. Chromatography on acid-washed alumina gave 0.22 g (ether–hexane 1:19) of a 9:1 mixture of ethyl *m*-biphenylylacetate and the starting material. Saponification of 90 mg of this mixture in 100 ml of 2% ethanolic KOH for 1 hr gave, after dilution with water and acidification, 70 mg of crude acid, mp 95–105°. Recrystallization of the acid from benzene–petroleum ether (bp 30–60°) gave pure *m*-biphenylylacetic acid: mp 135° (lit.[12] mp 133–135°); uv max (C_2H_5OH) 249 mμ (log ϵ = 4.03) [lit.[12] 249 mμ (log ϵ = 4.12)].

When the irradiation of 3 (400 mg in 150 ml) was carried out in methanol for 13 hr, a dark residue was obtained from the irradiated solution after the solvent was removed. Chromatography of the residue on acid-washed alumina yielded only about 30 mg of the *meta* isomer (7.5%). No other well-defined products could be isolated.

When the irradiation was carried out in a solution of sodium ethanolate in ethanol for 6 hr, the acetate was recovered in 60% yield while the balance was the hydrolyzed acid.

Irradiation of Diethyl *o*-Biphenylylmalonate (5).—A solution of the malonate (625 mg, 2 mmol) in 145 ml of absolute ethanol containing 80 mg of Na (3.5 mmol) was irradiated for 2 hr. Aliquots of the mixture were removed, neutralized and monitored by tlc. Tlc showed the presence of a new product (less polar and strongly fluorescent) and some of the starting material. Most of the solvent was removed under reduced pressure. The concentrated solution was diluted with 50 ml of water and extracted with three 50 ml of ether. The crude mixture was chromatographed over 80 g of acid-washed alumina. A portion of the malonate (205 mg) was recovered and 255 mg of the product was isolated (70% based on the malonate reacted). The compound exhibits mp 119–120° (petroleum ether); uv max (C_2H_5OH) 246 mμ (ϵ 42,200), 255 (22,800), 261 (21,200), 270 (13,300), 292 (7100), 314 (5850), 326 (7100), 324.5 (5050), 360 (5000); ir (KBr) 6.11 and 6.17 μ; nmr δ 1.50 (t, 3, J = 7 Hz, OCH_2CH_3), 4.52 (q, 2, J = 7 Hz, OCH_2CH_3), 7.17–1.80 (m, 4, ArH), 8.25–8.75 (m, 4, ArH), and 13.23 ppm (s, 1, ArOH).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30; mass spectrum, 266.0943. Found: C, 76.54; H, 5.18; mass spectrum, 266.0942.

The malonate was then treated with Na in ethanol under the same conditions as above in the absence of uv light. No reaction took place after 6 days at room temperature and the malonate was recovered in 95% yield. Irradiation of the malonate in the

(10) H. J. S. Winkler and H. Wickler, *J. Org. Chem.*, **32**, 1695 (1967).

(11) M. Carissimi, I. Grasso, E. Grimelli, E. Milla, and F. Ravenna, *Farmaco, Ed. Sci.*, **18** (10), 705 (1963); see *Chem. Abstr.*, **60**, 1742*b* (1964).

(12) D. L. Turner, *J. Amer. Chem. Soc.*, **72**, 3823 (1950); D. D. Phillips and D. N. Chatterjee, *ibid.*, **80**, 1360 (1958).

absence of Na gave no product after 4 hr and the malonate was recovered unchanged. Heating of the malonate at 180° for 1.5 hr caused a slight decomposition without cyclization.

Irradiation of Ethyl 2-Carbethoxy-3-methyl-4-phenyl-2-butenoate (7a) in the Presence of Sodium Ethanolate.—A solution of **7a** (1.38 g, 5 mmol) in 80 ml of absolute ethanol containing sodium ethanolate (from 0.23 g of sodium, 10 mmol) was deaerated and irradiated through a Corex filter at room temperature for 6.5 hr. Tlc on silica gel showed an intense new spot (R_f 0.55) in addition to **7a** (R_f 0.25) when developed with benzene. After the solvent was removed under reduced pressure, water (40 ml) and ether (30 ml) was added to the reaction mixture. It was then acidified with 10% HCl, the layers were separated, and the aqueous layer was extracted with five 30-ml portions of ether. The combined ethereal extracts were dried over Na_2SO_4 and evaporated to give a crude mixture (1.27 g). The crude mixture was extracted with five 10 ml portions of hexane. The hexane-soluble part (968 mg) was chromatographed over silica gel (40 g) to yield ethyl 1-hydroxy-3-methyl-2-naphthoate (**9**, 497 mg) by eluting with hexane. **7a** (396 mg) was recovered from the column by eluting with benzene and from the hexane-insoluble residue. The yield of **9** was 57% based on the malonate reacted. **9** gives a positive maroon $FeCl_3$ test and after recrystallization from hexane and then ethanol exhibits white prisms: mp 67°; ir (KBr) 3400 (broad, OH) and 1640 cm^{-1} (intramolecularly H-bonded C=O); nmr (CCl_4) δ 1.43 (t, 3, J = 7.1 cps, OCH_2CH_3), 2.60 (s, 3, $ArCH_3$), 4.44 (q, 2, J = 7.1 cps, OCH_2CH_3), 6.94 (s, 1, ArH), 7.18–7.60 (m, 3, ArH), 8.37 (m, 1, ArH) and 12.79 ppm (s, 1, H-bonded ArOH); mass spectrum, parent ion, 230.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.91; H, 6.25.

Irradiation of Ethyl 2-Cyano-3-methyl-4-phenyl-2-butenoate (8a) in the Presence of Sodium Ethanolate.—Ethyl 2-cyano-3-methyl-4-phenyl-2-butenoate (**8a**, 2.29 g, 10 mmol) in a freshly prepared sodium ethanolate solution (0.40 g of sodium in 90 ml of absolute ethanol) was deaerated with high purity nitrogen for 30 min and irradiated with the light source through a Pyrex filter at room temperature under a slow stream of nitrogen. Aliquots of the solution were taken during the irradiation, neutralized with dilute HCl, and monitored with tlc. When they were spotted on a Kodak silica gel strip and developed with EtOAc–ethanol (5:1), the R_f value of **8a** was 0.73 and a new spot having a R_f value of 0.30 appeared. The new spot became more intense upon further irradiation. After 7 hr of irradiation, ethanol was removed from the mixture under reduced pressure, water (60 ml) was added, and the mixture was extracted with five 30-ml portions of benzene. The benzene extracts were combined, dried and evaporated to give the recovered **8a** (665 mg). The aqueous layer was acidified with 10% HCl and extracted with six 30-ml portions of benzene. The combined benzene extracts were dried and evaporated to give a crude mixture (1.20 g). The product, 3-methyl-2-cyano-1-naphthol (**10**, 370 mg), crystallized out from the mixture on standing which gave a positive green $FeCl_3$ test. The filtrate (690 mg) was chromatographed over silica gel (20 g) and eluted successively with benzene, chloroform, and chloroform–ethanol (1:1) to give crude **10** (390 mg). Crude **10** was recrystallized from benzene to give an additional amount of **10** (310 mg). The yield of **10** based on the ester consumed was 57%. The product was further purified by recrystallization from benzene containing a little ethanol and sublimation to give white prisms: mp 202°; ir (KBr) 3210 (OH) and 2210 cm^{-1} (CN); nmr [$(CD_3)_2SO$] δ 2.53 (s, 3, $ArCH_3$), 3.73 (s, broad, 1, OH), 7.32 (s, 1, ArH), 7.38–7.93 (m, 3, ArH) and 8.56 ppm (m, 1, ArH); mass spectrum, parent ion, 183.

Anal. Calcd for $C_{12}H_9ON$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.47; H, 5.10; N, 7.84.

Irradiation of the Condensation Products from Phenylacetaldehyde and Diethyl Malonate in the Presence of Sodium Ethanolate.—The condensation products from phenylacetaldehyde and diethyl malonate [1.31 g of ethyl 2-carbethoxy-4-phenyl-2-butenoate (**7b**)–ethyl 4-phenyl-2-butenoate (**9**) 1:4] in a freshly prepared sodium ethanolate sclution (0.23 g of sodium in 80 ml of absolute ethanol) was deaerated and irradiated through a Corex filter at room temperature for 12 hr. Tlc on silica gel showed the presence of a new product which has R_f 0.56 in benzene relative to that of the starting material of 0.26. The reaction mixture was concentrated at room temperature, water (60 ml) and ether (30 ml) were added, the mixture was acidified with 10% HCl, layers were separated, and the aqueous layers were extracted with three 25-ml portions of ether. The combined ether extracts were dried and evaporated to yield a residue (1.08 g). The residue exhibited an ir spectrum virtually identical with that of starting material and was digested with hexane. The hexane soluble part (48 mg) was chromatographed over silica gel (2 g). The fraction which was eluted with hexane was crystallized from ethanol to give ethyl 1-hydroxy-2-naphthoate (20 mg), mp 45° (lit.[13] 47°) which gives a blue $FeCl_3$ test. It exhibits ir (KBr) 3410 (broad, H-bonded OH) and 1660 cm^{-1} (intramolecularly H-bonded C=O); nmr (CCl_4) δ 1.40 (t, 3, J = 7.0 cps, OCH_2CH_3), 4.41 (q, 2, J = 7.0 cps, OCH_2CH_3), 6.90–7.90 (m, 5, ArH), 8.25–8.65 (m, 1, ArH) and 12.16 ppm (s, 1, H-bonded ArOH); mass spectrum, parent ion, 216.

Irradiation of the Condensation Products from Phenylacetaldehyde and Ethyl Cyanoacetate in the Presence of Sodium Ethanolate.—The polymeric material prepared equivalent to 5 mmol of the monomer was irradiated in the procedure previously described through a Corex filter. After 24 hr, the reaction mixture showed no appreciable change by tlc, and the starting material was quantitatively recovered.

Registry No.—**6**, 19293-78-8; **7a**, 19293-79-9; **8a** (*cis*),[14] 19293-80-2; **8a** (*trans*),[14] 19317-72-7; **9**, 19293-81-3; **10**, 5333-06-2.

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(13) "Elsevier's Encyclopedia of Organic Chemistry," Vol. 12B, 4283.

(14) Note that the 3-methyl group is *cis* or *trans* to the ester group.

Solution Photolysis of *cis*- and *trans*-2-Methylcyclopropyl Methyl Ketone[1]

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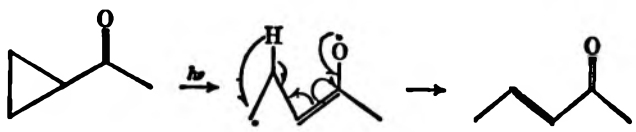
The photolysis of *cis*- (1) and *trans*-2-methylcyclopropyl methyl ketone (2) was studied in pentane and isopropyl alcohol. Irradiation of *cis* ketone 1 in either solvent yielded, exclusively, 1-hexen-5-one (3). *trans* ketone 2 slowly formed 3 in pentane, presumably through isomerization to 1, but in addition gave two saturated ketones, *n*-butyl methyl ketone (4) and isobutyl methyl ketone (5). The formation of 4 and 5 occurs *via* opening of either of the cyclopropane bonds α to the carbonyl group, followed by hydrogen abstraction from the solvent. These results show that when an intramolecular γ hydrogen abstraction (Norrish "type II") can occur, this process will prevail over any other type of hydrogen migration. In addition, the efficiency of isopropyl alcohol to trap the intermediate radicals is demonstrated.

The cleavage of the cyclopropyl ring during the irradiation of conjugated cyclopropyl ketones has been well established.[2-5] In the cases studied, one of the bonds adjacent to the carbonyl group breaks and a subsequent hydrogen migration leads to a conjugated enone.



In fused bicyclic systems,[3] geometrical factors appear to control the direction of ring opening, *i.e.*, if the cyclopropane ring is held in a rigid conformation with respect to the carbonyl π system, excitation of an electron into the π^* orbital leads to rupture of that cyclopropane bond which has greater overlap with the π electrons of the carbonyl group. When free rotation is possible and when both cyclopropane bonds are able to overlap the carbonyl π cloud, the stability of the radical formed determines the product ratio.[3,6]

In the present study, the photochemical behavior of *cis*- (1) and *trans*-2-methylcyclopropyl methyl ketone (2) has been examined in solvents which have differing abilities to donate hydrogen atoms. Three products were observed: 1 hexen-5-one (3), *n*-butyl methyl ketone (4) and isobutyl methyl ketone (5). The experimental results are summarized in Table I.

The sole product of irradiation of *cis* ketone 1 was 1-hexen-5-one (3), the structure of which was established by comparison of its ir and nmr spectra with those of an authentic sample. The formation of ketone 3 is analogous to the formation of 2-methyl-1-hexen-5-one observed in the irradiation of 2,2-dimethylcyclopropyl methyl ketone.[5,7,8] Two possible mechanisms have been proposed for such a ring opening.[5] The first mechanism follows an intramolecular Norrish "type II" process (Figure 1a), whereas the second mechanism (b) involves an initial rupture of the cyclopropane ring followed by an internal 1,4-hydrogen shift.

(1) This work was supported in part by Public Health Service Grant No. 00709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) J. N. Pitts, Jr., and I. Norman, *J. Amer. Chem. Soc.*, **76**, 4815 (1954).

(3) W. G. Dauben and G. W. Shaffer, *Tetrahedron Lett.*, 4415 (1967).

(4) L. D. Hess and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **89**, 1973 (1967).

(5) L. D. Hess, J. L. Jacobsen, K. Schaffner, and J. N. Pitts, Jr., *ibid.*, **89**, 3684 (1967).

(6) R. E. K. Winter and F. R. Lindauer, *Tetrahedron Lett.*, 2345 (1967).

(7) R. M. Roberts and R. G. Landolt, *J. Amer. Chem. Soc.*, **87**, 2281 (1965).

(8) G. Huppi, Frl. G. Eggart, S. Iwasaki, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chem. Acta*, **49**, 1986 (1966).

TABLE I

THE IRRADIATION OF *cis*- (1) AND *trans*-2-METHYLCYCLOPROPYL METHYL KETONE (2) IN PENTANE AND ISOPROPYL ALCOHOL

Compd	Solvent	Irradiation time, hr	Material in reaction mixture, % 1	2	3	4	5
1	Pentane	2	45		55		
1	Isopropyl alcohol	2	28		70		
2	Pentane	7[a]	*b*	26	23	6	9
2	Isopropyl alcohol	2.5		58		30	10

[a] Owing to the long irradiation time several over-irradiation products were observed of which acetone (14%) was identified. Acetone is a known photoproduct of ketone 4 [W. Davis, Jr., and W. A. Noyes, *J. Amer. Chem. Soc.*, 69, 2153 (1947)]. [b] *cis* ketone 1 could not be separated from ketone 4 but its presence was indicated by ir (1695 cm^{-1}) and the mass spectrum (*m/e* 98 and 83).

The study of the irradiation of *trans* ketone 2 has given more definitive information with regard to the mechanism of the photolytic process. As shown in Table I, there was a dramatic difference between the irradiation times and the products of irradiation of *cis* and *trans* isomers (1 and 2), respectively. This rules out the mechanism as depicted in Figure 1b, where *trans* ketone 2 would be expected to behave like *cis* ketone 1, because it would give the same intermediate a. In the "type II" process (Figure 1a) only *cis* isomer 1 can yield 1-hexen-5-one (3). It seems likely that the same mechanism (Figure 1a) applies to the irradiation of 2,2-dimethylcyclopropyl methyl ketone,[5,7,8] as the additional methyl group is not expected to cause drastic changes.

About 23% 1-hexen-5-one (3) was found in the irradiation of 2 in pentane. However, early in the irradiation a peak was observed in the vpc trace which had retention time corresponding to *cis* ketone 1 and to product 4. This material was collected from the vpc and its infrared spectrum indicated that the major component was ketone 4 (1718 cm^{-1}) and the minor component was *cis* ketone 1 (1695 cm^{-1}). Further support for the presence of *cis* ketone 1 was provided by finding the characteristic *m/e* 98 and 83 peaks in the mass spectrum.

cis ketone 1 did not build up as the irradiation of 2 in pentane proceeded. This result is expected, since 1 readily photolyzes to give ketone 3. The absence of 3 when 2 was irradiated in isopropyl alcohol as compared to its presence when 1 was treated similarly supports the hypothesis that *trans* ketone 2 is unable to form unsaturated ketone 3 directly, and the intermediate

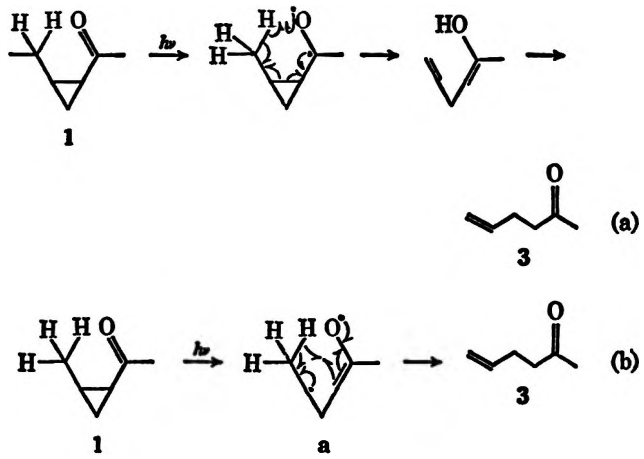


Figure 1

formation of *cis* ketone 1 *via* an isomerization step is required.

The presence of the two saturated ketones **4** and **5**, the structures of which were established by comparison of the vpc retention times and the ir and mass spectra with those of authentic samples, in the irradiation mixture of *trans* ketone **2** shows that both of the cyclopropane bonds adjacent to the carbonyl group undergo cleavage. This result might be expected, since both bonds should be able to overlap with the carbonyl π system. The intermediate radicals formed are especially well trapped in isopropyl alcohol, since no formation of ketone **3** was observed.

The reaction scheme proposed to explain the product distribution in the irradiation of *trans*-2-methylcyclopropyl methyl ketone (**2**) is depicted in Figure 2.

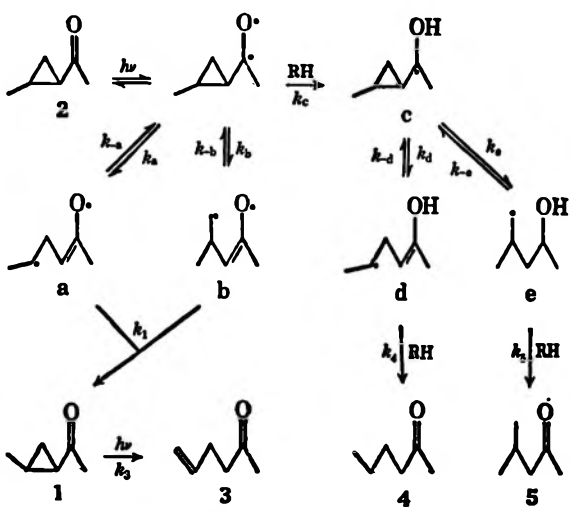


Figure 2.—In this scheme, cyclopropylhydroxycarbinyl radical c although the most likely intermediate, is not a necessary intermediate, since monoradicals d and e could be formed directly from a and b.

The initial process which is envisaged to occur is the excitation of an electron into an antibonding orbital followed by opening of the cyclopropane ring to form a and b (k_a and k_b) or by abstraction of a hydrogen atom from the solvent to form c (k_c). Inversion, rotation and closure of a or b provides *cis* ketone 1 (k_1), which rearranges readily to give ketone **3**. The independent irradiation of *cis* ketone **1** has shown that this over-irradiation process is rapid. Ring opening of monoradical species c yields d and e (k_d and k_e),[9] which abstract another hydrogen atom from the solvent to form saturated ketones **4** and **5** (k_4 and k_5).

When the photolysis of ketone **2** was conducted in isopropyl alcohol, only saturated products were observed. In addition, the irradiation time was short. This result suggests strongly that hydrogen abstraction in a good hydrogen-donating solvent is more rapid than inversion, rotation and reclosure (*i.e.*, $k_c > k_1$).

It is interesting to note that when the photolysis of **2** was conducted in isopropyl alcohol, the 3:1 product ratio of **4**:**5** reflects the relative stability of the intermediate radicals formed. Cleavage of the bond between C-1 and C-2 provides the more stable secondary radical d, whereas cleavage of the bond between C-1 and C-3 gives primary radical e (*i.e.*, $k_d > k_e$; $k_4 > k_{-d}$; $k_5 > k_{-e}$).

In pentane, the ratio of **4**:**5** was reversed, the ratio being 2:3. Since pentane is a poor hydrogen donor, abstraction is more selective than in isopropyl alcohol. The dissociation energies of primary *vs.* secondary radicals[10] indicate that primary radicals are more reactive than secondary radicals (*i.e.*, $k_5 > k_4$; $k_4 \leq k_{-d}$; $k_5 \leq k_{-e}$). The preferred formation of isobutyl methyl ketone (**5**) in pentane is in agreement with those reactivities. Also, from the long irradiation time, it can be seen that hydrogen abstraction in pentane proceeds at a slower rate than in isopropyl alcohol, and is, in fact, in competition with isomerization to *cis* compound **1**, detected as its over-irradiation product **3** (*i.e.*, $k_1 \sim k_3$). Since the conditions of irradiation in pentane and in isopropyl alcohol were similar, reclosure of the radicals formed appears to be a relatively rapid process (k_{-a} and k_{-b}).

Since no conjugated enones were found comparable to those reported in the irradiation of cyclopropyl methyl ketone in the vapor phase,[2] it may be inferred that internal hydrogen shifts, other than "type II" migrations, are less efficient than hydrogen abstraction from the solvent and *cis–trans* isomerization of the cyclopropane ring.[11]

Experimental Section

Syntheses.—*cis*- (**1**) and *trans*-2-methylcyclopropyl methyl ketone (**2**) were prepared from the corresponding *cis*- and *trans*-cyclopropylcarbinols using the Brown oxidation procedure.[12] The spectral data obtained are in agreement with those reported for these ketones.[13]

cis-2-Methylcyclopropylmethylcarbinol.—The Simmons–Smith procedure[14] as modified by Dauben and Berezin[15] was employed with *cis*-3-penten-2-ol, which in turn was prepared[16,17] from 3-pentyn-2-ol.[18]

(9) Ground-state radical rearrangements of this type have been studied. See D. C. Neckers, A. Schaap, and J. Hardy, *J. Amer. Chem. Soc.*, **88**, 1265 (1966).

(10) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 50.

(11) In this laboratory irradiation of cyclopropyl methyl ketone in pentane (3 hr, 50% conversion) also proceeded to give predominantly the saturated analog (20% propyl methyl ketone).

(12) H. C. Brown and C. P. Gary, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(13) R. M. Roberts, R. G. Landolt, R. N. Green, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967).

(14) See H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Amer. Chem. Soc.*, **86**, 1347 (1964), and references cited there.

(15) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).

(16) The Brown[2] hydrogenation apparatus was utilized. See C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966). The authors wish to thank Dr. C. A. Brown for his assistance in this hydrogenation.

(17) For ir spectral data on *cis*- and *trans*-3-penten-2-ol, see R. Heilmann, G. De Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 119 (1957). The ir spectra obtained in this laboratory were in agreement with the published data.

The data obtained for *cis*-2-methylcyclopropylmethylcarbinol were bp 81–83° (93 mm); ir (CCl_4) 3600, 3360 (OH), 1075, 1030, 1010, 995, 950, 910, 880, and 850 cm^{-1}; nmr (CCl_4) δ 3.83 (s, 1, OH), 3.28 (m, 1, CHOH), 1.23 (d, 3, J = 6 Hz, CH_3CHOH), 1.03 (d, 3, J = 3 Hz, c-$C_3H_5CH_3$), 0.87–0.75 (m, 3, cyclopropyl H), 0.1 (m, 1, cyclopropyl H); mass spectrum (prominent peaks) m/e 85 (M − 15), 82 (M − 18), 71, 67, 58 (B), 45.

Anal. Calcd for $C_6H_{12}O$ (100.17): C, 71.94; H, 12.07. Found: C, 71.96; H, 12.30.

trans-2-Methylcyclopropylmethylcarbinol.—Using the same procedure as described above, *trans*-cyclopropylcarbinol was prepared from *trans*-3-penten-2-ol.[17,19] The data obtained for *trans*-2-methylcyclopropylmethylcarbinol were ir (CCl_4) 3600, 3380 (OH), 1245, 1110, 1075, 1020, 995, 960, 937, 890, and 860 cm^{-1}; nmr (CCl_4) δ 3.29 (s, 1, OH), 3.1 (m, 1, CHOH), 1.17 and 1.04 (m, 6, at 1.17 a doublet of doublets, J = 6 and 1 Hz; at 1.04 a distorted doublet), 0.52 and 0.21 (2 m, 4, cyclopropyl H).

Irradiations were conducted in 125 ml (c 0.4–0.2%) solutions with an immersed Hanovia 450-W lamp, held in a water-cooled jacket and surrounded by a Corex filter (λ >280 mμ). The solutions were degassed with helium. The reactions were followed by vpc on a 5% XF-1150 cyanosilicone column (10 ft × 0.125 in., 60°, on a F & M 5750 gas chromatograph). After irradiation the solvent was carefully distilled from the product mixture and the products were collected from a 10 ft × 0.375 in. 20% XF-1150 cyanosilicone column on an Aerograph A-90-P gas chromatograph. Analyses were conducted by the Microanalytical Laboratory, University of California, Berkeley, Calif.

Registry No.—1, 2371-81-5; 2, 2863-92-5; *cis*-2-methylcyclopropylmethylcarbinol, 19293-89-1; *trans*-2-methylcyclopropylmethylcarbinol, 19293-90-4.

(18) I. M. Heilbron, E. R. H. Jones, and R. A. Raphael, *J. Chem. Soc.*, 264 (1943).

(19) K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, **63**, 2683 (1941).

Reactivity Studies in Free-Radical α Bromination of Cyclopropyl Compounds by N-Bromosuccinimide

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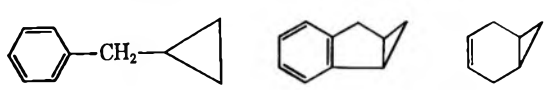
The relative reactivities of benzylcyclopropane, *trans*-1-benzyl-2-methylcyclopropane, cycloprop[2,3]indene, and bicyclo[4.1.0]hept-3-ene toward α-hydrogen abstraction in N-bromosuccinimide bromination have been determined. Rate accelerations resulting from electron release by the cyclopropyl substituents α to the incipient radical centers have been observed.

Product studies on the free-radical N-bromosuccinimide (NBS) brominations of the cyclopropyl compounds I, II, and III, which were reported earlier,[1]



I II III

showed that the reactions proceed predominantly *via* initial abstraction of hydrogen atoms from the carbons α to the cyclopropane rings. Bromide products resulting from both cyclopropylcarbinyl and rearranged allylcarbinyl radical intermediates were observed. No evidence was obtained, however, for the intermediacy of nonclassical cyclopropylcarbinyl radical species in product formation.

Various investigations[2] involving other methods for generation of cyclopropylcarbinyl radicals have also predominantly yielded either inconclusive or negative evidence for nonclassical intermediates in product formation. However, a number of examples have been reported[2e,3] in which α-cyclopropyl substituents do accelerate radical formation steps. Thus we became interested in determining whether rate acceleration also results from the presence of cyclopropyl substituents adjacent to the incipient radical centers in NBS α-bromination reactions. The model compounds, benzylcyclopropane (I), cycloprop[2,3]indene (II), and bicyclo[4.1.0]hept-3-ene (III), used for the reactivity investigation are the same as those used in the product study. Because of the difficulties involved in carrying out direct kinetic studies with heterogenous reactions, the alternate approach of investigating the relative rates of reaction of different substrates was used.

Results and Discussion

A summary of the reactivities relative to toluene toward NBS bromination at 77° in carbon tetrachloride solution for the compounds investigated is given in Table I. Literature values[4] for the relative reactivities in carbon tetrachloride solution of certain of the compounds and for several other compounds of interest are also given.

The data in Table I were obtained by successive comparisons of the relative reactivity values found for the individual competition experiments listed in Table II. Analyses of the competition product mixtures were done by quantitative nmr techniques[4a] as are described in the Experimental Section.

In most cases, hydrocarbon consumption and "normal bromide" formation per NBS reacted were approximately 90% or greater and no evidence was found in the nmr spectra of the competition product mixtures for significant side-product formation. Only in the competitions with benzylcyclopropane and *trans*-1-benzyl-2-

(1) E. C. Friedrich, *J. Org. Chem.*, **34**, 528 (1969).

(2) (a) S. J. Cristol and R. V. Barbour, *J. Amer. Chem. Soc.*, **90**, 2832 (1968); (b) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966); (c) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.*, **80**, 635 (1958); (d) E. Renk, P. R. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *ibid.*, **83**, 1987 (1961); (e) E. S. Huyser and J. D. Taliaferro, *J. Org. Chem.*, **28**, 3442 (1963).

(3) (a) C. G. Overberger and A. Lebovits, *J. Amer. Chem. Soc.*, **76**, 2722 (1954); (b) C. G. Overberger and M. B. Berenbaum, *ibid.*, **73**, 2618 (1951); (c) J. C Martin, J. E. Schultz, and J. W. Timberlake, *Tetrahedron Lett.*, **46**, 4629 (1967); (d) D. C. Neckers, A. P. Schaap, and J. Hardy, *J. Amer. Chem. Soc.*, **88**, 1265 (1966); (e) E. S. Huyser and D. T. Wang, *J. Org. Chem.*, **29**, 2720 (1964); (f) E. S. Huyser and L. R. Muson, *ibid.*, **30**, 1436 (1965); (g) C. Walling and P. S. Fredricks, *J. Amer. Chem. Soc.*, **84**, 3326 (1962).

(4) (a) S. S. Friedrich, E. C. Friedrich, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **34**, 900 (1969); (b) C. Walling, A. L. Rieger, and D. D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (c) M. M. Martin and G. J. Gleicher, *J. Org. Chem.*, **28**, 3266 (1963).

TABLE I

RELATIVE REACTIVITIES[a] OF VARIOUS COMPOUNDS TOWARD NBS BROMINATION

Compound	Relative Reactivities: Present work[b]	Relative Reactivities: Literature
Toluene (Std)	1.00	1 00
Isobutylbenzene	9.35 ± 0.31	
n-Butylbenzene	18.0 ± 0.46	28.5 ± 4[c]
Ethylbenzene		25.2 ± 0.46,[d] 23.6 ± 3.3[e]
Diphenylmethane		17.6 ± 0.3[d]
Benzylcyclopropane (I)	30.8 ± 0.88	
trans-1-Benzyl-2-methylcyclopropane	42.4 ± 0.74	
Allylbenzene	28.8 ± 0.58	26.2 ± 1.6[e]
Indan	92.8 ± 5.2	
Fluorene	32.8 ± 1.3	
Indene	76.0 ± 3.8	
Cycloprop[2,3]indene (II)	108 ± 5,[f] 119 ± 6[g,h]	
Cyclohexene	152 ± 7	129 ± 22[e]
Bicyclo[4.1.0]hept-3-ene (III)	260 ± 21	

[a] Per benzylic or allylic hydrogen. [b] At 77° in CCl_4 using azobisisobutyronitrile (AIBN) initiator. [c] Reference 4b, at 80° in CCl_4 using AIBN initiator. [d] Reference 4a, at 77° in CCl_4 using benzoyl peroxide initiator. [e] Reference 4c, at 69.50° in CCl_4 using photoinitiation. [f] From competition with cyclohexene. [g] From competition with fluorene. [h] Less accurate because of experimental difficulties.

TABLE II

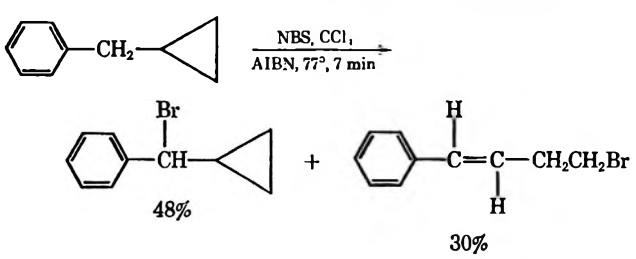
SUMMARY OF COMPETITIVE NBS BROMINATIONS[a]

A	B	k_a/k_b[b]	No. of runs
n-Butylbenzene	Diphenylmethane	1.02 ± 0.02	2[c]
Allylbenzene	Cumene	0.50 ± 0.005	2[c]
Isobutylbenzene	Diphenylmethane	0.53 ± 0.015	2[c]
Benzylcyclopropane	Diphenylmethane	1.75 ± 0.04	2[c]
trans-1-Benzyl-2-methylcyclopropane	Diphenylmethane	2.41 ± 0.01	2[c]
Fluorene	Cumene	0.57 ± 0.020	3[c]
Cyclohexene	Fluorene	4.65 ± 0.11	3[d]
Indan	Fluorene	2.83 ± 0.11	2[d]
Indene	Cyclohexene	0.50 ± 0.010	2[d]
Cycloprop[2,3]indene	Cyclohexene	0.71 ± 0.002	2[e]
Cycloprop[2,3]indene	Fluorene	3.62 ± 0.11	2[e,f]
Bicyclo[4.1.0]hept-3-ene	Cyclohexene	1.71 ± 0.11	3[e]

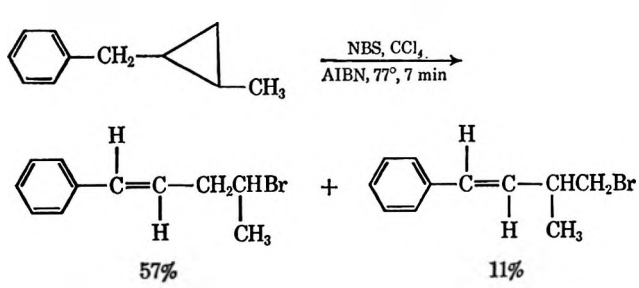
[a] At 77° in CCl_4 using AIBN initiator. [b] Per allylic or benzylic hydrogen. [c] Internal standard is benzyl chloride. [d] Internal standard is cumene. [e] Internal standard is diphenylmethane. [f] Less accurate because of experimental difficulties.

methylcyclopropane were low values obtained for substrate conversion.

For the benzylcyclopropane–diphenylmethane competitions, a 78% substrate conversion based on starting NBS was observed. This low substrate conversion must result mainly because of the observed formation of approximately a 10% yield of β-bromopropionylisocyanate from NBS rearrangement.[4b,5] In the earlier product study[1] it was observed that reaction of benzylcyclopropane with NBS in a 1:1 mol ratio gave only a 53% conversion of the benzylcyclopropane, and approximately 20% of the reacted benzylcyclopropane could not be accounted for as bromide products resulting from α-hydrogen abstraction.[6] Also, a 25–30% yield of β-bromopropionylisocyanate was obtained.



A similar argument holds for the *trans*-1-benzyl-2-methylcyclopropane–diphenylmethane competitions which showed only *ca.* 68% substrate conversions but from which approximately a 12% yield of β-bromopropionylisocyanate was observed. In the product studies,[1] reaction of *trans*-1-benzyl-2-methylcyclopropane with NBS in a 1:1 mol ratio resulted in 54% conversion of the starting material and gave a 68% yield of isomeric



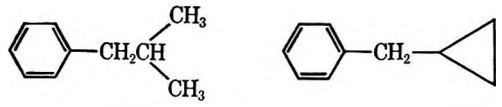
allylcarbinylbromides *via* α-hydrogen abstraction. Ap-

(5) (a) J. C. Martin and P. D. Bartlett, *J. Amer. Chem. Soc.*, **79**, 2533 (1957). (b) H. W. Johnson and D. E. Bublitz, *ibid.*, **79**, 753 (1957); **80**, 3150 (1958).

(6) The *ca.* 20% yield of undetermined, higher brominated materials observed in the product study may be accounted for as resulting from radical addition of bromine to the *trans*-1-phenyl-4-bromo-1-butene product rather than by addition of bromine to benzylcyclopropane. The former process gives a stabilized benzylic radical intermediate and should be favored over the latter which gives a secondary radical intermediate. Thus, the relative rate value of 30.8 for benzylcyclopropane given in Table I is felt to be that for α-hydrogen abstraction and not for competing processes.

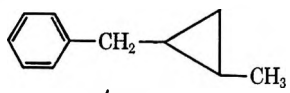
proximately 22–25% of the NBS rearranged to β-bromopropionylisocyanate.

From the data in Table I it is apparent that rate acceleration of α-hydrogen abstraction in NBS bromination is definitely obtained with benzylcyclopropane (I). This material is as reactive as allylbenzene, is almost twice as reactive as diphenylmethane or *n*-butylbenzene, and is over three times as reactive as isobutylbenzene. The latter comparison is probably the best, from



k/k_{Tol} 9.35

k/k_{Tol} 30.8



k/k_{Tol} 42.4

consideration of electronic stabilization and steric factors, for estimation of the magnitude of the cyclopropyl-induced acceleration. Evidence that the acceleration is due to an electron-releasing resonance effect by the cyclopropane ring is given by the observation that attachment of an electron-releasing *trans*-2-methyl substituent on benzylcyclopropane provides additional rate acceleration.[7]

Estimates of the magnitudes of the cyclopropyl accelerations in the cycloprop[2,3]indene (II) and bicyclo[4.1.0]hept-3-ene (III) systems could not be obtained in a straightforward manner. This is because of the difficulties involved in finding compounds to use as suitable bases for rate comparisons.

Compounds investigated as possible models for comparison with cycloprop[2,3]indene are indan, indene, and fluorene. However, both indene and fluorene are less reactive than indan. This must be related to a lowering of the ground-state free energies of fluorene and indene by resonance which is not compensated for by a corresponding lowering of the transition-state energies for hydrogen abstraction. Cycloprop[2,3]indene is, however, slightly more reactive than indan, and it is anticipated that a better compound for comparison, 2-methylindan, should be even less reactive than indan toward 1-hydrogen abstraction (*cf.* the relative rate values of *n*-butylbenzene and isobutylbenzene).

Only a single possible rate comparison, with cyclohexene, is available for bicyclo[4.1.0]hept-3-ene (III).[8] This cyclopropyl compound is of special interest since it is the only example investigated in which formation of a vinylcyclopropyl radical is involved. The fact that it is significantly more reactive than cyclohexene does indicate that the cyclopropyl substituent is providing some rate acceleration for α-hydrogen abstraction.

In conclusion, evidence was found with all of the cyclopropyl systems investigated for rate accelerations of hydrogen atom abstraction produced by the cyclopropyl substituents α to the incipent radical centers. The magnitudes of the accelerations are not large, but are well outside of experimental error. Evidence that the accelerations are probably due to electron release by the cyclopropyl substituents and not simply to release of strain at the transition states for hydrogen-atom abstraction was provided by the earlier product study.[1] The major products from the NBS α brominations of benzylcyclopropane (I) and cycloprop[2,3]indene (II) were found to possess retained cyclopropyl structures. However, it should be noted that only rearranged, allylcarbinyl products were observed from NBS bromination of bicyclo[4.1.0]hept-3-ene (III) and *trans*-1-benzyl-2-methylcyclopropane.

The mechanism of electron release by the cyclopropyl group in radical stabilization is still not clear. However, since evidence is available[9] which indicates that the cyclopropyl group should exhibit a rate-retarding polar inductive effect, the accelerations must be due to some type of electron release by resonance from the cyclopropane ring which stabilizes the activated complexes at the transition states for the radical formation steps. It is anticipated that future investigations of the reactivities of various mono- and dimethyl-substituted benzylcyclopropanes toward α-hydrogen abstraction may provide valuable information regarding the detailed nature of the electron-releasing resonance effect.

Experimental Section

Materials.—The methods of preparation and properties of benzylcyclopropane, *trans*-1-benzyl-2-methylcyclopropane, cycloprop[2,3]indene, and bicyclo[4.1.0]hept-3-ene are described elsewhere.[1] Commercial samples of *n*-butylbenzene, cumene, isobutylbenzene, fluorene, azobisisobutyronitrile (Eastman White Label), diphenylmethane, indan (Aldrich), benzyl chloride, cyclohexene (Mallinckrodt, AR), allylbenzene, 1,4-dihydrobenzene (Chemical Samples Co.), N-bromosuccinimide (Arapahoe), and carbon tetrachloride (J. T. Baker, AR) were used without further purification. Indene (Eastman Yellow Label) was purified before use by careful fractional distillation.

Competitive Brominations.—The choice of a particular pair of compounds used in an individual competition experiment was based both on the requirement that the compounds have similar reactivities toward NBS and the necessity that at least one-proton absorption for each of the compounds or their bromination products is resolved sufficiently for accurate quantitative measurements from all other proton absorptions in the nmr spectrum of the product mixture. In a typical experiment, 7 to 15 mmol of each of the competitors was weighed (using hypodermic syringes for liquids) into a 50-ml flask containing an 8–10 mmol weighed quantity of NBS covered with approximately 20–25 ml of carbon tetrachloride solvent. The exact ratios used of the two competing compounds and NBS depended on the relative reactivities of the competitors. When possible, ratios were varied in duplicate runs. The mixture was then treated with 0.1 g of azobisisobutyronitrile and heated quickly to reflux (reacting mixture 77°) while stirring with a magnetic stirrer. The apparatus was protected from atmospheric moisture by a drying tube filled with Drierite. When the reaction was completed (from 15 to 30 min following the induction period depending on the particular experiment), as indicated by the disappearance of NBS from the bottom of the reaction flask, refluxing was stopped and the mixture was cooled. An internal standard (*ca.* 4 to 6 mmol) was then weighed into the reaction mixture before sampling of the liquid portion for quantitative nmr analysis. The choice of internal standard was based on its suitability for the nmr analysis procedure, specifically on the chemical shift values of its proton absorptions.

Nmr Analyses.—Analyses of the NBS bromination competition mixtures were carried out in thin walled tubes using a Varian Associates Model A-60A instrument. Tetramethylsilane (TMS)

(7) P. von R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, **88**, 232 (1966).

(8) Attempts to obtain a reliable rate value for 1,4-cyclohexadiene which could be used for a second comparison were not successful. Formation of significant quantities of presumably dibrominated side products along with the normal product, benzene, were observed in competitions with this material: J. P. Wibaut and F. A. Haak, *Rec. Trav. Chim.*, **69**, 1387 (1950).

(9) (a) T. L. Brown, *J. Amer. Chem. Soc.*, **80**, 6489 (1958); (b) H. C. Brown and J. D. Cleveland, *ibid.*, **88**, 2051 (1966).

was employed as the standard for determining chemical shift values of individual proton absorptions. At least six integrations were carried out on selected proton absorptions for the competitors or their bromination products (or both) and the weighed internal standard. Integral amplitudes were maximized to obtain the highest possible accuracy. The average deviation of individual integrations from the mean was generally on the order of 1%. The average value from integration of each different proton absorption was then corrected for the number of protons contributing to the absorption. From these values, by comparison with the per hydrogen integration value obtained for the known amount of internal standard, it was possible to calculate the numbers of millimoles of each competitor which remained. In certain cases this could be done directly, and in the other cases it was done indirectly by substraction of the number of millimoles of a bromide product observed from the number of millimoles of competitor weighed into the reaction. A decision as to which one of these procedures or both were used depended on whether the individual proton absorptions necessary for nmr analysis were better separated for the starting materials or for their bromide products from other proton absorptions in the competition product mixtures. The average chemical shift values (δ in parts per million downfield from TMS), which vary slightly in different mixtures, for the various individual proton absorptions of the internal standards, competitors, and bromide products used for calculation of the product compositions are as follows: benzyl chloride, δ 4.5 (s, 2 H, CH_2Cl); diphenylmethane, 3.9 (s, 2 H, CH_2); benzhydryl bromide, 6.2 (s, 1 H, CHBr); cumene, 1.2 (d, 6 H, J = 6.5 Hz, CH_3); cumyl bromide, 2.1 (s, 6 H, CH_3); *n*-butylbenzene, 2.6 (t, 2 H, J = 7.5 Hz, $C_6H_5CH_2$); α-bromo-*n*-butylbenzene, 4.9 (t, 1 H, J = 7.5 Hz, C_6H_5CHBr); isobutylbenzene, 0.9 (d. 6 H, J = 6.5 Hz, CH_3), 2.5 (d, 2 H, J = 7.0 Hz, CH_2); α-bromoisobutylbenzene, 0.85 and 1.15 (for each, d, 3 H, J = 6.5 Hz, CH_3), 4.6 (d, 1 H, J = 8.0 Hz, CHBr); benzylcyclopropane, 0.2 (m, 2 H, cyclopropyl); *trans*-1-benzyl-2-methylcyclopropane, 0.4 (m, 4 H, cyclopropyl); fluorene 3.7 (s, 2 H, CH_2); 9-bromofluorene, 5.7 (s, 1 H, CHBr); 1-bromoindan, 5.3 (t, 1 H, J = 4.0 Hz, CHBr); indene, 3.3 (s, 2 H, CH_2), 6.3 (m, 1 H, CH_2CH=); cycloprop[2,3]indene, 0.0 (m, 1 H, cyclopropyl), 3.0 (m, 2 H, $C_6H_5CH_2$); 3-bromocyclohexene, 4.6 (m, 1 H, CHBr), 5.6 (m, 2 H, vinyl); and bicyclo[4.1.0]hept-3-ene, 0.3 (m, 2 H, cyclopropyl).

Calculation of Relative Reactivities.—Relative reactivities from individual competition experiments were calculated using the integrated rate equation (1), where A_0 and B_0 are the initial and A_f and B_f the final amounts of the two competitors. A

$$k_A/k_B = \log (A_0/A_f)/\log (B_0/B_f) \quad (1)$$

summary of the results obtained from the individual competitions, along with the number of runs carried out and the internal standard used in each competition, is given in Table II. Experimental errors are average deviations from the mean. The reactivities per active benzylic or allylic hydrogen relative to toluene given in Table I were obtained by stepwise comparisons of suitable pairs using the values of Friedrich, *et al.*,[4a] for the relative reactivities of diphenylmethane to toluene (17.6 ± 0.3) and cumene to toluene (57.5 ± 1.0). The indirect comparisons were necessary for purposes of accuracy because of the marked differences in reactivity between toluene and most of the compounds investigated. Experimental errors given in Table I were obtained by use of the usual formula[10] for propagation of errors.

Registry No.—I, 1667-00-1; II, 15677-15-3; III, 16554-83-9; NBS, 128-08-5; *trans*-1-benzyl-2-methylcyclopropane, 18933-49-8.

Acknowledgment.—The author is indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to his wife, Sevgi Sümer Friedrich, for running a number of the nmr spectra.

(10) H. Margenau and G. M. Murphy, "The Mathematics of Physics and Chemistry," 2nd ed, D. Van Nostrand and Co., Inc., New York, N. Y., 1956, p 515.

The Effect of Ring Size on the Rate of Reaction of Cycloalkyl Phenyl Ketones with Sodium Borohydride

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Kinetic experiments have been carried out for the reactions of acetophenone, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, cyclopentyl phenyl ketone, and cyclohexyl phenyl ketone with sodium borohydride at 0, 25 and 35°, respectively. At 0° the relative rates of the four cycloalkyl phenyl ketones are cyclopropyl, 0.12; cyclobutyl, 0.23; cyclopentyl, 0.36; and cyclohexyl, 0.25 (relative rate constant of acetophenone is unity). The data are discussed in terms of the conformation theory.

In the study of the effect of ring size on the rate of pyrolysis of cycloalkyl phenyl sulfoxides, Kice and Campbell[1] found that the relative rates of decomposition are in the following order: cyclopentyl > cyclohexyl < cycloheptyl. The pyrolysis rate seems to be related to the physical properties of the rings. The well-known heat of combustion per methylene group is in the same order. Measurements of diffusion coefficients of medium sized monocyclic compounds in carbon tetrachloride were also shown to follow this order.[2]

In this paper we report the results of a study on the effect of different ring sizes on the reactivity of some aromatic ketones. Brown and coworkers[3] have demonstrated that sodium borohydride is an excellent reagent to study kinetically the effects of structures on the reactivity of aldehydes and ketones. They have investigated[4-6] the reaction rates of sodium borohydride with various ketones including cyclic and bicyclic ketones, as well as aromatic and aliphatic ketones.

(1) J. L. Kice and J. D. Campbell, *J. Org. Chem.*, **32**, 1631 (1967).

(2) S. F. Sun, R. J. Beshinske, and K. E. Van Holde, *J. Amer. Chem. Soc.*, **89**, 6417 (1967).

(3) H. C. Brown, E. J. Mead, and B. C. S. Rao, *ibid.*, **77**, 6209 (1955).

(4) (a) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); (b) H. C. Brown and K. Ichikawa, *ibid.*, **1**, 221 (1957).

(5) H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962).

(6) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

TABLE I
RATE CONSTANTS OF THE REACTIONS OF AROMATIC KETONES

Phenyl ketone	Temp, °C	$k \times 10^4$, l. mol^{-1} sec^{-1}
Methyl[a]	0.0	2.07
	25.0	13.6
	35.0	26.0
Cyclopropyl	0.0	0.257
	25.0	6.25
	35.0	18.7
Cyclobutyl	0.0	0.470
	25.0	2.49
	35.0	5.18
Cyclopentyl	0.0	0.740
	25.0	3.50
	35.0	7.35
Cyclohexyl	0.0	0.515
	25.0	2.38
	35.0	4.78

[a] Previous results: 2.05 at 0°, 14.0 at 25°, 26.2 at 35.15° [H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962)].

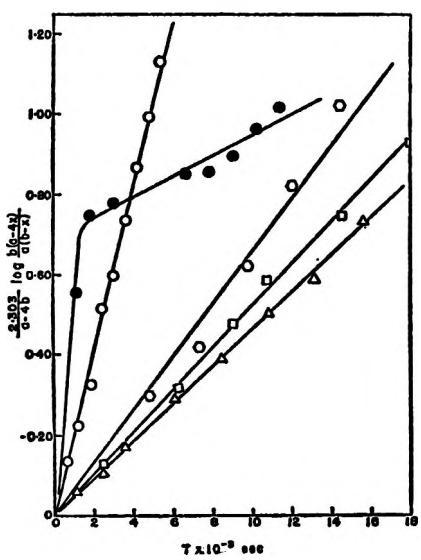


Figure 1.—Second-order reaction of sodium borohydride with cycloalkyl phenyl ketones: ○, acetophenone; ●, cyclopropyl phenyl ketone; △, cyclobutyl phenyl ketone; ⬡, cyclopentyl phenyl ketone; □, cyclohexyl phenyl ketone.

They did not, however, include in their list any cycloalkyl phenyl ketones.

We have carried out kinetic experiments for reactions of sodium borohydride with acetophenone, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, cyclopentyl phenyl ketone, and cyclohexyl phenyl ketone. Acetophenone is included for comparison only.

Results

The experimental data for rate constants at 0, 25, and 35°, respectively, are presented in Table I. Each kinetic experiment was carried out at least twice. The reproducibility of each rate constant was within 5%.

In all experiments the reaction is first order with respect to the ketone and first order with respect to sodium borohydride. The linearity of the second-order plots for these reactions is shown in Figure 1.

The reaction of cyclopropyl phenyl ketone was relatively slower than any other cycloalkyl phenyl ketone at 0° but faster at higher temperatures. The reaction was only followed to 50% completion, while all other compounds reacted to 100% completion. After 4 days, although some cyclopropyl phenyl ketone (initial concentration 0.136 *M*) was still found in the system, sodium borohydride (initial concentration 0.040 *M*) was completely consumed. It should be pointed out that according to the stochiometry the initial concentration of sodium borohydride was in excess by 0.006 *M*. The rate constant of cyclopropyl phenyl ketone shown in Table I was determined from the linear portion of the second-order plot.

Table II lists the activation parameters of the reactions of cycloalkyl phenyl ketones with sodium borohydride. Least-squares method was used for the determination of the slopes and intercepts for each of the ln k *vs.* $1/T$ data. The error limits for enthalpies of activation were calculated from the standard deviations of the slopes, whereas those of entropies of activation were determined from the standard deviations of the y intercepts. All the computations were carried out on the C-E-I-R Multi-Access computer service (System 420).

TABLE II
RELATIVE RATES AND DERIVED DATA FOR THE REACTIONS OF AROMATIC KETONES AT 0°

Phenyl ketone	Relative rates	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Methyl[a]	1.00	11.5 ± 0.3	−32.9 ± 0.3
Cyclopropyl	0.12	19.9 ± 0.1	−6.15 ± 0.3
Cyclobutyl	0.23	10.7 ± 0.1	−38.7 ± 1.8
Cyclopentyl	0.36	10.2 ± 0.6	−39.8 ± 2.0
Cyclohexyl	0.25	9.8 ± 0.6	−41.8 ± 2.0

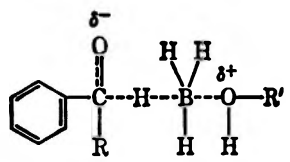
[a] Previous results: $\Delta H^{\ddagger}$ = 11.70 kcal/mol, $\Delta S^{\ddagger}$ = −32.4 eu [H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962)].

Discussion

The difference in the reaction rates among cycloalkyl phenyl ketones is small as found in the case of rate constants for the pyrolysis of cycloalkyl phenyl sulfoxides.[1] The small rate difference among cycloalkyl phenyl ketones is presumably due to the resonance interactions between the phenyl group and carbonyl group. Such interactions are believed to stabilize the ground states of reactants and thus possibly slow down their reaction rates.

However, the trend of change clearly follows the size of these rings. At 0° the three-membered ring reacted the slowest, while the five-membered ring reacted faster than both the four-membered and six-membered rings. The observation of the latter (three-, four-, five-membered compounds) holds at higher temperatures (25 and 35°) also and is in accord with almost all kinetic studies for reactions involving these three rings. During a reaction, if the breakage or formation of a bond directly or indirectly involves a ring atom, the rate of reaction of a five-membered-ring compound seems always in between a four-membered-ring and a six-membered-ring compound.[4]

The rate-determining step in the reaction of sodium borohydride with ketones is known to involve the transfer of the hydride ion to the carbonyl group.[3] In the transition state of cycloalkyl phenyl ketones the



possibility exists that bond angles or torsional strains may release or enforce the strain which already exists in the ketonic carbon.[7] The relatively low rate of reaction of cyclopropyl phenyl ketone at 0° is perhaps due to the high angular strain of the cyclopropyl group. The transition of the strain from the ring to the reaction site may reduce the affinity of the ketonic carbon to the hydride ion. As the angular strain decreases from cyclobutyl phenyl ketone to cyclohexyl phenyl ketone the reaction rate likewise increases. As to why the rate of cyclohexyl phenyl ketone is slower than that of cyclopentyl phenyl ketone, there seems to be no satisfactory answer. One can only parallel the physical properties of the rings with the reactivities of ring compounds. For almost any quantitative measurements, *e.g.*, diffusion coefficient and heat of combustion, the value of six-membered ring is always in between those of the five-membered ring and seven-membered ring, just as the five-membered ring is in between four-membered and six-membered rings. If kinetic data for cycloheptyl phenyl ketone with sodium borohydride were available, it is believed that the reaction rate for the seven-membered ring would be higher than that for the six-membered ring.

Changes in the enthalpy of activation for these reactions are expected to follow the same direction as the changes in the strain of the rings. As far as the principal values are concerned, such a trend seems to exist. But, in the first place, the change is so small, and in the second place the relative errors are so large that great significance should not be attached to the calculated data. This is also the case with the change in entropies of activation. Presumably there is not much effect of geometric configuration on the reaction rate when a ring is connected to the ketonic carbon.

The reaction of cyclopropyl phenyl ketone with sodium borohydride seems complicated. The enthalpy of activation is very high and the entropy of activation is abnormally low. In the ultraviolet absorption spectra study, Rogers[8] suggested that cyclopropyl phenyl ketone, when excited, may undergo ring breakage. Recently it was reported[9] that carbon–carbon single bonds of a cyclopropyl ring are cleaved by electrophilic reagents. This leads[10] us to suspect that the reaction of cyclopropyl phenyl ketone with sodium borohydride in isopropyl alcohol may not be a single reaction and that the product may be a mixture.

In conclusion, the characteristic features of the small rings are revealed not only in the reactions directly involved with ring atoms such as cyclanones but also in the reaction where ring atoms are not directly involved, such as cycloalkyl phenyl ketones. Relative rates depend upon a delicate balance between ring properties (*e.g.*, bond angles and torsional strain) and resonance interactions; hence changes in reaction rates may be expected to be small.

Experimental Section

Materials.—Acetophenone was obtained from Eastman Organic Chemicals, while the four cycloalkyl phenyl ketones were obtained from Frinton Laboratories. All the ketones were purified by vacuum distillation. The physical properties of the purified ketones used for kinetic measurements are listed in Table III.

TABLE III
PHYSICAL PROPERTIES OF THE KETONES USED IN THIS WORK

Phenyl ketone	Mp or bp, °C (mm)	$n^{25}D$
Methyl	82.8 (12)	1.5429
Cyclopropyl	60.0 (8)	1.5530
Cyclobutyl	114.5 (10)	1.5455
Cyclopentyl	118.7 (10)	1.5427
Cyclohexyl	47.2	

Isopropyl alcohol (Baker Analyzed Reagent) and sodium borohydride (Metal Halides) were purified according to the method described by Brown and coworkers.[3] All the other chemicals were reagent grade without further purification.

Kinetic Measurement.—To a standardized solution of sodium borohydride in isopropyl alcohol was added a known volume of ketone which was also dissolved in isopropyl alcohol. The mixture was prepared in a water bath at 25 or 35°, or in an ice bath at 0°, and was vigorously stirred. The accuracy of the temperature in the water bath was ±0.02° and that in the ice bath was ±0.5°. At intervals 10-ml aliquots were withdrawn and the borohydride content was analyzed by the iododate method.[11]

Product Analysis.—The solution of a ketone in isopropyl alcohol was added to the solution of sodium borohydride in the identical solvent and, after shaking, the mixture was left standing for 3 hr. The alcohol was distilled off by vacuum distillation. The infrared spectra were taken with Perkin-Elmer Infracord 137 for the product as well as for the starting material. Since $NaBH_4$ does not absorb in the carbonyl region, the disappearance (*i.e.*, reduction) of the ketone stretching vibrations at ~1680 cm^{-1} accompanied by the strong appearance of O–H bending at 3400–3600 cm^{-1} and of C–O stretching at 950–1010 cm^{-1} observed in the ir spectra is an indication of the reaction of the ketone with sodium borohydride.

Registry No.—Sodium borohydride, 1303-74-8; acetophenone, 98-86-2; cyclopropyl phenyl ketone, 3481-02-5; cyclobutyl phenyl ketone, 5407-98-7; cyclopentyl phenyl ketone, 5422-88-8; cyclohexyl phenyl ketone, 712-50-5.

(7) R. P. Mariella and R. R. Raube, *J. Amer. Chem. Soc.*, **74**, 521 (1952).
(8) M. Rogers, *ibid.*, **69**, 2544 (1947).
(9) R. J. Ouellette, R. D. Robins, and A. South, Jr., *ibid.*, **90**, 1619 (1968).
(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 590.
(11) D. A. Lyttle, E. H. Jensen, and W. A. Struck, *Anal. Chem.*, **24**, 1843 (1952).

The Role of Solvent Hydrogens in the Dehydro Diels–Alder Reaction

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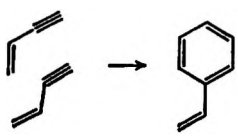
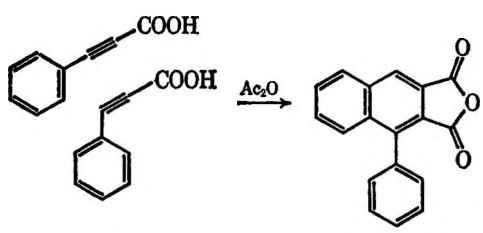
The hydrogen transfers associated with the dimerization of phenylpropiolic acid, a dehydro Diels–Alder reaction, proceed by an intermolecular rather than an intramolecular pathway.

The Diels–Alder reaction involving enynes, typified by the dimerization of vinylacetylene to styrene[1] (eq 1),



(1)

represents a surprisingly general variant of the Diels–Alder reaction.[2] The oldest and best studied example of this reaction is the high-yield dimerization of phenylpropiolic acid to 1-phenylnaphthalene-2,3-dicarboxylic acid anhydride (eq 2) on refluxing a solution of the acid



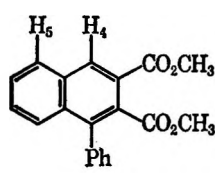
(2)

I II

in acetic anhydride. This dimerization was discovered by Michael and Bucher[3] in 1895 and the product (II) was correctly formulated[4–8] and the generality[9] of the reaction, employing simple functional derivatives of I, demonstrated in the succeeding years.

The ability of this dimerization to proceed undisturbed in the presence of a wide variety of functional groups[9–12] on the aromatic rings has been of considerable value in the synthesis of lignan derivatives.[13,14] Arylpropiolic acids other than phenyl have been demonstrated to undergo the isomerization.[15,16]

The fact that such peculiar intermediates must be proposed if one rationalizes this as an ordinary Diels–Alder reaction has prompted us to synthesize 2-deuteriophenylpropiolic acid (I-d_1) and examine its fate in this dimerization reaction. Refluxing a solution of I-d_1 in acetic anhydride containing a large molar excess of acetic acid produces an approximately 1:1 mixture of II-d_1 and II-d_2 (Table I). Decreasing the amount of acetic acid in the reaction mixture leads to an increased II-d_2:II-d_1 ratio. Cyclization of deuterium-free I with a mixture of acetic anhydride and acetic acid-d_1 results in substantial if not complete formation of II-d_1. Examination of the nmr spectrum of the dimethyl ester of II (III) enables one to locate the deuterium on the naphthalene ring in the deuterated derivatives of II. The nmr spectrum of III shows a singlet of area 1 H at δ 8.62 assignable to H_4 and a multiplet of area 1 H at δ 8.0 assignable to H_5. In the spectrum of the III-d_1/III-d_2 mixture from cyclization of I-d_1 in acetic anhydride–acetic acid the signal at δ 8.62 still corresponds to one hydrogen but the multiplet at δ 8.0 has been reduced in area by one-half. The nmr spectrum of III-d_1 (64% d_1, 36% d_0) from cyclizing I in the presence of acetic acid-d_1 had the multiplet at δ 8.0 unchanged in area but now the singlet at δ 8.62 corresponded to only 0.3 hydrogen.



III

Discussion

Our labelling results, although rather crude, require that the fates of the protons involved in this rearrangement are as in Figure 1.[17]

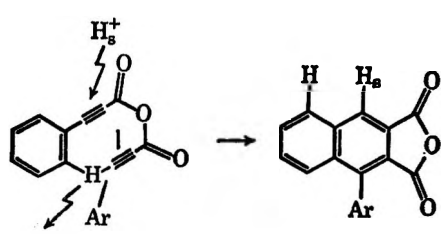


Figure 1.—H_s = solvent protons.

Moreover, the nmr experiments require that no skeletal isomerization leading to net movement of the side chains about the aromatic rings can be occurring during the course of the cyclization. This is also

(1) H. B. Dykstra, *J. Amer. Chem. Soc.*, **56**, 1625 (1934).
(2) See the numerous examples by A. S. Onishchenko, "Diene Synthesis," L. Mandel, Trans., Daniel Davey and Co., Inc., New York, N. Y., 1964, pp 249–254 ff and pp 635–637.
(3) A. Michael and J. E. Bucher, *Chem. Ber.*, **28**, 2511 (1895).
(4) A. Michael and J. E. Bucher, *Amer. Chem. J.*, **20**, 89 (1898).
(5) A. Michael and J. E. Bucher, *Chem. Ber.*, **41**, 70 (1908).
(6) J. E. Bucher, *J. Amer. Chem. Soc.*, **30**, 1244 (1908).
(7) H. Stobbe, *Chem. Ber.*, **39**, 1908 (1906).
(8) H. Stobbe, *ibid.*, **41**, 70 (1908).
(9) J. E. Bucher, *J. Amer. Chem. Soc.*, **32**, 212 (1910).
(10) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).
(11) R. D. Haworth and W. Kelley, *ibid.*, 745 (1936).
(12) F. G. Baddar, L. S. El-Assal, and N. A. Doss, *ibid.*, 1027 (1959), and previous papers.
(13) D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965).
(14) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelley, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966).
(15) B. L. West, *J. Amer. Chem. Soc.*, **42**, 1656 (1920)
(16) L. I. Vereshchagin, S. P. Korshunov, S. L. Aleksandrova, and R. L. Bolshedvorskaya, *Zhur. Org. Khim*, **1**, 960 (1965).
(17) One must qualify this statement by pointing out that we generally detect between 2 and 4% more II-d_1 than should be there in the acetic anhydride–acetic acid cyclization of I-d_2. Whether this is the result of some intramolecular hydrogen transfer to C-4 of II, a small isotope effect associated with rate-limiting deprotonation of a reversibly formed intermediate or experimental instrumental vagaries we are not prepared to say. Our gross conclusions are unchanged, however.

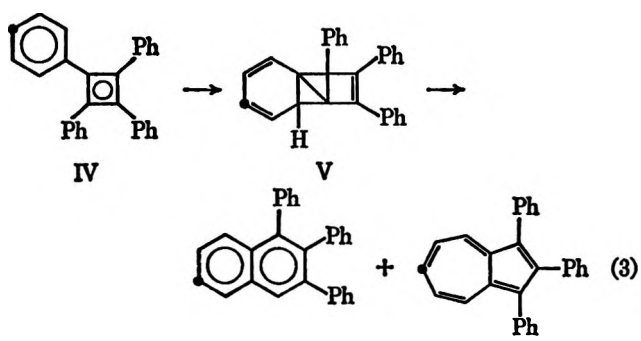
TABLE I

Expt	Phenylpropiolic acid	Solvent mixture	Reflux time, hr	Yield of II, %	Isotope analysis of II		
					d_0	d_1	d_2
1	d_0	Ac_2O	3.5	66			
2[a]	d_0	Ac_2O DOAc	3.5	82	76	64	0
3[b]	d_1	Ac_2O	3.5	68	1	43	56
4[c]	d_1	Ac_2O HOAc	26	22	2	44	52

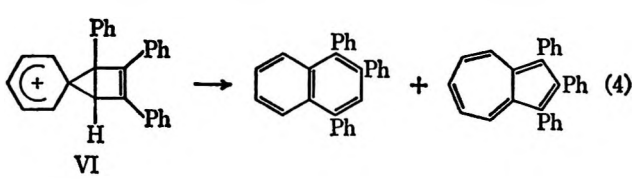
[a] The molar ratio of acetic acid-d_1:phenylpropiolic acid was 15:1 which would be decreased through the reaction to a value of approximately 10:1. [b] No acetic acid was added. The relatively high retention of two deuterium atoms is due to substantial contribution of the liberated *o*-hydrogens to the proton pool. [c] The molar ratio of acetic acid:phenylpropiolic acid d_1 was 80:1. The phenylpropiolic acid was 95.6% d_1, 2.2% d_0, 2.2% d_2, these values being ±0.5%. The quoted isotope composition is of the crude product, mp 263–265°. The product also had 2% d_3. Repetition of this experiment using a 65 equiv excess of 1:1 acetic acid acetic anhydride and refluxing 4 hr afforded a 28% yield of II. Isotope analysis indicated the composition 1.5% d_0, 47.2% d_1, 51.2% d_2.

required by the many studies of the cyclization of substituted phenylpropiolic acids.[9–14]

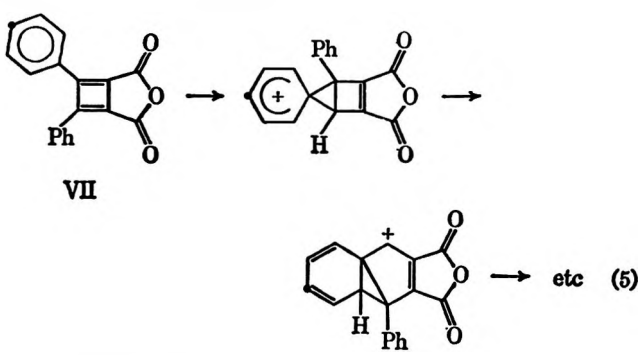
There are a number of reactions similar to the above in their over-all result (formation of trisubstituted naphthalenes) that have been suggested to proceed by way of cyclobutadiene intermediates. Buchi and coworkers[18] have suggested that the irradiation of tolane proceeds *via* IV and V (eq 3), while Breslow and



Battiste[19] have suggested that the dehydration of diphenylcyclopropyldiphenylcarbinol proceeds *via* VI (eq 4). Several masked derivatives of VI have been suggested as intermediates in similar reactions.[20,21]

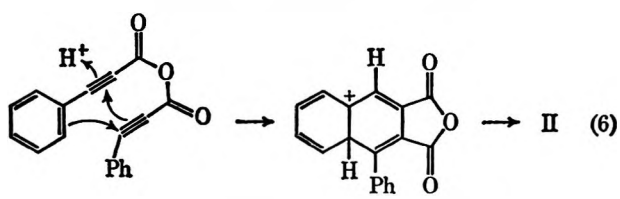


Although one can fit the phenylpropiolic acid dimerization to a scheme of this sort that involves initial cyclobutadiene formation (VII, eq 5) and in a



manner that generates the correct arrangement of groups on the naphthalene ring, the process involves choosing only a narrow set of reactions from a relatively large number of equally plausible looking possibilities that would be expected to give at least some positional or structural isomers of II.

The simplest mechanism for the dimerization of I consistent with the known facts would seem to be acid-catalyzed cyclization as in eq 6. A concerted cyclization of the type in eq 6 is not without precedent[22] and



catalysis by acid is at least consistent with qualitative observations to this effect.

Experimental Section[23]

2-Deuteriobenzyldimethylamine.—The general procedure of Jones, Zinn, and Hauser[24] was employed. A solution of 13.5 g (0.1 mol) of benzyldimethylamine and *n*-butyllithium (0.2 mol, 78 ml of a 2.6 *M* solution in heptane) in 300 ml of ether was allowed to stand at room temperature (26°) for 3 days. With stirring 18 ml of deuterium oxide (99.5% deuterium) was added and stirring was continued over 1 hr. The mixture was filtered and the filtrate was dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation afforded 7.5 g (55% yield) of 2-deuteriobenzyldimethylamine, bp 78° (25 mm). By mass spectrometry the material was ~95% d_1. Interference by the prominent P − 1 peak, even at low voltage, prevented more accurate assessment of the isotopic purity so that the amine was carried through to phenylpropiolic acid-d_1 which was assayed by mass spectrometry.

2-Deuteriobenzoic Acid.—Oxidation of 2-deuteriobenzyldimethylamine by the procedure of Jones and Hauser[25] gave 2-deuteriobenzoic acid in 90% yield. Examination of its nmr spectrum confirmed the position of deuterium, the low-field multiplet assigned to the two *o*-hydrogens having a relative area of one. This acid was converted into its acid chloride in 96% yield by reaction with thionyl chloride.

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(19) R. Breslow and M. Battiste, *J. Amer. Chem. Soc.*, **82**, 3626 (1960).
(20) H. H. Freedman, *J. Org. Chem.*, **27**, 2298 (1962).
(21) R. Breslow and J. Dowd, *J. Amer. Chem. Soc.*, **85**, 2729 (1963).
(22) H. W. Whitlock and P. E. Sandvick, *J. Amer. Chem. Soc.*, **88**, 4525 (1966).
(23) Isotope analyses were carried out at low voltages on either a CEC-103C mass spectrometer fited with an all-glass heated inlet system held at 250–300° or on an MS-902 mass spectrometer *via* its direct access probe. Results obtained on both machines were consistent with one another, as were the calculated and experimentally determined P + 1 and P + 2 values of the compounds in question. Results at 70 V ionizing voltage varied in the manner expected for loss of hydrogen from the parent ions.
(24) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).
(25) F. N. Jones and C. R. Hauser, *ibid.*, **26**, 2979 (1961).

Diethyl 2-deuteriobenzoylmalonate, bp 128–130° (0.2 mm), was prepared by the ethoxymagnesium malonic ester procedure of Hauser.[26]

Diethyl 2-Deuteriobenzoylmalonate Enol *p*-Bromobenzenesulfonate.—A modification of the procedure of Fleming and Harley-Mason[27] was used. To a stirred suspension of 6 g (0.11 mol) of sodium methoxide in 50 ml of dry tetrahydrofuran was added dropwise a solution of 24 g (0.1 mol) of diethyl 2-deuteriobenzoylmalonate in 35 ml of tetrahydrofuran. After stirring at 25° for 3 hr the mixture was cooled to −78° and a solution of 34 g (0.14 mol) of *p*-bromobenzensulfonyl chloride in 100 ml of tetrahydrofuran was added. The reaction mixture was allowed to warm to room temperature and to stand at room temperature 2 days. The reaction mixture was concentrated and poured into water, and the aqueous layer was extracted with ether. The ether extracts were washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to afford, after one recrystallization from ethanol, 29 g (60% yield) of the enol bromobenzenesulfonate, mp 91–93° (lit.[27] mp 91–91.5°).

2-Deuteriophenylpropiolic Acid.—The procedure of Fleming and Harley-Mason[27] was employed. 2-Deuteriophenylpropiolic acid was isolated in 50% yield. Isotopic analysis was carried out at 9–12 V, nominal, using either the parent ion region of the acid, *m/e* 144, or (better) the parent ion of phenylacetylene produced from the acid in the heated inlet. In a typical preparation of 2-deuteriobenzyldimethylamine, the phenylpropiolic acid had the composition 1.5% d_0, 1.5% d_2, 97% d_1.

1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride.—The procedure of Michael and Bucher[3] as generalized by Baddar, *et al.*,[28] was used. Typically, a solution of 1.26 g of phenylpropiolic acid in 60 ml of acetic anhydride was heated under reflux for 3.5 hr. Evaporation of the solvent *in vacuo* and washing of the precipitate with ether gave a 66% yield of the anhydride, mp 264–265°. Decreasing the concentration of phenylpropiolic acid, and diluting the acetic anhydride with acetic acid decreased the yield under these reflux conditions. When a solution of 100 mg of phenylpropiolic acid (d_1) in a mixture of 4.5 ml of acetic anhydride and 1 ml of acetic acid was refluxed 16 hr, the yield of 1-phenylnaphthalene-2,3-dicarboxylic anhydride was 26%. Substantial amounts of recovered phenylpropiolic acid were detected in those reactions that were incomplete.[29] In experiments using a solvent mixture of acetic anhydride and acetic acid-d_1, the solvent was prepared by addition of the requisite amount of deuterium oxide to acetic anhydride, followed by brief refluxing. Results of the various experiments using labeled and unlabeled phenylpropiolic acid and labeled and unlabeled acetic acid-containing acetic anhydride as solvent are in Table I.

Registry No.—I, 637-44-5.

(26) (a) H. G. Walker and C. R. Hauser, *J. Amer. Chem.*, **68**, 1386 (1946). (b) *Org. Syn.*, **30**, 70, (1950).

(27) I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 4771 (1963).

(28) F. G. Baddar and L. S. El-Assal, *ibid.*, 1267 (1948).

(29) The recovered phenylpropiolic acid was of undiluted isotope composition by mass spectrum.

The Transmission of Electronic Effects. Proton Magnetic Resonance Chemical Shifts for Benzyl Halides in Several Solvents[1a]

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Proton magnetic resonance (pmr) shifts are reported for substituted benzyl fluorides, chlorides, and bromides in several solvents. At finite concentrations, molecules of the same or different compounds interact specifically. Thus the apparent association constant for benzyl chloride and *p*-nitrobenzyl chloride in carbon tetrachloride at *ca.* 37° is $K = 0.27\ M^{-1}$. Obviously, comparisons of substituent effects should be made with chemical shifts at infinite dilution (v^0). Even so, each v^0 of the benzyl halides still reflects specific interactions with the solvent peculiar to itself. Attempted correlations of v^0 of the benzyl halides according to Hammett or Yukawa–Tsuno relations are poor. A literature survey of *ca.* 100 Hammett correlations of pmr data indicates that the majority of them have unsatisfactory correlation coefficients, *e.g.*, <0.90–0.95. The ρ values appear to have no pattern. However, the use of a polar solvent with certain families, *e.g.*, DMSO for phenols and amines, gives large ρ values and excellent correlations; presumably enhanced electronic effects typical of chemical reactions dominate possible anisotropy effects on v^0. In general, ρ's cannot be used in the way that reactivity ρ's are used, namely as indices of transmission efficiency in aryl systems Ar–T–H.

It is generally agreed that proton magnetic resonances (pmr) chemical shifts at any point in a molecule are in some sense related to the rest of the molecule and its environment. By examining this relation, a number of workers have attempted to reduce its complexity. Contributions from π-electron density, resonance, electric field, magnetic field, van der Waals forces, and ring currents have all appeared to be important at least for some systems or some substituents.[2] On this basis, it has sometimes appeared that the factors that affect substituent chemical shifts (SCS) are understood. In our own survey of the transmission of electronic effects from a substituent (R) to a proton in *ca.* 30 aryl systems, *e.g.*, R–C_6H_4T–H, we too seemed to uncover an underlying regularity that appeared to apply to some systems.[3] In this study we examine the transmission of electronic effects in the benzyl halides in some depth and find that such regularities are often more apparent than real.

As a family, the benzyl halides are of considerable interest.[4] Pmr studies of related families are available and comparison with the toluenes, say, is possible. Our work was completed about the time that a paper on both the ^1H and ^{19}F nmr spectra of benzyl fluorides appeared.[5] A graphical comparison of the pmr chemical shifts for the ten substituted benzyl fluorides common to Béguin's work and ours, indicated significant discrepancies for seven of the compounds. After coping with this problem, we could approach the initial issue, namely, substituent effects on chemical shifts.

(1) (a) This work was supported by the National Science Foundation, Grant GP 5740. (b) Postdoctoral fellow, 1966–1967. (c) Author to whom inquiries should be addressed.

(2) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, Chapter 4.

(3) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

(4) R. R. Fraser, Gurudata, C. Reyes-Zamora, and R. B. Swingle, *Can. J. Chem.*, **46**, 1595 (1968).

(5) C. Béguin, *Bull. Chim. Soc. Fr.*, 4214 (1967).

Experimental Section

Spectra.—Proton nmr spectra were measured by a Varian A 60 spectrometer operating at 60 Mc. The spectra were calibrated by the side-band technique with a Hewlett-Packard 200 CDR wide range oscillator and 5245 L electronic counter. The sample temperature was 37 ± 1°. The sample tubes were 5 mm o.d. Tetramethylsilane (TMS) was used in the solution as an internal standard. Each sample was scanned several times at a rate of 1 Hz/sec. The solvents used were spectrograde or freshly distilled before use.

Initially, shifts ν were obtained at several concentrations in the range 0.4–1.5 mol/l.; but since the dilution plots of ν were usually curved and quite specific for each compound, ν was measured on four or five solutions in the range 0.01–0.2 mol fraction (solute/solvent), accurately prepared by weight and extrapolated to ν^0 at infinite dilution.

It has been reported that the SCS of a benzyl halide was independent of both concentration and the presence of another benzyl halide.[4,6] To investigate these claims, we investigated dilution effects in several straightforward ways; some of the results are given in Figures 1 and 2.

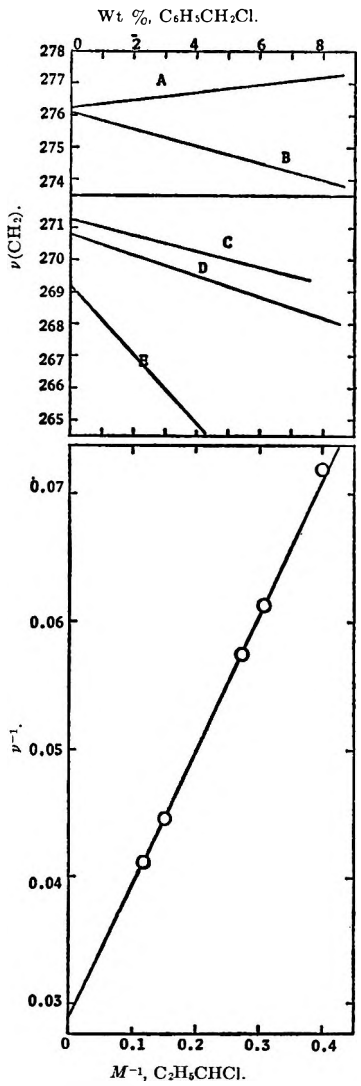


Figure 1.—Solute–solute interactions and chemical shifts of the benzyl chlorides in carbon tetrachloride. Upper box: A, p-$O_2NC_6H_4CH_2Cl$; B, p-$O_2NC_6H_4CH_2Cl$ in the presence of $C_6H_5CH_2Cl$, $(NO_2):(H) = 2:1$; C, $C_6H_5CH_2Cl$ in the presence of p-$O_2NC_6H_4CH_2Cl$, $(NO_2):(H) = 2:1$; D, $C_6H_5CH_2Cl$ in the presence of p-$ClC_6H_4CH_2Cl$, $(H):(Cl) = 4.95:2.55$; E, p-$ClC_6H_4CH_2Cl$ in the presence of $C_6H_5CH_2Cl$, $(H):(Cl) = 4.95:2.55$. The weight ratios in solution are indicated here. Lower box: $\nu(CH_2)$ for *ca.* 0.1 M p-$O_2NC_6H_4CH_2Cl$ in the presence of $C_6H_5CH_2Cl$. A slope of 0.1055 and intercept of 0.0295 lead to an apparent equilibrium constant for association of $K = 0.27\ M^{-1}$.

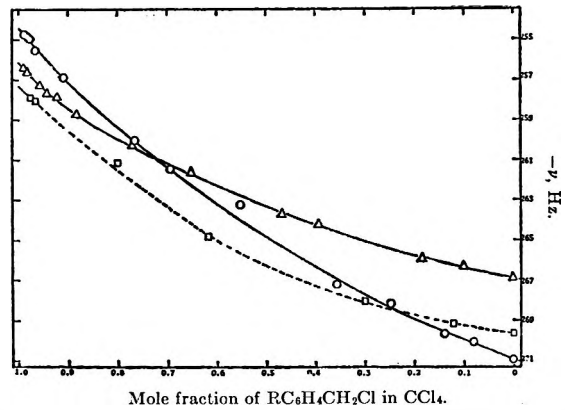


Figure 2.—Dilution plots of the benzyl chlorides, $RC_6H_4CH_2Cl$: ○, R = H; □, R = 4-CH_3; △, R = 4-Cl.

Benzyl Halides.—The origins and properties of the benzyl halides are given in Table I. Several bromides were made from the benzyl alcohols or by bromination of the toluenes. The benzyl fluorides were made more or less according to the following procedure, with variations to suit individual compounds, as needed. p-Methoxybenzyl chloride, p- and m-methyl- and p-fluorobenzylfluorides appeared to be unstable and decomposed, even when kept in sealed tubes.

***m*-Trifluoromethylbenzyl Fluoride.**—In a 300-ml three-necked flask, fitted with a mercury sealed stirrer, reflux condenser, and a dropping funnel, was placed anhydrous potassium fluoride powder (15 g, 0.26 mol), which had been dried at 140° overnight, and freshly distilled N-methyl-2-pyrrolidone (40 ml). The reflux condenser and the dropping funnel were fitted with drying tubes. The mixture was heated to 165° in an oil bath. m-Trifluoromethylbenzyl chloride (22.5 g, 0.116 mol) was added slowly during 1 hr, and the heating and the stirring were continued for 2 hr. After cooling, the reaction mixture was treated with ice water and extracted with ether. The ether solution was washed with water to remove the methylpyrrolidone, dried over Drierite and evaporated. Distillation of the residue gave the following fractions: m-trifluoromethylbenzyl fluoride (8.1 g), bp 66–68° (22 torr); m-trifluoromethylbenzyl chloride (13.3 g), bp 70–71° (11 torr). The yield of fluoride was 96% based on the reacted chloride and 40% based on the starting chloride. The fluoride was purified by redistillation in a Vigreux column: bp 49.0–49.5° (11 torr); $n^{26}D$ 1.4252. *Anal.* Calcd for $C_8H_6F_4$: C, 53.94; H, 3.39. Found: C, 53.63; H, 3.34.

Results and Discussion

Since SCS and solvent effects on SCS have been dealt with theoretically by many groups without notable success, we shall remain fairly close to the data. We shall have some concrete things to say about how to and how not to go about correlating pmr data. We have also extended our survey of Hammett-type pmr correlations and have made a value judgement on them.

Solute–Solute and Solute–Solvent Interactions.—Our pmr data for substituted benzyl halides are given in Tables I and II. Infinite dilution chemical shifts (ν^0) were obtained from concentration dependence plots of ν (Figures 1 and 2). The solvents in Table II were chosen to test various hypotheses concerning solvent effects on ν^0; since these tests were inconclusive, they are not elaborated on here.

Since the previously mentioned differences between Béguin's chemical shifts and ours are outside experimental uncertainties, we investigated the idea that his method could involve specific solute–solute interactions. Béguin obtained $\nu_R(CH_2)-\nu_H(CH_2)$ from a single solution of 8% substituted benzyl fluoride and 4% benzyl fluoride; we obtained $\nu_R{}^0(CH_2)-\nu_R{}^0(CH_2)$ for such systems by extrapolating shifts referenced to TMS

TABLE I

PREPARATION AND PROPERTIES OF BENZYL HALIDES, $RC_6H_4CH_2X$

R	Mp or bp (torr), °C	$n^{25}D$	Lit. mp or bp (torr), °C	Lit. $n^{25}D$	Ref	$-\nu^0$ (CH_2), Hz
			X = Cl			
H	63–64 (12)	1.5386	69 (15)	1.5390	*a, b, i*	271.5
p-CH_3	89–90 (16)	1.5328	192		*a*	268.4
m-CH_3	91.5–93.5 (20)	1.5329	96 (23)	1.5345	*b, c*	268.2
p-F	75–76 (20)	1.5114	73 (18)	1.5118	*l, i*	270.3
m-F	73–74 (25)	1.5128	70 (36)	1.5131	*l, c*	270.5
p-Cl	105–106 (19)		114–117 (30)		*b, d*	270.1
m-Cl	101–102 (18)	1.5546	44 (0.3)	1.5556[n]	*c, g*	268.7
m-CF_3	70–71 (11)	1.4622				274.8
p-NO_2	71–72		71.8–72.4		*a, d*	276.9
m-NO_2	45–46					278.2
p-OCH_3	92.8–93.0 (2.5)	1.5489	92.5 (1.5)	1.5491	*a*	268.8
m-OCH_3	87.0–87.5 (2)	1.5430	55 (0.3)		*c*	269.8
			X = Br			
H	197–198		84 (13)		*a, i*	264.6
p-Br	129–130 (18)		117–119 (10)		*f*	261.6
m-CN	92–93		92.5–93.5		*g*	266.6
p-*t*-Bu	132.5 (13)		132.5 (14)		*h, i*	263.0
p-Ph	85–86		85		*j*	268.4
			X = F[m]			
H	45–46 (18)	1.4886	50 (27)	1.4980	*f, i*	318.6
p-CH_3	50–50.5 (12)	1.4918	60 (14)	1.4918	*f, i*	313.7[m]
m-CH_3	63.0–63.2 (10.5)	1.4948	48.5 (8.5)	1.4952	*f*	315.6[m]
p-F	45–46 (19)	1.4654	54 (28)	1.4667	*f*	317.0[m]
m-F	38.5 (11)	1.4652	41 (15)	1.4660	*f*	320.0[m]
p-Cl	76.5–78.0 (21)	1.5140	72–73 (16)	1.5149	*f*	318.0
m-Cl	64 (10.5)	1.5148	65 (11)	1.5158	*f*	318.0
p-Br	85–86 (18)		80–81.5 (10)		*f*	316.5[m]
m-CF_3	49.2–49.8 (12)	1.4252			*k*	324.1
p-NO_2	37–38		38.2–38.5		*f*	332.3[m]
m-NO_2	128.0–128.5 (13)	1.5328	91 (3.5)	1.5381	*f*	328.3[m]
p-*t*-Bu	84.8–85.2 (13)	1.4760	90 (12)		*i*	316.0

[a] C. G. S. Swain and W. P. Langsdorf, *J. Amer. Chem. Soc.*, **73**, 2813 (1951). [b] M. S. Kharasch and H. C. Brown, *ibid.*, **61**, 2142 (1939). [c] R. Fuchs and D. M. Carlton, *ibid.*, **85**, 104 (1963). [d] R. Fuchs, *ibid.*, **79**, 6531 (1957). [e] H. Schmidt and P. Karrer, *Helv. Chim. Acta*, **29**, 573 (1946). [f] J. Bernstein, J. S. Roth, and W. T. Miller, Jr., *J. Amer. Chem. Soc.*, **70**, 2310 (1948). [g] J. Von Braun and H. Reich, *Ann.*, **445**, 225 (1925). [h] J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 300 (1936). [i] C. W. L. Bevan, *ibid.* 1347 (1960). [j] L. Zervas and I. Dilaris, *J. Amer. Chem. Soc.*, **77**, 5354 (1955). [k] New compound. [l] Pierce Chemical Catalog, F-16, 1967. [m] Values of the HF coupling constants, given as R(J_{HF}), are H (47.71), *p*-CH_3 (48.04), *m*-CH_3 (47.97), *p*-F (47.74), *m*-F (47.86), *p*-Cl (47.80), *m*-Cl (47.52), *p*-Br (48.23), *m*-CF_3 (47.37), *p*-NO_2 (46.92), *m*-NO_2 (47.08). Additional or alternate values of $\nu(CH_2)$ and J_{HF} at finite concentrations are given in ref 5. [n] At 25°.

TABLE II

SUBSTITUENT CHEMICAL SHIFTS ($-\nu$) AT INFINITE DILUTION, IN HERTZ FROM TETRAMETHYLSILANE, OF BENZYL CHLORIDES $RC_6H_4CH_2Cl$ IN SEVERAL SOLVENTS AT 37°

Solvents	Registry no.	R							
		H[a]	*p*-CH_3	*m*-CH_3	*p*-Cl	*m*-Cl	*p*-NO_2	*m*-NO_2	*m*-CF_3
C_6H_{12}	100-44-7	265.0	262.8	262.4	262.6	262.4		271.0	267.3
CCl_4	104-82-5	271.5	268.4	268.2	270.1	268.7	276.9	278.2	268.7
Et_2O	620-19-9	273.2			273.0				
Dioxane	104-83-6	277.0			276.3				
$(CH_3)_2CO$	620-20-2	281.3			282.8				
CH_3CN	100-14-1	279.4	277.2		278.4	280.1	284.8	285.8	
C_6H_6	619-23-8	245.2	245.2	247.4	233.3	230.5	229.0	227.5	
n-Hexane	705-29-3	265.5	263.2	263.6	263.5				

[a] Additional data for $C_6H_5CH_2Cl$: $CHCl_3$ (275.4), CH_2Cl_2 (276.7), $(CH_3)_3CCl$ (271.8), *n*-C_4H_9Cl (272.3), $CHBr_3$ (278.3), CH_2Br_2 (276.6), $(BrCH_2)_2$ (276.2), $(CH_3OCH_2)_2$ (278.0), $(n\text{-}C_4H_9)_2O$ (269.5), THF (276.7), CH_3OH (276.6), $(HOCH_2)_2$ (280.0), DMF (287.0).

to infinite dilution. Since the dilution shifts of Figure 1 do not vary in a standard way for different pairs of compounds, it is clear that nonsystematic discrepancies arise in the data from the two approaches. We believe that the complicating factor of specific solute–solute interactions has been minimized in our data.

Recent work has shown that many solvent effects on pmr data can be regarded as arising from complex formation of solvent and solute.[6] We hesitate to

(6) (a) I. D. Kuntz, Jr., and M. D. Johnston, Jr., *J. Amer. Chem. Soc.*, **89**, 6008 (1967); (b) R. C. Fort, Jr., and T. R. Lindstrom, *Tetrahedron*, **23**, 3227 (1967).

characterize all of the solute–solute interactions of the benzyl chlorides in this way, because of the lack of a consistent pattern in our dilution plots of Figure 1. The slopes of differing magnitude and occasionally of opposite sign are particularly difficult to explain. One possible association reaction, p-$O_2NC_6H_4CH_2Cl$ + $C_6H_5CH_2Cl \rightleftharpoons (p\text{-}O_2NC_6H_4CH_2Cl)\cdots(C_6H_5CH_2Cl)$, was investigated. A standard double reciprocal plot[6a] was used to obtain an apparent $K = 0.27\ M^{-1}$ at 37° in carbon tetrachloride (Figure 1). We call this an "apparent" association, because we have not assessed the well known, but poorly characterized, "aromatic" effects on ν.

At the beginning of our research, we were inclined to obtain accurate ν values at some common concentration, *e.g.*, 5%. Certainly, this was less tedious than collecting data for dilution plots. We discovered, however, that the form of the dilution plot for any benzyl halide in carbon tetrachloride was not readily predictable from the behavior of others in the family. This is shown in the fact that the plots cross, and worse, do not have the same slope at infinite dilution (Figure 2). Whereas Figure 1 illustrates the mutual effect of two solutes, Figure 2 indicates the specific effects of like molecules on one another.

We were also concerned about the possibility that differential solvent factors might be contained in ν^0. Several groups have found solute–solute correlations which may bear on this point. Thus, Marcus and Miller found that the infinite dilution shifts of benzenethiol and *n*-butanethiol or chloroform and 1-alkynes in a variety of solvents are linearly related.[7] The interpretation is that these solutes must evoke a parallel response from diverse solvents, whether specific interactions be large or small. This idea was tested here. (To conserve space, these plots have been deleted.)

$$\nu^0(\text{solute 1}) = A\nu^0(\text{solute 2}) + B \qquad (1)$$

Although more points would have been desirable, it appears that the ν^0 values of benzyl chloride and *p*-chlorobenzyl chloride *may be*, while those of benzyl chloride and *m*-nitrobenzyl chloride *are not*, linearly related. *We must conclude that ν^0 of each benzyl chloride probably reflects specific solvent–solute interactions different from those of other benzyl chlorides.*

Pmr Data and Linear Free Energy Relations.—The effect of structure may be examined by means of the Hammett equation[3] (eq 2). Briefly, the model for

$$\nu = \rho\sigma + \nu_0 \qquad (2)$$

aryl families R–C_6H_4T–H is based on the notion that the substitutent and the terminal proton are sufficiently remote so that differential effects, *e.g.*, anisotropy, were negligible or at least constant for the transmitting group, C_6H_4T. Provided that the substituent constant σ were an invariant index of the electronic properties of R, ρ would characterize T as well as the reaction conditions. Because ρ derives from a family of compounds, one hopes that specific irregularities of solvent, conformation, etc., tend to be smoothed and averaged.[3] Unfortunately, this model is largely based on untenable assumptions, as we shall see.

(7) S. H. Marcus and S. I. Miller, *J. Phys. Chem.*, **73**, 453 (1969).

Our data on benzyl halides may be treated in various ways, but we need only display a few of them. For example, we have used standard Hammett σ values to test eq 2 for the benzyl fluorides in carbon tetrachloride and benzyl chlorides in cyclohexane. The correlations are poor and eq 2 is *not* obeyed. Béguin had already shown that a plot of ν of the benzyl fluorides against σ^+ deviates grossly from linearity.[5] It is interesting, however, that the correlation of ^{19}F ν values with σ is eminently satisfactory.[5]

Incidentally, using our data and Béguin's, we have attempted to correlate the coupling constants (J_{HF}) of the benzyl fluorides with the Hammett σ. Here too the data scatter. In any case, we are not aware of any theoretical connection between J and substituent constants, although a few examples have been published.[8]

Several workers have attempted to improve deficient Hammett correlations by using more parameters. Of these, the Yukawa-Tsuno equation has been tested most recently, but chiefly for reactivity data.[9] Adapted

$$\nu = \rho(\sigma^0 + r\Delta\bar{\sigma}_R^+ + r'\Delta\bar{\sigma}_R^-) + \text{constant} \qquad (3)$$

to nmr data, it takes the form[10,11] of eq 3. The substituent constants σ^0 are based on phenylacetic acid and ester reactivities, and $\Delta\bar{\sigma}_R^+ = (\sigma^+ - \sigma^0)$ and $\Delta\bar{\sigma}_R^- = (\sigma^- - \sigma^0)$, in which σ^+ and σ^- are the usual resonance substitutent constants.[9] Because $\Delta\bar{\sigma}_R^{\pm} = 0$ for *meta* substituents, we would normally expect these to define a Hammett line. Since eq 3 separates inductive and resonance effects in a way which is related to, but not identical with, Taft's approach, we shall not consider the latter.[12,13]

Wittstruck and Trachtenberg have tried another approach.[14] They assume that the chemical shift in RC_6H_4T–H is made up additively from the shift in some parent [δ_0(H)] plus changes ascribed to the substituents R interacting through inductive (**I**), resonance (**R**), field (**F**), and magnetic field (**M**) effects over the chain C_6H_4 and T connecting R and H. The last terms $\Delta\delta^F$ and $\Delta\delta^M$ can be approximated by the

$$\delta_R(H) = \delta_0(H) + \sum(\Delta\delta^I + \Delta\delta^R + \Delta\delta^F + \Delta\delta^M) \qquad (4)$$

equations of Buckingham and McConnell; these of course have an explicit dependence on molecular geometry.[2,14] The fact that SCS of one β proton of a family of styrenes was linearly related to the SCS of the other with unit slope was a strong indication that the last two terms of eq 4 cannot be significant, because of the spatial difference in the β protons. At the same time, the expectation that resonance and inductive effects might be identical at the β carbon was confirmed. Although the symbolism is different, the analysis of Wittstruck and Trachtenberg now resembles that used by Taft, *et al.*,[12,13] or Yukawa and Tsuno for substituent effects,[9] or that used by Marcus, *et al.*, for attenuation of electronic effects.[3] *If* one is to use a multiparameter treatment, one might just as well use eq 3.

(8) Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967).

(9) Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jap.*, **39**, 2274 (1966); Y. Yukawa and Y. Tsuno, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 71 (1966).

(10) Y. Yukawa, Y. Tsuno, and H. Yamada, *ibid.*, **23**, 79 (1966).

(11) Y. Yukawa and H. Yamada, *Nippon Kagaku Zasshi*, **85**, 501 (1964).

(12) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(13) P. Wells, S. Ehrenson, and R. W. Taft, *ibid.*, **6**, 147 (1968).

(14) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3803, 3810 (1967).

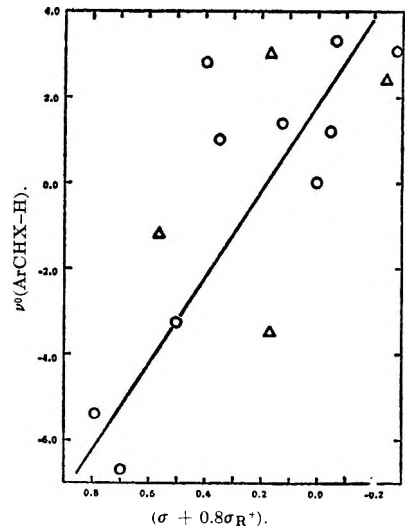


Figure 3.—Attempted correlation of the type $\Delta\nu^0 = \rho(\sigma + 0.8\Delta\sigma_R^+)$. Data taken in carbon tetrachloride: ○, X = Cl; △, X = Br.

Our attempts to correlate the benzyl halide data with versions of eq 3 were not very promising (see Figure 3). The scatter in the *meta* substituents and the gross departure for ν^0(H) and ν^0(phenyl) from the other points are simply not reconcilable with the basic assumptions behind the relation.

Yukawa, *et al.*, have used eq 3 for the phenylacetylenes,[11] and the 1,1-diphenylethylenes.[10] To obtain a satisfactory fit for the diphenylenes, Buckingham and McConnell corrections for anisotropy and field effects were applied.[10] It is not clear why these families should require different treatment. Moreover, Wittstruck and Trachtenberg indicated that the Buckingham and McConnell corrections are probably insignificant for similar families.[14]

We then sought a more limited relation. Granting that there might be specific interactions, we selected pairs of related families in which cancellation of these effects could reaonably be expected, when ν^0 values were compared (Figures 4 and 5). Some of the pairs are benzyl chlorides (bromides) *vs.* benzyl fluorides; benzyl chlorides *vs.* toluenes;[3] 1,1-diphenylethylenes[10] *vs.* styrenes.[8] Again, the scatter is often more impressive than the fit. It is not merely a question that *certain* substituents *sometimes* deviate. Depending on the

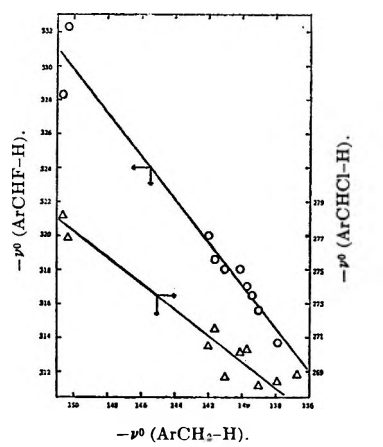


Figure 4.—Chemical shift correlations of related families in carbon tetrachloride. Toluene data is from ref 3.

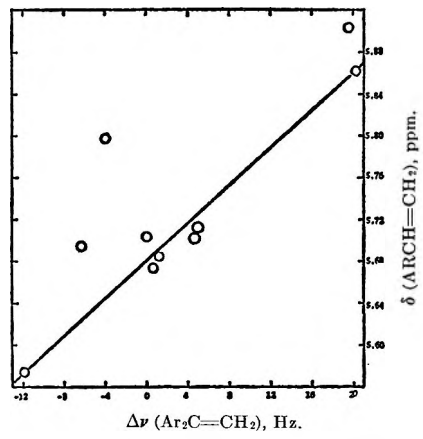


Figure 5.—Chemical shift correlation for β protons, *cis* to aryl. Pmr data from refs 8 and 10.

families, errant points may belong to *m*- or *p*-nitro, hydrogen, halogen, alkyl, etc., substituents. Clearly, many, if not all, ν^0 values reflect specific interactions which preclude precise parallel behavior of a given substituent in different systems.

Transmission of Electronic Effects and Pmr Data.—The Hammett relation is not simply intended for concise data storage or display, although this might be considered as a minimum requirement.[9,12,15] The line parameters have, or at least they should have, meaning. Now, ρ values have been used to assess the efficiency of transmission of electronic effects. Whether the comparison is made with a standard, as eq 7, in which the

$$\rho_{C_6H_4T}/\rho_{C_6H_4} = \epsilon \qquad (7)$$

fall-off factor ϵ is obtained, or in some other way, the magnitude of ρ might be expected to vary systematically.[15]

A number of the reported Hammett correlations of pmr data have been collected.[3] We extend this compilation here to probe further the question of the meaning of ρ. Table III follows a standard format.[3] The numbers identifying the families follow those of Table II, ref 3. Equation 2 and the McDaniel-Brown σ values were used, only when we processed the data. Previously, we noted that perhaps two-thirds of the pmr correlations coefficients (r) of eq 2 were less than 0.95. Judging from our data in the benzyl halides and plots of literature data, this pattern seems general. In fact, most workers do not give r.

For the present, we disregard low correlation coefficients and plot ρ *vs.* chain length T in Figure 6. Data from strongly polar solvents *e.g.*, acetone, DMSO, etc. were not included. From an earlier version of this figure, it was concluded that the "standard" $-\rho$ values of 36, 13, 7 could be discerned for $T = 0$, 1, or 2 atoms in the side chain to benzene.[3] These ρ values also seemed to show the conventional fall-off of 2–3 per atom in T. Exceptionally high ρ values were considered to be superconducting and seemed to be related to the structure of T. Figure 6 now makes it clear that "standard" values of ρ cannot be assigned.

The most numerous entries in Table III are for $T = 1$ and 2 and these also show the largest spread in ρ. Clearly, *there is no clustering in ρ around one value for*

(15) W. K. Kwok, R. A. More O'Ferrall, and S. I. Miller, *Tetrahedron*, **20**, 1913 (1964), and related papers.

TABLE III

GROUP ATTENUATION FACTORS FOR PMR SHIFTS AS INDICATED BY HAMMETT ρ VALUES[a]

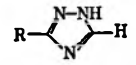
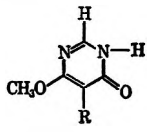
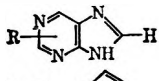
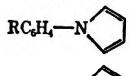
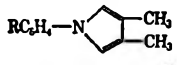
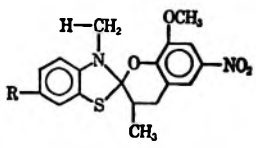
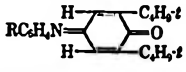
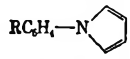
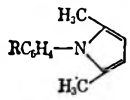
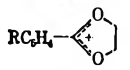
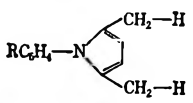
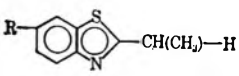
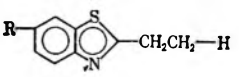
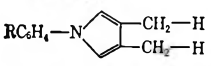
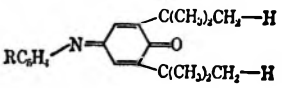
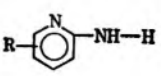
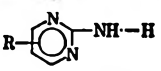
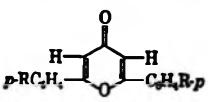
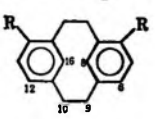
Code no.	RC_6H_4T-H		Atoms in T	$-\rho/\sigma$, Hz	No. of R	Solvent	Ref
32			0	64	14	$(CD_3)_2CO$	*b*
33	5-R-2-(*trans*-C_6H_5CH=CH-)C_6H_3-H		0	18.6	5	$CDCl_3$	*c*
34		1-H	0	76	5	DMSO	*d*
35		2-H	0	23.2	5	DMSO	*d*
36	$RC_6H_4C(=CH_2)$—H		1	16	8	$(CD_3)_2CO$	*e*
37	$RC_6H_4CH(CH_2COOH)$—H		1	8.2	5	$(CD_3)_2CO$	*e*
38	$RC_6H_4CH(CH_3)$—H		1	14	6	$(CD_3)_2CO$	*e*
39	*trans*-RC_6H_4C(=CHCOOH)—H		1	8.6	11	$(CD_3)_2CO$	*e*
40	*cis*-RC_6H_4C(=CHCOOH)—H		1	20.4	9	$(CD_3)_2CO$	*e*
41	*trans*-4-$RC_6H_4C(=CHC_6H_5)$—H		1	*Ca.* 2.5	17	$CDCl_3$	*c*
42	$RC_6H_4CH_2$—H		1	12	8	$CDCl_3$	*f*
43	$RC_6H_4CH(OH)$—H		1	12.6	6	$CDCl_3$	*f*
44	$RC_6H_4CH(OCH_3)$—H		1	9	6	$CDCl_3$	*f*
45	RC_6H_4CH(2-dihydropyranyl)-H		1	9	8	$CDCl_3$	*f*
46	$RC_6H_4CH(SCH_3)$—H		1	6	4	$CDCl_3$	*f*
47	$RC_6H_4CH(SC_6H_5)$—H		1	4.8	5	$CDCl_3$	*f*
48	$RC_6H_4CH(SOCH_3)$—H		1	7.8	5	$CDCl_3$	*f*
49	$RC_6H_4CH(SOC_6H_5)$—H		1	12	5	$CDCl_3$	*f*
50	$RC_6H_4(SO_2CH_3)$—H		1	9.6	5	$CDCl_3$	*f*
51	$RC_6H_4(SO_2C_6H_5)$—H		1	9.6	5	$CDCl_3$	*f*
52	RC_6H_4CHCl—H		1	6.6	5	$CDCl_3$	*f*
53	RC_6H_4CHBr—H		1	1.2	5	$CDCl_3$	*f*
54	4-R-2,6-(t-C_4H_9)$_2C_6H_2O$-H		1	45.6	6	CCl_4	*g*
55	RC_6H_4O-H		1	109.8	18	HMPA	*h*
56	RC_6H_4O-H		1	92 (79)	20 (16)	DMSO	*i*, *v*
57	$RC_6H_4CH_2CH_2$-H		2	4.6	6	$(CD_3)_2CO$	*e*
58	$RC_6H_4CH_2CH(COOH)$-H		2	8.2	5	$(CD_3)_2CO$	*e*
59	$(RC_6H_4)_2C$=CH-H		2	15	16	CCl_4	*j*
60	*cis*-RC_6H_4CH=CH-H		2	24	8	$(CD_3)_2CO$	*e*
61	*trans*-RC_6H_4CH=CH-H		2	23.6	8	$(CD_3)_2CO$	*e*
62	*trans*-RC_6H_4CH=C(COOH)-H		2	20.6	11	$(CD_3)_2CO$	*e*
63	*trans*-RC_6H_4CH=C(COOH)-H		2	16.2	6	CF_3COOH	*k*
64	*trans*-RC_6H_4CH=C(COOH)-H		2	20	10	DMSO	*k*
65	*cis*-RC_6H_4CH=C(COOH)-H		2	23.6	9	$(CD_3)_2CO$	*e*
66	*trans*-RC_6H_4CH=C(C_6H_5)-H		2	16.6	17	$CDCl_3$	*c*
67	*cis*-RC_6H_4CH=C(C_6H_5)-H		2	17.6	7	$CDCl_3$	*l*
68	$RC_6H_4C(O)O$-H		2	88	13	pyridine	*m*
69	$RC_6H_4CH_2O$-H		2	24	7	DMSO	*n*
70	$RC_6H_4CH(CH_3)O$-H		2	27	5	DMSO	*n*
71	$RC_6H_4C(CH_3)_2O$-H		2	30.6	4	DMSO	*n*
72	$RC_6H_4C(CH_3)$(i-C_3H_7)O-H		2	37.8	3	DMSO	*n*
73	$RC_6H_4C(CH_3)(C_6H_5)O$-H		2	40.8	6	DMSO	*n*
74	R-2-$CH_3C_6H_3C(CH_3)_2O$-H		2	40.2	4	DMSO	*n*
75	4-R-2-$NO_2C_6H_3S(O)CH(CH_3)$-H		2	7.2	5	$CDCl_3$	*o*
76	4-$RC_6H_4N(CH_3)CH_2$-H		2	10.1	15	$CHCl_3$	*p*
77			2	20.5	17	DMSO	*q*
78		α-H	2	14	7	CCl_4	*r*
79		α-H	2	14	8	CCl_4	*r*
80			2	8.3	10	$CDCl_3$	*s*
81		*syn*-H	3	15	13	CCl_4	*t*
82		*anti*-H	3	1.1		CCl_4	*t*
83	4-R-2-$NO_2C_6H_3S(O)CH_2CH_2$-H			4.8	5	$CDCl_3$	*o*

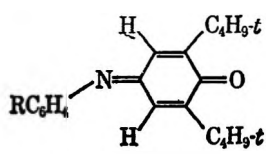
TABLE III (*Continued*)

Code no.	RC_6H_4T–H		Atoms in T	$-\rho/\sigma$, Hz	No. of R	Solvent	Ref
84		β-H	3	6	7	CCl_4	*r*
85		β-H	3	8	8	CCl_4	*r*
86			3	14.1	14	FSO_3H	*u*
87			3	3.3	8	CCl_4	*r*
88			3	11	11	$CDCl_3$	*s*
89			4	7.9	11	$CDCl_3$	*s*
90			4	1.9	8	CCl_4	*r*
91		*syn*-H	6	~2.2	12	CCl_4	*t*
92		*anti*-H	6	~2.4	12	CCl_4	*t*
56a	RC_6H_4NH–H		1	79.27	15	DMSO	*v*
56b			1	76.87	5	DMSO	*v*
56c			1	81.1	4	DMSO	*v*
67a			2	5.0	5	$CDCl_3$	*w*
35a		(8,16) H	~0	17.6	4	CCl_4	*x*
35b		(6,12) H	0	36.0	4	CCl_4	*x*
35c		(9,10 equatorial) H	1	9.7	5	CCl_4	*x*

[a] The general format of this table follows that of Table II, ref 3. Thirty one ρ values are listed there. [b] W. Freiberg and C.-F. Kröger, *Tetrahedron Lett.*, 2109 (1967). [c] H. Güsten and M. Salzwedel, *Tetrahedron*, **23**, 173 (1967). [d] G. M. Kheifets, N. V. Khromov-Borisov, A. I. Koltsov, and M. V. Volkenstein, *Tetrahedron*, **23**, 1197 (1967). [e] Reference 14. [f] Reference 4. [g] V. F. Bystrov, V. V. Ershov, and V. P. Lezina, *Opt. Spectrosc.*, **17**, 290 (1964). [h] Reference 23. [i] Reference 22. [j] Reference 10. [k] A. R. Katritzky and F. J. Swinbourne, *J. Chem. Soc.*, 6707 (1965). [l] H. Güsten and M. Salzwedel, *Tetrahedron*, **23**, 187 (1967). [m] Y. Kondo, K. Kondo, T. Takemoto, and T. Ikenoue, *Chem. Pharm. Bull. Jap.*, **12**, 514 (1964). [n] Reference 16. [o] C. Brown and D. R. Hogg, *Chem. Commun.*, 150 (1965). [p] I. D. Rae and L. K. Dyall, *Aust. J. Chem.*, **19**, 835 (1966). [q] W. C. Coburn, Jr., M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, **30**, 1110 (1966). [r] R. A. Jones, T. M. Spotswood and P. Cheuychit, *Tetrahedron*, **23**, 4469 (1967). [s] R. Gugliemetti, E.-J. Vincent, and J. Metzger, *Bull. Soc. Chim. Fr.*, 4195 (1967). [t] Reference 17. [u] D. A. Tomalia and H. Hart, *Tetrahedron Lett.*, 3389 (1966). [v] Reference 20. [w] H. C. Smitherman and L. N. Ferguson, *Tetrahedron*, **24**, 923 (1968). [x] S. Akabori, T. Sato, and K. Hata, *J. Org. Chem.*, **33**, 3277 (1968).

each T in a given solvent, which would be expected for regular or systematic transmission of electronic effects.[15] All in all, the ρ values seem to make no traditional sense.

Limited "explanations" for limited sets of ρ values have appeared. Two groups have provided rationalizations based on the probable conformation of the benzylic proton with respect to the aromatic ring: in one case the ring diminishes[4] and in the other it enhances transmission[16] (see 42–53 and 69–74 in Table III). We have found an analogous and striking example in the data of Reiker and Kessler for[17]



Here $\rho(syn):\rho(anti) \simeq 15:1$ for the quinoid protons (entries 81 and 82, Table III), a clear case of enhanced transmission to a proton near the face of an aryl system. The magnitude of this effect, which seems to be dependent on molecular geometry and on the proximate aryl group, is too large for a substituent anisotropy or electric field.[3]

The solvent can also have an enormous effect on ρ. Consider data for the anilines and phenols given in

(16) R. J. Ouellette, D. L. Marks, and D. Miller, *J. Amer. Chem. Soc.*, **89**, 913 (1967).

(17) A. Reiker and H. Kessler, *Tetrahedron*, **23**, 3723 (1967).

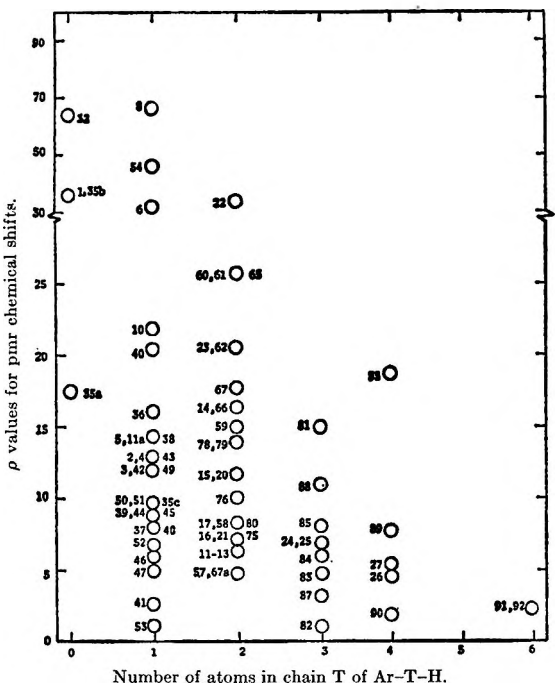


Figure 6.—Transmission of substituent effects and Hammett ρ values. The pmr data are given in Table IV or ref 3. ρ values for highly polar solvents are not included here.

Table IV.[18–23] The enhanced ρ values, *e.g.*, in DMSO, have been ascribed to hydrogen bonding[18,20,22] as well as to the interaction of the polarizable medium with the conjugated system.[19] We have also seen that even in an "inert" solvent, ν^0 may reflect differential solvent effects within a given family, *e.g.*, the benzyl halides. Since such solvent effects on ν are not really well understood, their effect on ρ cannot very well be treated.

Aside from theory, there may yet be a useful application of a *large* solvent effect on SCS and on ρ. The

TABLE IV

Solvent	$-\rho(ArNH_2)/\sigma$, Hz	Solvent	$-\rho(ArOH)/\sigma$, Hz
C_6H_{12}	21[a]	CCl_4	67[d]
CCl_4	32[a]	DMSO	79, 92, 101[c,e]
CH_3CN	55[b]	HMPA	110[f]
DMSO	79[c]		

[a] Reference 18. [b] Reference 19. [c] Reference 20. [d] Reference 21. [e] Reference 22. [f] Reference 23.

Hammett correlations of anilines in acetonitrile[19] or anilines, phenols, aminopyridines, and aminopyrimidines in DMSO[20] have relatively high (for their chain length *T*) and similar $\rho \simeq -7.8$, as well as high ($r > 0.95$) correlation coefficients. In DMSO, for example, the proton site may look like $ArT\text{–}H^{\delta+}\cdots^{\delta-}OS(CH_3)_2$. This "chemical" interaction has rendered the proton more sensitive to substituent effects that are scaled to reactivity (σ). If SCS may be ascribed to both magnetic anisotropy as well as chemical effects, then these solvents seem to "bring out" or enhance the latter so that it dominates. (There is an analogy here with ^{19}F nmr in which the magnetic anisotropy effects on SCS are considered to be unimportant.) Therefore, it would seem interesting to investigate correlations in "active" solvents, particularly when the fit to eq 2 for families in relatively inert solvents, such as carbon tetrachloride, is poor.

We return to the important issue, namely, that pmr correlations are usually poor relative to reactivity correlations. Although an equation such as eq 3 may often improve the correlation, this is by no means certain (Figure 3).[10] Even what we regard as minimum correlations, that is between SCS of related families, *e.g.*, Figures 4 and 5, do not stand up well. These deal purely with SCS and involve no reactivity criteria of substituent effects, as in eq 2. The particular aryl familes we chose for comparison, *e.g.*, toluenes *vs.* benzyl halides or styrenes *vs.* 1,1-diphenylethylenes, provide an important test of both theoretical and phenomenological approaches to SCS. Any possible adjustments by most theoretical approaches to SCS or by theories of the solvent effect on SCS should be unnecessary here, because of the similar disposition of the protons being compared. If theory cannot cope with the systems of Figures 4 and 5 they should be less than adequate for more complex correlations.

At the present time, we must conclude that pmr correlations of the Hammett type are of little value. Certainly, if they are to be attempted, it is desirable to have infinite dilution data on a fair number (>10) of representative compounds.[24] As for correlations in Table III, the majority of them do not satisfy the basic requirement of being precise, *e.g.*, correlation coefficient $r > 0.95$.[3] More important, the theoretical significance of the acceptable correlations is usually obscure. MO calculations, for example, which lead to charge density *vs.* ν correlations[20] tell us nothing about ρ and presumably reflect the "chemical" as opposed to the magnetic factors on SCS. A large number of effects on, or contributions to, SCS have been noted, *e.g.*, conformation, solvent, anisotropy, charge density, ring current, etc. To attempt to identify and isolate these appears to be most urgent.

Registry No.—*m*-Trifluoromethylbenzyl fluoride, 19519-94-9.

(18) Y. Yonemoto, W. F. Reynolds, H. M. Hutton, and T. Schaeffer, *Can. J. Chem.*, **43**, 2668 (1965); W. F. Reynolds, Ph.D. Thesis, University of Manitoba, 1963.

(19) L. K. Dyall, *Aust. J. Chem.*, **17**, 419 (1964).

(20) B. M. Lynch, B. C. Macdonald, and J. G. K. Webb, *Tetrahedron*, **24**, 3595 (1968).

(21) This ρ value is for the 2,6-di-*t*-butylphenols. If anything, the value for phenols without *ortho* substituents should be lower.[16] L. A. Cohen and W. M. Jones, *J. Amer. Chem.*, **85**, 3403 (1963).

(22) R. J. Ouellette, *Can. J. Chem.*, **43**, 707 (1965); J. G. Traynham and G. A. Knesel, *J. Org. Chem.*, **31**, 3350 (1966).

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Electrochemical Reduction of 1,1'-Ethylenebis(3-carbamidopyridinium bromide)[1]

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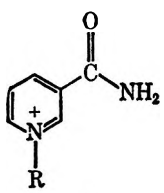
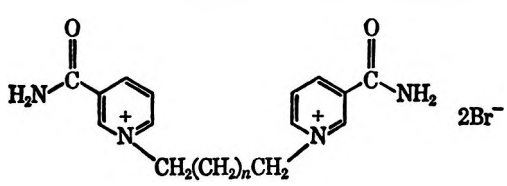
1,1'-Ethylenebis(3-carbamidopyridinium bromide) undergoes a 2-electron reduction at a cathode of controlled potential to yield a product in which the two pyridine rings are linked by a new bond between the 6 positions. The original pyridinium salt is regenerated upon electrochemical oxidation at controlled anode potential, but partial oxidation with oxygen yields a stable, deep red free radical. The same radical is obtained in better yield by exhaustive oxidation with oxygen followed by a 1-electron electrochemical reduction. The esr spectrum of the radical is similar to that obtained upon reduction of 1,1'-ethylene-2,2'dipyridylium dibromide ("Diquat"); differences between the spectra can be explained by the absence of carbamide groups in the "Diquat" case. Reasonable structures may be advanced for the various species on the basis of ultraviolet and esr spectra.

The electrochemical reduction of 1-substituted nicotinamide salts (I), including the biologically



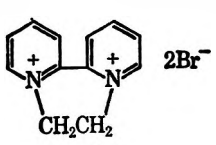
I

important pyridine coenzymes di- and triphosphopyridine nucleotide, has been carefully studied in this laboratory.[2-6] Briefly, these compounds exhibit two reduction processes at well-separated potentials; the first represents free radical formation followed by dimerization, while the second leads to the two-electron reduction product, *viz.*, the substituted 1,4-dihydropyridine. Interest in biologically active pyridinium salts has led us to investigate the electrochemical reduction of several 1,1'-polymethylenebis(3-carbamidopyridinium bromides) (II), with particular emphasis



II

upon the ethylene compound (II, $n = 0$). Interesting chemistry has developed during this study in the observation of quite stable free radicals. Parallel work on the herbicide 1,1'-ethylene-2,2'-dipyridylium



III

dibromide (known commercially as "Diquat") (III) has proved correlative and helpful.

Experimental Section

Materials.—1,1'-Polymethylenebis(3-carbamidopyridinium bromides) (II, where $n = 0$, 1, 2, and 3) were prepared by a procedure similar to that of Hartwell and Pogorelskin[7] and of Hazard, *et al.*[8] The crude products were recrystallized twice from aqueous ethanol (1:1, v/v), washed with cold ethanol and then with ether, and dried *in vacuo* at 65°. Results of C, H, and N analyses[9] agreed well with calculated values. Melting points were as follows: II, $n = 0$, 307–309° dec; II, $n = 1$, 274–276° dec; II, $n = 2$, 287–288°; II, $n = 3$, 216–218°.

Apparatus.—Polarograms were recorded at ambient temperature (controlled at 24 ± 1°) with a Sargent Model XV polarograph, using a conventional H cell with a saturated calomel anode (sce). Macroscale electrolyses were performed using a Wenking Model 61TRS potentiostat with a large mercury pool cathode, silver–silver chloride anode, and sce reference in a special cell which was purged with prepurified nitrogen. The anolyte was separated from the main solution, with electrolytic contact through a sintered disk. The solution was stirred by a magnetic bar at the mercury–solution interface. The coulometer was similar to that of Wise[10] and Bard.[11] The apparatus for cyclic voltammetry was similar to that used before[6] except that Philbrick chopper-stabilized operational amplifiers replaced Heath units. Absorption spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer. Esr spectra were obtained with a Varian Model 4500 X-band spectrometer using 100-kc modulation; the sample was held in a special quartz flat cell. A Kewaunee glove box with nitrogen atmosphere was used for all operations involving reduction products, except, as noted, where oxygen was intentionally introduced.

Results

Polarography.—All of the compounds in the series (II, $n = 0$–3) exhibited a reduction wave at −0.7 to −1.0 V *vs.* sce. Halfwave potentials were independent of pH over the range studied (5–9 in 0.1 *M* acetate, phosphate, and pyrophosphate buffers). The dependence of limiting currents upon corrected mercury heights indicated diffusion control. Assuming on the basis of controlled potential coulometry (see below) that the wave represented a two-electron process, plots of potential *vs.* log $i/(i_d - i)$ showed irreversibility in all cases. The pentamethylene compound (II, $n = 3$) exhibited an adsorption-controlled, concentration-

(1) This investigation was supported by the U. S. Public Health Service through Research Grant No. GM 08282 from the Division of General Medical Sciences, National Institutes of Health, and by N. I. H. Biomedical Science Research Award No. 5 S05-FR-07023-02. Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967. Taken from a dissertation presented by D. J. McClemens in partial fulfillment of the requirements for the Ph.D. degree in Chemistry, Emory University, 1968.

(2) J. N. Burnett and A. L. Underwood, *J. Org. Chem.*, **30**, 1154 (1965).

(3) J. N. Burnett and A. L. Underwood, *Biochemistry*, **4**, 2060 (1965).

(4) A. J. Cunningham and A. L. Underwood, *Arch. Biochem. Biophys.*, **117**, 88 (1966).

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(6) A. J. Cunningham and A. L. Underwood, *ibid.*, **6**, 266 (1967).

(7) J. L. Hartwell and M. A. Pogorelskin, *J. Amer. Chem. Soc.*, **72**, 2040 (1950).

(8) R. Hazard, J. Cheymol, J. A. Gautier, E. Cortegiani, and E. Leroi, *Arch. Int. Pharmacodyn. Ther.*, **90**, 271 (1952).

(9) Midwest Microlab Inc., Indianapolis, Ind.

(10) E. N. Wise, *Anal. Chem.*, **34**, 1181 (1962).

(11) A. J. Bard and E. Solon, *ibid.*, **34**, 1181 (1952).

Table I

Polarographic Results

II, n	pH	Buffer	$E_{1/2}$, V *vs.* sce	Diffusion current constant $I = i_d/(Cm^{2/3}t^{1/6})$
0	5.1	Acetate	−0.83	3.57
	7.0	Phosphate	−0.82	2.98
	9.0	Pyrophosphate	−0.82	2.69
1	5.1	Acetate	−0.78	2.92
	7.0	Phosphate	−0.78	2.86
	9.0	Pyrophosphate	−0.78	2.85
2	6.0	Acetate	−1.00	3.02
	7.0	Phosphate	−0.98	2.98
	9.0	Pyrophosphate	−0.98	2.81
3	6.0	Acetate	−1.0[a]	2.90[b]
	7.0	Phosphate	−1.0[a]	3.20
	9.0	Pyrophosphate	−1.0[a]	2.55

[a] Approximate; "prewave" at *ca.* −0.82 V *vs.* sce. [b] Based upon total wave height, *i.e.*, "prewave" plus "normal" wave.

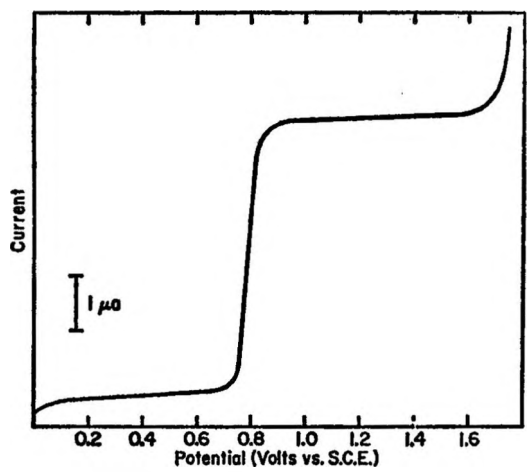


Figure 1.—Typical polarogram [1.0×10^{-3} *M* 1,1′-ethylenebis(3-carbamidopyridinium bromide) in 0.1 *M* pyrophosphate buffer of pH 9.0].

independent "prewave." Polarographic data are summarized in Table I; Figure 1 shows a typical polarogram. At pH values above 8, an additional, poorly defined reduction process was seen near the breakdown of the background electrolyte solution. Severe maxima were present on this wave which did not yield to the usual suppressors, currents were irregular and nonreproducible, and coulometric values were scattered. The appearance and behavior of this wave suggested that it represented catalytic hydrogen evolution.

Cyclic Voltammetry.—Typically, solutions of the ethylene compound (II, $n = 0$) exhibited two cathodic and two anodic peaks in cyclic scans. The less negative cathodic peak and the less positive anodic peak probably represented adsorption phenomena; these peaks disappeared upon the addition of the surfactant Triton X-100 (a common polarographic maximum suppressor) at a level of 0.004%, leaving one cathodic peak at −0.80 V and one anodic peak at −0.15 V *vs.* sce when the sweep rate was 1.0 V/sec in both directions. Linear graphs were obtained upon plotting peak current *vs.* concentration in the range 1×10^{-4} to 1×10^{-3} *M* at constant sweep rate, and peak current *vs.* the square root of the sweep rate from 0.05 to 1.0 V/sec at constant concentration. Results were essentially the same at pH values of 5, 7, and 9. The behavior of the other

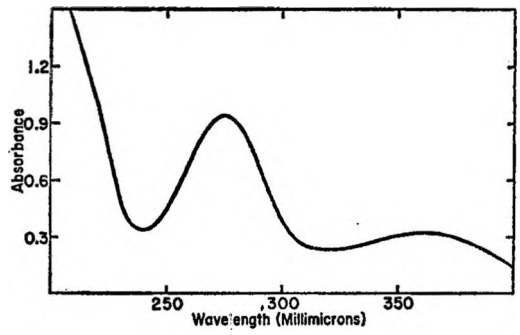
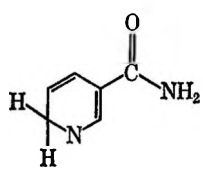


Figure 2.—Ultraviolet spectrum of initial reduction product [46.5 mg of 1,1′-ethylenebis(3-carbamidopyridinium bromide) in 0.1 *M* phosphate buffer of pH 7.2 electrolyzed at −1.0 V *vs.* sce; solution diluted tenfold to obtain the spectrum].

compounds in the series (II, $n = 1$, 2, and 3) was similar; these were not studied in detail. The large separation of cathodic and anodic peaks indicates, of course, a high degree of irreversibility for the observed process, the results essentially confirming the polarography. Reversible reoxidation of an intermediate radical was not seen at high sweep rates as it was with the nicotinamides.[6]

Controlled Potential Electrolysis.—Macroscale electrolyses were generally performed on 100–250-mg samples of the compounds in 200 ml of 0.1 *M* buffers of pH 5 (acetate), 7 (phosphate), and 9 (pyrophosphate) at potentials well on the plateaus of the polarographic waves and at least 0.2 V more positive than electrolyte breakdown (−1.0 V *vs.* sce for II, $n = 0$ and 1; −1.20 V for II, $n = 2$ and 3). Coulometry in all cases yielded a value of two electrons taken up per molecule of starting material.

The original solutions of the pyridinium salts all exhibited an absorption band at 266–267 mμ. Upon electrolysis to the completion of the two-electron reduction, the ethylene compound (II, $n = 0$) yielded a two-banded spectrum, with absorption maxima at 275 mμ (log ε 4.24) and 350 (3.77). The spectrum is shown in Figure 2 because it is important in establishing the structure of the reduction product. On the basis of previous work with the nicotinamides,[2,3] it was expected that reduction product IV (see Scheme I) would form, analogous to the nicotinamide dimers, with the preexisting ethylene bridge between the pyridine rings favoring the formation of the new bond at the 6 and 6′ positions. The ultraviolet spectrum suggested that the reduction product was indeed IV. According to Wallenfels and Schüly,[12] as well as Schenker and Druey,[13] among the three isomeric dihydropyrindines formed by the nicotinamides, 1,6-dihydro compound V is characterized by a two-banded

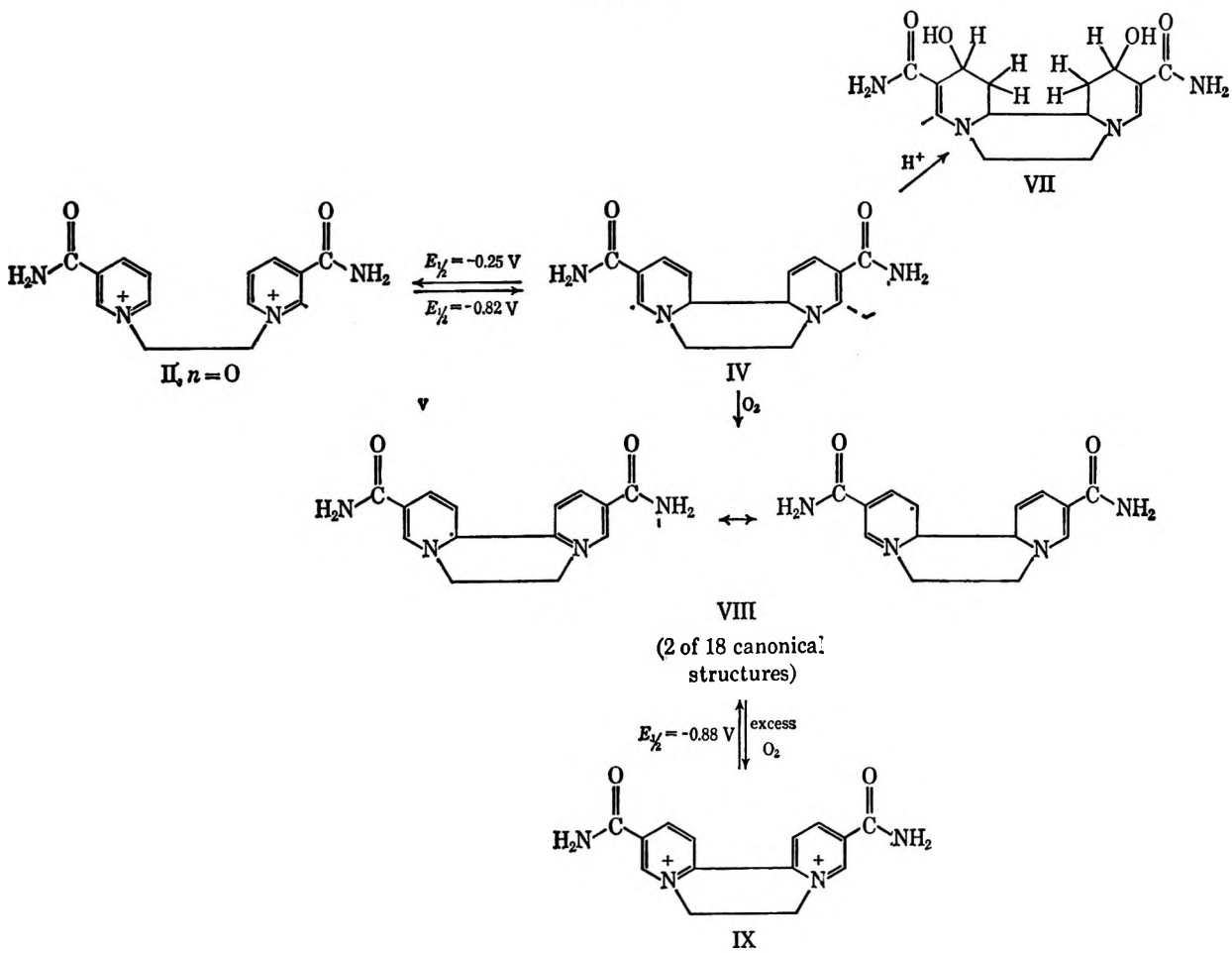


V

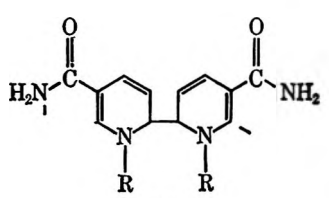
ultraviolet spectrum with absorption maxima in the

(12) K. Wallenfels and H. Schüly, *Angew. Chem.*, **67**, 517 (1955).
(13) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959).

SCHEME I



vicinity of 270 and 360 mμ. On the basis of their ultraviolet spectra, Wallenfels and Gellrich[14] assigned the 6,6′ structure (VI) to dimers prepared by zinc

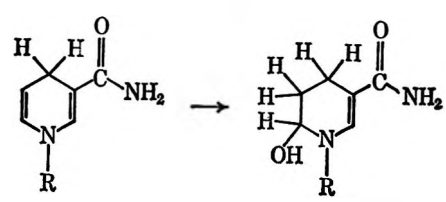


VI

reduction of 1-substituted nicotinamides. The spectral data given[14] for VI where R = *n*-propyl were λ_{max} 276 mμ (log ε 3.59), 357 (3.92).

The other compounds in the series (II, n = 1, 2, and 3) behaved somewhat differently. To be sure, ultraviolet bands at ~276 and 350 mμ appeared in the early stages of electrolysis, but during the time required to ensure complete reduction (about 1.5 hr) these bands were replaced by a new band at 294 (II, n = 1) or 297 mμ (II, n = 2 and 3). This new band appeared most rapidly at pH 5 and most slowly at pH 9, and the rate of its appearance increased as n increased in II. (The ethylene compound (II, n = 0) yielded the same band in a reduction at pH 4, but at pH 5 or above it behaved as described in the previous paragraph.)

Numerous examples may be found in the literature of absorption in the 290-300-mμ region associated with the chromophore >NC=CC=O. For example, the acid-catalyzed addition of water to 1,4-dihydronicotinamide derivatives, shown below, leads to such a band.[15] This reaction is favored by an acidic medium,



but occurs in neutral solution as well in the presence of certain anions including $H_2PO_4^-$ which act catalytically.[15,16] The reaction is presumably initiated by protonation at the 5 position of the 1,4-dihydropyridine, reflecting the nucleophilicity of an enamine system. An acceptable interpretation of the results reported here is a similar addition of water to the 4,5-double bonds, involving protonation at the 5 positions. Products such as VII in Scheme I would be formed.

After electrolysis at a potential on the cathodic wave as described above, the solution of the ethylene compound (II, n = 0) exhibited an anodic wave with a halfwave potential of −0.25 V *vs.* sce. Electrolysis on this wave removed two electrons (the experimentally

(14) K. Wallenfels and M. Gellrich, *Ber.*, **92**, 1406 (1959).

(15) *E.g.*, see C. C. Johnston, J. L. Gardner, C. H. Suelter, and D. E. Metzler, *Biochemistry*, **2**, 689 (1963), and literature cited therein.

(16) S. G. A. Alivisatos, F. Ungar, and G. J. Abraham, *ibid.*, **4**, 2616 (1965).

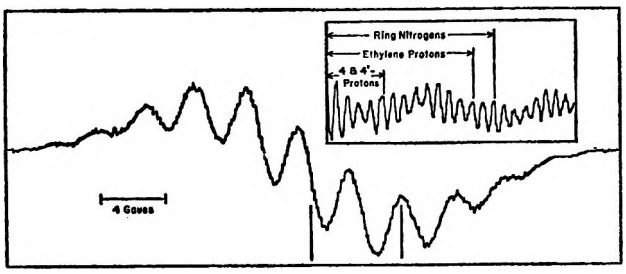


Figure 3.—Recorder trace of the 11-line esr spectrum of radical VIII prepared by electrochemical reduction of IX. Insert shows the portion of the spectrum between the vertical lines under conditions for higher resolution; assigned splittings are indicated.

measured value was 1.8) per initial molecule of II; the ultraviolet spectrum after this oxidation was identical with that of the original pyridinium salt.

Esr Experiments.—The above results were obtained under an atmosphere of nitrogen. If, after electrolysis on the cathodic wave at pH 5, 7, or 9, a little air or oxygen was introduced into the yellow reduced solution of the ethylene compound (II, $n = 0$), a deep red color developed, and a new absorption band appeared in the visible region (545 mμ). No photochemical phenomenon was involved; identical results were obtained under daytime lighting and in the dark. The red solutions yielded significant esr signals, although experiments at several concentrations failed to give complete resolution of the hyperfine structure. Eleven main lines could be discerned, with splittings of 3.0 ± 0.3 G between peaks. The g factor of all observed spectra was measured and found to be 2.004 ± 0.002.

On the other hand, if the electrolytically reduced solution of the ethylene compound was allowed to stand for 30 min while saturated with oxygen, oxidation beyond the red free radical stage occurred to yield another compound. This oxidized solution, after nitrogen purging, exhibited a cathodic wave at -0.88 V *vs.* sce. Coulometry during macroelectrolysis at a potential on this wave (-1.1 V *vs.* sce) indicated an uptake of one electron, and the resulting solution was deep red. The esr spectrum of this solution exhibited the same eleven main lines as above, but the signal was stronger and the resolution better. Typical recorder traces of the spectra are shown in Figure 3. The visible spectrum of the red solution showed a band at the same wavelength as before.

A detailed study of the electrochemistry of "Diquat" (III) and the esr spectrum of the electrogenerated "Diquat" radical will be reported separately. Briefly, "Diquat" exhibited (as others had reported[17–20]) a reversible, one-electron reduction ($E_{1/2} = -0.62$ V *vs.* sce) to yield a very stable free radical. A solution of this radical, conveniently prepared by macroelectrolysis at -0.75 V *vs.* sce, yielded an excellent spectrum consisting of 133 lines. Reasonable assumptions regarding the relative magnitudes of hyperfine splittings by the nitrogen atoms and the several protons, and consideration of published interpretations of the spectra of 2,2′-bitolyl and 2,2′-bipyridyl anion radicals, led to the assignment of hyperfine splitting constants enabling calculation of a "Diquat" radical spectrum which fitted well to the experimental one.

The esr spectrum of the "Diquat" radical and that of the radical described above were similar. The large splittings by the ring nitrogens and the ethylene protons were clearly comparable in the two spectra. However, the splitting assigned to the protons at the 5 positions in the "Diquat" radical could not be observed in the spectrum of the radical described above, as would be expected when carbamide groups replace the single protons. Thus with guidance from the analysis of the well-resolved "Diquat" radical spectrum and measurements from spectra such as shown in Figure 3, hyperfine splitting constants for the radical reported here were assigned as follows: ring nitrogens, 3.56 G; ethylene protons, 2.80 G; protons at the 4 positions of the pyridine rings, 1.20 G; protons at the 3 and 6 positions, 0.20 G. Splittings due to the carbamide groups could not be assigned from the observed spectra. The additional lines due to these groups are thought to be responsible for the poorer resolution of the spectrum of the radical reported here as compared with that of the "Diquat" radical.

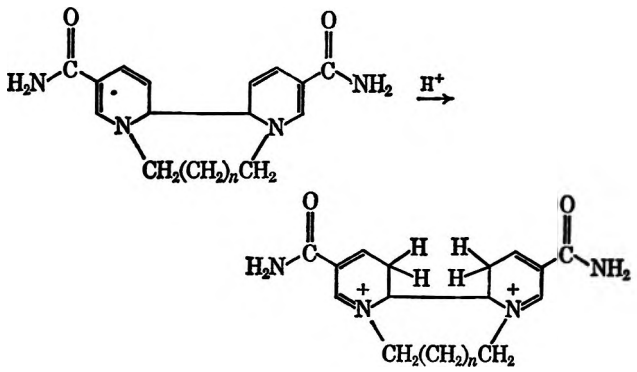
The magnetic field was scanned through 100 G on each side of the center line of the spectrum. Only the basic spectrum mentioned above, with eleven main lines, was ever observed. This permits the elimination of a possible diradical; a triplet would be expected to give rise to a signal in the "wings," and such was not seen in the present case.

Discussion

All of the evidence is consistent with Scheme I. It would be difficult, in the light of previous work on dimer formation with the nicotinamides, to envision a two-electron reduction leading to any product other than IV. Furthermore, the ultraviolet spectrum of the reduction product is consistent with this formulation in terms of Wallenfels' generally accepted work on the spectra of the isomeric dihydropyridines and nicotinamide dimers. The esr spectrum of the radical obtained by partial oxidation of IV provides convincing evidence for formulation VIII in the scheme. It is plausible that a stronger esr signal resulted from complete oxidation to IX followed by the one-electron electrochemical reduction; production of the radical from IV by O_2 doubtless overshot considerably, forming IX as well as VIII, whereas at controlled cathode potential only one electron was added to IX. It is interesting although not surprising that the electrochemical reoxidation of IV led to a different product (II) than did oxidation with O_2 (VIII and IX).

The heightened tendency to form products like VII as n is increased in II may be rationalized. The intuitive idea that increasing "flexibility" of the ring system may sterically facilitate attack at the two 5 positions is supported by the observation of models. Further, it may be argued that the relative reactivities of the compounds as n is increased could reflect the stabilities of the respective iminium salts generated by protonation. These stabilities could in turn be deter-

(17) R. F. Homer, G. C. Mees, and T. E. Tomlinson, *J. Sci. Food Agr.*, **11**, 209 (1960).
(18) R. F. Homer and T. E. Tomlinson, *Nature*, **184**, 20121 (1959).
(19) J. Engelhardt and W. P. McKinley, *J. Agr. Food Chem.*, **14**, 377 (1966).
(20) W. R. Boon, *Chem. Ind.* (London), **752**, (1965).



mined by differences in energies of double bonds exocyclic to rings of various sizes.

Workers in the field of pyridine chemistry will recognize the difficulties in the classical approach of isolating and characterizing compounds of intermediate oxidation state such as described here. Physical evidence like ultraviolet and esr spectra must be relied upon heavily. Obviously, the most convincing test of the present scheme would involve the unequivocal synthesis of the carbamido-substituted "Diquat" IX and a study of the radical obtained upon its reduction. Unhappily, attempts to prepare IX by a synthetic route independent of the work reported here have so far been unsuccessful.

Registry No.—II, $n = 0$, 19293-83-5; II, $n = 1$, 19293-84-6; I, $n = 2$, 19293-85-7; II, $n = 3$, 19293-86-8.

Acknowledgments.—The authors are deeply grateful to Professors David J. Goldsmith, Leon Mandell, and Peter Pappas for their interest in this work and for many helpful discussions.

Application of the Hammett Equation to Nonaromatic Unsaturated Systems. VII. Heterovinylene Sets

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School of Engineering and Science, Pratt Institute, Brooklyn, New York 11205

Received July 29, 1968

Ionization constants for 10 heterovinylene sets have been correlated with the extended Hammett equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Sets studied include disubstituted oximes, disubstituted glyoximes, *syn*- and *anti*-substituted aldoximes, substituted acetyl oximes, substituted methyl oximes, *syn*- and *anti*-substituted phenyl oximes, substituted phenylimines, and substituted ethoxyimines. Good results were generally obtained. The magnitude of α is dependent upon molecular geometry. Assignment of configuration by means of correlation with the Hammett equation is discussed.

In previous papers of this series we have considered the application of the Hammett equation[1] to *trans*-[2] and *cis*-vinylene,[3] vinylidene,[4] and heterovinylidene[5] sets. Our purpose in this paper is to extend these studies to include *cis*- and *trans*-heterovinylene sets. Two types of heterovinylene sets have been investigated: (1) oximes, in which the reaction site is the hydroxyl group bonded to the nitrogen atom; (2) imines, in which the reaction site is a full nonbonding orbital on the nitrogen atom.

Ionization constants for oximes and imines taken from the literature have been correlated with the extended Hammett equation

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \qquad (1)$$

by multiple linear regression analysis. The data used in the correlations are given in Table I. The σ_I constants were taken from our collection;[5] the σ_R constants were obtained from

$$\sigma_R = \sigma_p - \sigma_I \qquad (2)$$

The σ_p constants were from the compilation of McDaniel and Brown.[6] In some cases values of σ were taken from previous papers in this series or were estimated by our method.[7]

The justification for the correlation of the ionization constants (as pK_a values) of the disubstituted oximes (set 1) with eq 1 is as follows. The effect of the substituent may be written

$$Q_X = \alpha_{syn}\sigma_{I,X^1} + \alpha_{anti}\sigma_{I,X^2} + \beta_{syn}\sigma_{R,X^1} + \beta_{anti}\sigma_{R,X^2} + h \qquad (3)$$

As $X^1 \equiv X^2$, eq 3 becomes

$$Q_X = (\alpha_{syn} + \alpha_{anti})\sigma_{I,X} + (\beta_{syn} + \beta_{anti})\sigma_{R,X} \qquad (4)$$

equivalent to eq 1 with

$$\alpha = \alpha_{syn} + \alpha_{anti}, \qquad \beta = \alpha_{syn} + \beta_{anti}$$

The correlation of the *anti*-disubstituted glyoximes II with eq 1 may be justified in the same manner. The

(1) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y. 1956, p 565; V. Palm, *Russ. Chem. Rev.* (Eng. Transl.) **31**, 471 (1961); P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

(2) M. Charton and H. Meislich, *J. Amer. Chem. Soc.*, **80**, 5940 (1958); M. Charton, *J. Org. Chem.*, **30**, 552 (1965).

(3) M. Charton, *ibid.*, **30**, 974 (1965).

(4) M. Charton, *ibid.*, **30**, 557 (1965).

(5) M. Charton, *ibid.*, **29**, 1222 (1964).

(6) D. H. McDaniel and H. C. Brown, *ibid.*, **23**, 420 (1958).

(7) M. Charton *ibid.*, **28**, 3121 (1963).

TABLE I

DATA USED IN CORRELATIONS

1. Ionization constants of $X_2C{=}NOH$ in water at 25°

X	Me	Et	Ph	Ac	CF_3
pK_a	12.42	12.60	11.18	7.38	6.0
Ref	*a*	*a*	*b*	*c*	*d*

2. Ionization constants of $(XC{=}NOH)_2$ in water at 25°

X	H	Cl	Me	NH_2	Et	Pr	2-Furyl
pK_a	9.02	2.94	10.72	10.62	10.67	10.81	9.80
Ref	*e*	*e*	*e*	*f*	*g*	*g*	*h*

3. Ionization constants of *syn* aldoximes in water at 25°

X	3-$C_6H_4NO_2$	4-$C_6H_4NO_2$	4-$C_6H_4NMe_2$	2-Furyl	Ph	4-C_6H_4OMe	t-PhC_2H_3	CF_3
pK_a	10.16	9.96	11.25	10.85	10.68	10.92	10.55	8.9
Ref	*i*	*i*	*i*	*i*	*j*	*j*	*j*	*d*

4. Ionization constants of *anti* aldoximes in water at 25°

X	Ph	3-$C_6H_4NO_2$	*t*-PhC_2H_3	2-Furyl	2-thienyl	*n*-C_6H_{14}
pK_a	11.33	10.74	10.80	11.16	10.76	11.60
Ref	*j*	*j*	*j*	*k*	*k*	*j*

5. Ionization constants[c] of $XAcC{=}NOH$ in water at 25°

X	H	Me	Et	*i*-Pr	Ac	CO_2Et[e]
pK_a	8.30	9.30	9.38	9.50	7.38	7.07

6. Ionization constants of $XMeC{=}NOH$ in water at 25°

X	Me	Et	Ph	Ac	NO_2
pK_a	12.42	12.45	11.35	9.30	7.4
Ref	*a*	*a*	*b*	*c*	*m*

7. Ionization constants of *syn*-phenyl ketoximes in water at 25°

X	4-$O_2NC_6H_4$	Ph	H
pK_a	10.47	11.18	11.33
Ref	*i*	*b*	*j*

8. Ionization constants of *anti*-phenyl ketoximes in water at 25°

X	4-$O_2NC_6H_4$	Ph	H	Me
pK_a	10.85	11.18	10.68	11.35
Ref	*i*	*c*	*j*	*c*

9. Ionization constants of $XPhC{=}NH_2{}^+Cl^-$ in water at 25°

X	MeS	EtS	PhS	MeO	EtO	Ph	NH_2
pK_a	5.85	6.049	4.481	5.68	6.37	7.00	11.9
Ref	*n*	*n*	*n*	*o*	*p*	*q*	*r*

10. Half-neutralization potentials of $X(OEt)C{=}NH_2{}^+$ in $MeNO_2$[s]

X	Ph	Me	EtO_2CCH_2	CCl_3	4-$O_2NC_6H_4$
HNP	308	198	385	770	441

11. Ionization constants[t] of α-substituted tetronic acids in water at 25°

X	H	Cl	Br	I	Me	Et	CO_2Me	Ac	NO_2	Ph	*i*-$PrCH_2CH_2$
pK_a	3.76	2.13	2.23	2.31	4.19	4.00	1.80	1.80	1.68	3.69	4.16

12. Ionization constants[u] of 3-substituted 2-hydroxy-1,4-naphthoquinones in water at 26–33°

X	H	Bz	Ph	$PhCH_2$	*i*-$PrCH_2CH_2$	*t*-MeCH=CH
pK_a	4.00	2.17	4.35	4.90	5.13	4.8

13. Ionization constants[v] of 3-substituted 1-aza[2.2.2]bicyclo-2-octanes in water at 25°

X	H	Ph	$CONH_2$	CO_2Me	CN
pK_a	10.95	10.23	9.67	9.40	7.81

14. Second ionization constants[w] of 3-substituted 4-pyridones in water at 20°

X	H	CO_2NH_2	CN	NO_2
pK_{a_2}	10.5	9.3	7.35	7.0

15. Second ionization constants[x] of 5-substituted 2-pyridones in water at 20°

X	H	Me	Cl	I	Br	NO_2
pK_{a_2}	11.70	12.01	9.87	9.93	10.03	7.97

16. Second ionization constants[z] of 3-substituted 2-pyridones in water at 20°

X	H	Me	Cl	Br	NO_2
pK_{a_1}	11.70	12.59	10.40	10.42	8.52

[a] C. V. King and A. P. Marion, *J. Amer. Chem. Soc.*, **66**, 977 (1944). [b] C. Calzolari, *Univ. Studi Trieste. Fac. Sci., Inst. Chim.*, 4 (1954); *Chem. Abstr.*, **49**, 7338*d* (1954). [c] A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956). [d] B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965). [e] H. E. Ungnade, G. Fritz, and L. W. Kissinger, *ibid.*, **19**, *Suppl.* 1, 235 (1963). [f] H. E. Ungnade, L. W. Kissinger, A. Narath, and D. C. Barham, *J. Org. Chem.*, **28**, 134 (1963). [g] C. V. Banck and S. Anderson, *Inorg. Chem.*, **2**, 112 (1963). [h] V. M. Sarostina, E. K. Astrakhova, and V. M. Peshkova, *Vestn. Mosk. Univ., Ser. II Khim.*, 18 (2), 43 (1963). [i] O. L. Brady and N. M. Chekshi, *J. Chem. Soc.*, 946 (1929). [j] O. L. Brady and R. F. Goldstein, *ibid.*, 1918 (1926) [k] S. G. Tandon, *J. Phys. Chem.*, **65**, 1644 (1961). [l] P. T. Muller and E. Bauer, *ibid.*, **2**, 472 (1904). [m] J. Armand, *Bull. Soc. Chim. Fr.*, 882 (1966). At 21°. [n] R. H. Hartigan and J. B. Cloke, *J. Amer. Chem. Soc.*, **67**, 709 (1945). [o] J. Stieglitz, *Am. Chem. J.*, **39**, 29, 156 (1908). [p] E. S. Hand and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 3505 (1962). [q] K. Koehler, W. Sandstrom, and E. H Cordes, *ibid.*, **86**, 2413 (1964). [r] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2940 (1948). Includes statistical factor of ½. [s] C. A. Streuli, *Anal. Chem.*, **31**, 1652 (1959). HNP values are half-neutralization potentials. [t] L. J. Haynes and J. R. Plimmer, *Quart. Rev.*, **14**, 292 (1960). [u] M. G. Ettinger, *J. Amer. Chem. Soc.*, **72**, 3085 (1950). [v] C. A. Grob, *Chem. Ind.* (London), 598 (1957). [w] T. Wieland, C. Fest, and G. Pfleiderer, *Ann.*, **642** 163 (1961). [x] E. Spinner and J. C. B. White, *J. Chem. Soc., B*, 991 (1966).

TABLE II

RESULTS OF CORRELATIONS WITH EQ 1

Set	$-\alpha$	$-\beta$	h	R[a]	F[b]	r[c]	s_{estd}[d]	s_α[d]	s_β[d]	s_h[d]
1	11.5	4.53	11.55	0.997	196.7	0.864	0.305	1.45	1.97	0.247
2	15.9	3.39	9.66	0.990	98.21	0.288	0.493	1.13	0.806	0.241
2A	15.8	3.44	9.59	0.990	49.96	0.212	0.644	1.59	1.07	0.396
3	4.43	1.01	10.94	0.985	81.06	0.835	0.151	0.758	0.748	0.169
4	3.10	0.627	11.31	0.892	3.654	0.146	0.240	1.15	1.64	0.249
4A	3.41	0.923	11.37	0.946	8.439	0.166	0.171	0.831	1.17	0.203
5	3.28	2.89	8.80	0.950	13.95	0.683	0.359	0.725	1.05	0.176
6	5.95	3.19	11.73	0.9992	607.5	0.722	0.126	0.297	0.604	0.0818
8	−0.408	4.48	10.74	0.954	5.034	0.484	0.159	0.878	1.51	0.146
9	20.6	5.41	9.15	0.947	17.42	0.200	0.949	4.82	1.72	1.38
10	−1360	542	162	0.988	40.27	0.780	48.3	218.	678	78.2
11	3.61	1.79	3.61	0.955	41.28	0.159	0.350	0.434	0.783	0.156
11A	4.43	2.54	3.64	0.996	495.8	0.0653	0.0976	0.147	0.231	0.0436
12	3.84	6.27	4.18	0.992	90.79	0.767	0.179	1.10	1.11	0.141
13	5.75	−2.33	11.02	0.998	261.5	0.657	0.102	0.301	0.763	0.07895
14	5.91	−4.68	10.48	0.993	363.0	0.591	0.106	0.361	2.44	0.105
15	4.89	2.53	11.58	0.998	392.7	0.050	0.116	0.181	0.400	0.0868
16	4.54	2.95	11.85	0.997	180.1	0.059	0.162	0.254	0.558	0.122

Set	n[e]	C.L.[f]	t_α[g]	C.L.[h]	t_β[g]	C.L.[h]	t_h[g]	C.L.[h]
1	5	99.0	7.931	98.0	2.299	80.0	46.76	99.9
2	7	99.9	14.07	99.9	4.206	98 0	40.08	99.9
2A	5	97.5	9.930	99.0	3.229	90 0	24.20	99.0
3	8	99.9	5.844	99.0	1.350	50 0	64.73	99.9
4	6	<90.0	2.696	90.0	0.482	20.0	45.42	99.9
4A	5	<90.0	4.103	90.0	0.789	20.0	56.01	99.9
5	6	95.0	4.524	95.0	2.752	90.0	50.0	99.9
6	5	99.5	20.03	99.9	5.281	95.0	143.4	99.9
8	4	<90.0	0.465	20.0	2.967	50.0	73.56	99.0
9	7	97.5	4.274	98.0	3.145	95.0	6.630	99.0
10	5	97.5	6.239	95.0	0.799	20.0	2.072	80.0
11	11	99.9	8.318	99.9	2.286	90.0	23.14	99.9
11A	10	99.9	30.14	99.9	10.00	99.9	83.49	99.9
12	6	99.5	3.491	95.0	5.649	98.0	29.65	99.9
13	5	99.5	19.10	99.0	3.054	90.0	139.7	99.9
14	4	95.0	16.37	95.0	1.918	50.0	99.81	99.0
15	6	99.9	27.02	99.9	6.325	99.0	133.4	99.9
16	5	99.0	17.87	99.0	5.287	95.0	97.13	99.9

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient of σ_I on σ_R. [d] Standard errors of the estimate, α, β, and h, respectively. [e] Number of points in the set. [f] Confidence level for regression. [g] Student "t" test for significance of α, β, and h. [h] Confidence levels for α, β, and h.

effect of the substituent is given by

$$Q_X = \alpha_{21}\sigma_{I,X^1} + \alpha_{24}\sigma_{I,X^2} + \alpha_{31}\sigma_{I,X^2} + \alpha_{34}\sigma_{I,X^2} + \beta_{21}\sigma_{R,X^1} + \beta_{24}\sigma_{R,X^1} + \beta_{31}\sigma_{R,X^2} + \beta_{34}\sigma_{R,X^2} + h \quad (5)$$

where

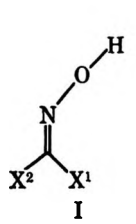
$$\alpha_{21} = \alpha_{34}, \quad \alpha_{24} = \alpha_{31}, \quad \beta_{21} = \beta_{24}, \quad \beta_{24} = \beta_{21} \quad (6)$$

As $X^1 \equiv X^2$, we obtain

$$Q_X = (2\alpha_{21} + 2\alpha_{24})\sigma_{I,X} + (2\beta_{21} + 2\beta_{24})\sigma_{R,X} + h \quad (7)$$

equivalent to eq 1 with

$$\alpha = 2\alpha_{21} + 2\alpha_{24}, \quad \beta = 2\beta_{21} + 2\beta_{24} \quad (8)$$



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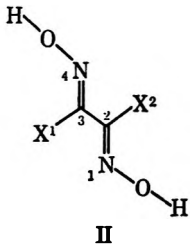


II

Results

The results of the correlations with eq 1 are presented in Table II. In some sets only three points were available and therefore correlation with eq 1 was not possible. In this event the data were correlated with the simple Hammett equation

$$Q_X = \rho\sigma_X + h \quad (9)$$

using the σ_I, σ_m, and σ_p constants. The σ_m constants were taken from McDaniel and Brown. The results of these correlations are given in Table III.

Oximes.—Very good results were obtained for the disubstituted oximes (set 1). The results for the disubstituted glyoximes (set 2) are significant at the 99.9% C.L., indicative of an excellent correlation. Excellent results were obtained for the *syn* aldoximes (set 3). Poor results were obtained for the correlation of the *anti* aldoximes (set 4); although the results are significantly improved by the exlusion of the value for X = *trans*-cinnamyl (set 4A), they are still not significant at the 90% C.L. Correlation of the data with the σ_I constants by means of eq 9 (set 4B, Table III)

TABLE III

RESULTS OF CORRELATIONS WITH EQ 9

Set	$-\rho$	h	r^a	s^b	s^b	t^c	n^d	C.L.^{e}
4B	3.30	11.45	0.928	0.159	0.765	4.317	5	95.0
7 I	3.98	11.42	0.953	0.196	1.26	3.152	3	80.0
m	4.02	11.37	0.995	0.0668	0.415	9.674	3	90.0
p	3.33	11.24	0.980	0.130	0.678	4.908	3	80.0
8A I	1.82	11.29	0.970	0.0878	0.459	3.969	3	80.0
m	1.74	11.25	0.993	0.0434	0.212	8.227	3	90.0
p	1.26	11.55	0.998	0.0248	0.0874	14.46	3	95.0
10A	1221	220	0.984	45.3	128	9.532	5	99.0

[a] Correlation coefficient. [b] Standard errors of the estimate and ρ, respectively. [c] Student "t" test for significance of the regression. [d] Number of points in set. [e] Confidence level.

TABLE IV

CALCULATED VALUES OF pK_a

	pK_a						
Compound	Obsd	Calcd	Set	Δ	pK_a, calcd	Set	Δ
Acetyl aldoxime	8.30	9.4	3	1.1	10.5	4B	2.2
Benzoyl aldoxime	8.25	9.5	3	1.2	10.5	4B	2.2
Propionyl aldoxime	8.37	9.6	3	1.2	10.5	4B	2.1

gave fair results, however. Fair and excellent correlations, respectively, were obtained for the acetylketoximes (set 5) and methyl ketoximes (set 6).

Very poor results were obtained for the *anti*-phenyl ketoximes (set 8). Elimination of the value for X = H (set 8A) gave fair correlation with eq 9 using the σ_p constants. Correlation of the *syn*-phenyl ketoximes (set 7) with eq 9 gave best results with the σ_m constants. That the results are poor is probably due to the set containing only three points.

cis-**Enols.**—For comparison we have correlated data for α-substituted tetronic acids (set 11) and for 3-substituted 2-hydroxy-1,4-naphthoquinones (set 12) with eq 1. Although excellent results were obtained for set 11, a great improvement results from the exclusion of the value for X = NO_2 (set 11A). The results obtained for set 12 were excellent.

Imines.—Good results were obtained both for the ionization constants of the substituted phenylimines (set 9) and the half-neutralization potentials of the substituted ethyl imidates (set 10). Correlation of the half-neutralization potentials with the σ_I constants by means of eq 9 gave very good results.

Enamines and Enamides.—It was desirable for purposes of comparison to examine data for *trans*-enols. As such data are unavailable, we have turned to the *trans*-enamines as an appropriate system for comparison. The results of the correlation of the 3-substituted 1-aza[2.2.2]bicyclo-2-octenes (set 13) are excellent. It must be noted, however, that the value of β is undoubtedly in error as it is opposite in sign to the value of α. A "t" test shows β to be statistically significant at the 90% C.L. The 95% C.L. for β is 2.33 $\pm$ 3.28 (or the range -0.95 to 5.63). Thus a negative value of β is quite possible.

Fair correlation was obtained for the 3-substituted 4-pyridones. Again the value of β was positive. In this case however, a "t" test shows that β is significant only at the 60% C.L. and may probably be disregarded. The 5- and 3-substituted 2-pyridones gave excellent and very good correlations respectively (sets 15 and 16).

Discussion

Stereochemistry.—The configuration of the oximes in sets 4 and 7 are known, as are all those of set 8 with the exception of acetophenone oxime, all those of set 3 with the exception of the trifluoroacetyl aldoxime, and all those of set 2 with the exception of diethyl and dipropyl glyoximes. As the values of α, β, and h for set 2A, which excluded diethyl and dipropyl glyoxime, are essentially the same as those obtained including these compounds (set 2), we conclude that these compounds have the *anti* configurations.

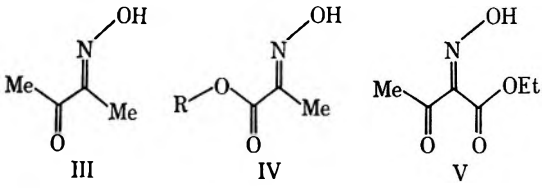
Inspection of models suggests that the substituted acetyl ketoximes (set 5) should have the *anti*-acetyl configurations. For acetyl aldoxime this is supported to some extent by a calculation of the pK_a of the *syn* and *anti* isomers from the correlations obtained for sets 3 and 4B, respectively. The results are shown in Table IV; the results for benzoylaldoxime and propionyl aldoxime are also presented in Table IV.

As the agreement between calculated and observed values is poor, and the uncertainty in α and β for set 4B is large, this evidence is not conclusive. The existence of the acyl aldoximes in a hydrogen-bonded *syn*-acyl configuration can be ruled out, as the hydrogen bond would decrease the predicted acid strength, which should result in a higher pK_a than that calculated for set 4B, rather than one which is lower by $\sim$2.2 pK_a units. We believe, therefore, that the more likely configuration of the acyl aldoximes is the *anti*-acyl configuration.

Some support for the assignment of the *anti* configuration to acetyl methyl ketoximes (3-oximino-2-butanone) is obtained from the work of Lustig,[8] who reports that the nmr spectra of methylcarbonalkoxy ketoximes show that only one configuration is present, and suggests that this is the *syn*-methyl configuration.

In view of the closeness of the pK_a values of the ethyl and isopropyl acylketoximes to that for the methyl

(8) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961).



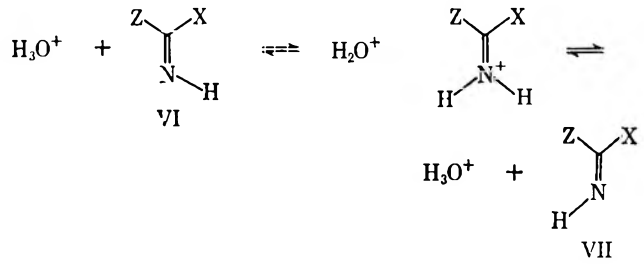
III IV V

compound the configuration for all of the alkyl acetyl ketoximes should be the same. Thus all of the members of set 5 (X = H, Me, Et, *i*-Pr, Ac) ought to have an acetyl group *anti* to the OH group. The successful correlation of set 5 with eq 1 is a necessary but not sufficient condition for the identity of configuration. Thus, although good correlation was obtained for set 5, this does *not* constitute proof of the identity of configuration throughout the set. That inclusion of the value for X = CO_2Et does not result in any significant change in α, β, or h does suggest that both of the members of the set do indeed have the same configuration and that the configuration of ethyl α-oximinoacetoacetate (ethyl-2-oximino-3-butanonoate) is also the *anti*-acetyl configuration, V.

Lustig reports that acetophenone oxime exists as a pure stereoisomer. He states in a later paper[9] that in all of the cases he has studied the *syn*-methyl configuration predominates. It seems likely then that acetophenone oxime exists in the *syn*-methyl configuration. This conclusion is supported by the work of Karabatsos and Taller[10] who find that in CCl_4 acetophenone exists in the *syn*-methyl configuration to the extent of 94%. Reasons for believing the configuration of dimethylglyoxal monoxime to be *anti*-acetyl (this is identical with *syn*-methyl) were noted above. Lustig reports that methyl ethyl ketoxime exists as a mixutre of *syn* and *anti* forms. As he states that the *syn*-methyl form predominantes, and the pK_a observed for methyl ethyl ketoxime is in good agreement with that found for dimethyl ketoxime for which no stereoisomers are possible, it would seem that the observed pK_a is close to the pK_a of the *syn* isomer of methyl ethyl ketoxime. Thus we believe that in all of the members of set 6 the *syn*-methyl configuration predominates.

The assignment of the *syn* configuration to trifluoroacetyl aldoxime is based on the configurations of aldoximes reported by Karabatsos and Taller.[10] The results of these authors show that increasing bulk of the X group in XC(NOH)H favors the *syn* configuration. The trifluoromethyl group is considerably larger than a methyl group (the minimal prependicular van der Waals radii of the groups are 1.72 Me, and 2.11 CF_3).[11] This suggests that trifluoroacetyl aldoxime exists predominantly in the *syn* configuration.

The imines studied are capable of existing in two tautomeric forms, one in which substituent and proton are *syn* (VI), the other in which they are *anti* (VII). As the localized effect predominates in these sets and all of the substituents studied are acceptors by the localized effect, it seems likely that one of the two tautomers is predominant. At the present, no assignment of configuration to the predominant tautomer is possible.



VI VII

The Magnitude of the Electrical Effect in Heterovinylene Sets.—As a measure of the magnitude of the electrical effect we may take the value of α or ρ. The values of α for oxime configurations in which the substituent and hydroxyl group are *syn* (sets 4B, 5, and 8A) are 3.30, 3.28, and 1.26, respectively. By comparison the values of α for the *cis*-enols (sets 11A and 12) are 4.43 and 3.84, respectively. Owing to there being only three points in set 8A, the uncertainty in its value of α is quite large. Thus no successful comparison can be made between the *cis*-enols and the *anti*-phenyl ketoximes. The α values obtained for the *cis*-enols are in fairly good agreement with those obtained for the *anti* aldoximes and the acetyl ketoximes. This is in accord with the concept that α values are determined predominantly by molecular geometry. For the oximes in which substituent and hydroxyl group are *anti* we may make comparisons with the *trans*-enamines. The values of α for the *syn* aldoximes (set 3), methyl ketoximes (set 6), and *syn*-phenyl ketoximes (set 7A) are 4.43, 5.95, and 4.02, respectively. For the 3-substituted 1-aza[2.2.2]bicyclo-2-octenes (set 13), 3-substituted 4-pyridones (set 14), and 5-substituted 2-pyridones (set 15) we observed α values of 5.75, 5.91, and 4.89. To correct for the difference between OH and NH acids, we multiply the average α value for the *trans*-enamines by the ratio of ρ for phenols to ρ for anilinium ions (the value of which is 0.76);[12] the result is 4.0. The results obtained for the *syn* aldoximes and *syn*-phenyl ketoximes are in good agreement with those for the *trans*-enamines. The value for methyl ketoximes seems too high. The sum of the average α values for *cis*-enols and that or the *trans*-enamines corrected as above should serve for comparison with the disubstituted oximes (set 1). The sum obtained is 8.2. The observed value of α for set 1 is about 11.5 which again seems somewhat high.

In the case of the disubstituted glyoximes (set 2), α_{24} may be estimated to be about that of the geometrically similar *cis*-3-substituted acrylic acids and related systems.[3] The ρ values for the *cis*-3-substituted acrylic and methacrylic acids and trans-3-methylacrylic acid are −2.34, −3.48, and −3.29, respectively. Using an average value of ρ of −3 and the value of ρ for 2-substituted acrylic acids as a model for α_{21} (the value is 4.25),[4] we may use eq 8 to calculate α for set 2. The calculated value of α is 14.5, in very good agreement with the observed value of 15.9.

The α value of the phenylimines (−20.0) may be compared with those of the C-substituted amidines, N-phenyl-O-substituted amidines, and the substituted methylamines for which the ρ values are −12.0, −12.1,

(9) E. Lustig, unpublished results.
(10) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3167 (1968).
(11) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969).
(12) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

and −8.57. The α value observed for the imines is very much larger than might have been expected.

Although the results are by no means conclusive, they suggest that the *syn* oximes are less sensitive to substitutent effects than are the *anti* oximes. Apparently the substitution of nitrogen for carbon in a double bond does not affect the magnitude of the electrical effect.

Composition of the Electrical Effect.—The composition of the electrical effect may be described by ϵ where[13]

$$\epsilon = \beta/\alpha \tag{10}$$

for correlations with eq 9, ϵ is determined by the type of substituent constant used in the calculation,

$$\sigma_X = \lambda\sigma_{I,X} + \delta\sigma_{R,X} \tag{11}$$

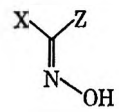
and

$$\epsilon = \delta/\lambda \tag{12}$$

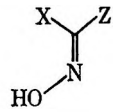
For the σ_m and σ_p constants the ϵ values are 0.33 and 1.00, respectively.

The three sets of oximes in which the substituent X has the *anti* configuration, VIII (sets 3, 6, and 7), have an average value of ϵ of 0.37. Thus these compounds can be correlated with eq 9 by means of the σ_m constants. In the case of those sets of oximes in which the substituent X has the *syn* configuration, IX, a value of ϵ of ~1 is observed for two of the sets, while for the third set ϵ is 0. We may compare these results with those of the *cis*-enols for which ϵ values of 0.56 and 1.5 are obtained. For the enamines and enamides the values of β are not good enough to permit a worthwhile comparison for sets 13 and 14. For sets 15 and 16 values of ϵ are 0.52 and 0.65, respectively.

For the substituted phenylimines a value of ϵ of 0.26 is obtained, while, for the substituted ethyl imidates, ϵ cannot be calculated owing to the uncertainty in β. The value obtained for the substituted phenylimines is in accord with the values observed for C-substituted and C-substituted N-phenylamidines.



VIII



IX

The Use of Correlatable Properties in the Assignment of Configuration.—Consider some property which may be correlated by eq 1 or eq 9. If data of this type for two sets differing in configuration is correlated with either eq 1 or eq 9 three possible situations may conceivably arise: (1) all of the data lie on the same line; (2) the data lie on two parallel lines; (3) the data lie on two nonparallel lines.

The magnitude of α, and therefore of ρ, depends upon the molecular geometry of the system. Then unless the two configurations have equivalent geometries, cases 1 and 2 will not be realized. Thus when the two configurations are geometric isomers or diastereomers case 3 is the usual result. Some important properties of case 3 must be noted. If the correlation lines are not parallel they must intersect. This means that the correlated property for one configuration cannot always be greater than that for the other configuration. That configuration with greater values on one side of the point of intersection of the correlation lines must have smaller values on the other side. Thus if the correlatable property is to be used in the assignment of configuration, the correlation equations for both of the configurations must be known.

The utility of this method of configurational assignment must be a function of the difference between the slopes of the correlation lines and the location of the point of intersection. In most systems the unsubstituted compound (for which X = H) is a member of both sets and is therefore the point of intersection. The smaller the difference in the slopes of the correlation lines, the wider the region in which the two configurations will not differ sufficiently to permit distinction between configurations.

(13) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).

Substituent Effects at Elements Other than Carbon. I. Phosphorus Acids

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Ionization constants of substituted phosphonic and phosphinic acids, rate constants for the benzylation of substituted dithiophosphinates, and ionization constants of substituted phosphazenes are successfully correlated by the extended Hammett equation using the σ_I and σ_R substituent constants defined for substituents bonded to carbon. The average value of ϵ (a parameter which measures the composition of the electrical effect) for the substituted phosphonic and phosphinic acids is 0.32; for the phsophazenes ϵ is 0.25. Thus these sets show an electrical effect which corresponds in composition to the σ_m constants. The magnitude of the electrical effect in substituted phosphonic and phosphinic acids is somewhat less than that observed for substituted carboxylic acids.

We have previously had occasion to study the application of the Hammett equation[1] (eq 1) to the ionization constants of substituted carboxylic acids[2] and substituted amidines.[3] It seemed of interest to consider, for purposes of comparison, the extension of the Hammett equation to substituted phosphonic acids, phosphinic acids, and phosphazenes. Kabachnik[4] has proposed a modified Hammett equation (eq 2) for use with the substituted phosphorus compounds. The

$$Q_X = \rho\sigma_X + h \quad (1)$$

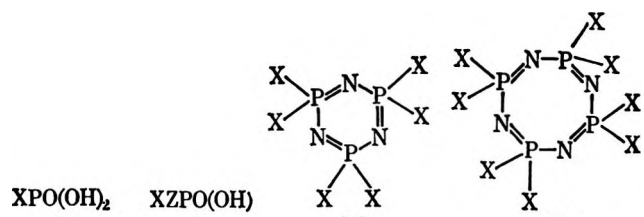
$$Q_X = \rho_\phi\sigma_{\phi X} + h \quad (2)$$

necessary σ_ϕ values were defined from the pK_a values of disubstituted phosphinic acids, XYPO(OH), in water at 25°, ρ_ϕ for this reaction being assigned a value of 1.000 and σ_H a value of 0. Thus, the reference compound is $H_2PO(OH)$ for which Kabachnik gives pK = 1.00. Equation 2 has been used for the correlation of pK_a values of substituted phosphonic and phosphinic acids in water and in ethanol–water mixtures.

It is of interest to determine whether the electrical effects of a substituent bonded to phosphorus are of the same type as those exhibited by a substituent bonded to carbon. Furthermore, we would like to know whether the magnitude of the electrical effects of a substituent bonded to phosphorus is comparable with that of the electrical effects of a substituent bonded to carbon. The Kabachnik equation does not answer these questions. To provide answers we can correlate data for substituted phosphorus sets with the equation proposed by Taft[5] (eq 3). A significant correlation as

$$Q_X = \alpha\sigma_I + \beta\sigma_R + h \quad (3)$$

determined by statistical tests, will answer the first question. In the event of a significant correlation the magnitude of α and β will answer the second. We have therefore correlated data from the literature for the ionization of substituted phosphonic (I) and phosphinic (II) acids, for substituted phosphazenes (III and IV).



XPO(OH)$_2$ I XZPO(OH) II III IV

We have also examined the rate constants for the benzylation of salts of substituted dithiophosphinic acids. Data used in the correlations are given in Table I. The σ_I constants used were taken from our compilation[6] unless otherwise noted (Table II). The σ_R constants required were obtained from[5] eq 4 using the σ_p constants of McDaniel and Brown[7] unless otherwise noted (Table II).

$$\sigma_R = \sigma_p - \sigma_I \quad (4)$$

Statistical factors have been applied to the ionization constants where necessary. Thus, for the substituted phosphonic acids when X = OH (K_1 for *o*-phosphonic acid) a statistical factor of $\frac{2}{3}$ was used, as there are three ionizable protons in this compound and two in the other members of the group. For the substituted hydrogen phosphonates (K_2 of I) when X = OH a statistical factor of $\frac{1}{2}$ is required. For the substituted phosphinic acids when X, Y = Ph, OH a statistical factor of $\frac{1}{2}$ is required.

Results

The results of the correlations with eq 3 are given in Table III.

σ_ϕ Constants.—We have correlated the σ_ϕ values of Kabachnik[4] with eq 3 (set 1). The results are significant at the 99.9% confidence level. A "t" test shows that the β value is significantly different from 0 at the 99% confidence level. Thus the evidence indicates a small but important resonance effect in the reactions

(1) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 565; V. Palm, *Russ. Chem. Rev.* (Engl. Transl.), **31**, 471 (1961); P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); C. D. Ritchie and W. F. Sager, Jr., *Prog. Phys. Org. Chem.*, **2**, 323 (1963).

(2) M. Charton, Abstracts of the 140th National Meeting of the American Chemical Society, Chicago, Ill., 1961, p 91Q.

(3) M. Charton, *J. Org. Chem.*, **30**, 969 (1965).

(4) M. I. Kabachnik, *Zeit. Chem.*, **1**, 2893 (1961).

(5) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).

(6) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).

(7) D. H. McDaniel and H. C. Brown, *ibid.*, **23**, 420 (1958).

TABLE I

DATA USED IN THE CORRELATIONS

1. σ_ϕ constants[a]

X	OH	MeO	EtO	PrO	*i*-PrO	BuO	Me	Et	Pr
σ_ϕ	−0.343	−0.124	−0.314	−0.315	−0.291	−0.411	−0.965	−1.101	−1.177
X	*i*-Pr	Bu	*t*-Bu	CH_2Cl	$CHCl_2$	CCl_3	CH_2Br	CH_2I	CH_2OH
σ_ϕ	−1.300	−1.219	−1.546	−0.034	0.272	0.30	−0.01	−0.11	−0.546
X	CF_3	Ph							
σ_ϕ	0.50	−0.481							

2, 3. pK_a values of $XPO(OH)_2$ in water at 25°[c]

X	Ph	CH_2OH	CH_2I	CH_2Br	CCl_2	$CHCl_2$	CH_2Cl	$BuCH_2$	*t*-Bu
pK_{a1}	1.824[b]	1.91	1.30	1.14	1.63	1.14	1.40	2.84	2.79
pK_{a2}	7.070[b]	7.15	6.72	6.52	4.81	5.61	6.30	8.65	8.88
X	*i*-Bu	*s*-Bu	Bu	*i*-Pr	Pr	Et	Me	CF_3	MeO
pK_{a1}	2.70	2.74	2.59	2.66	2.49	2.43	2.38	1.16	1.54[b]
pK_{a2}	8.43	8.48	8.19	8.44	8.18	8.05	7.74	3.93	6.31[d]
X	EtO	F	$PhCH_2$	OH	AcO	BuS			
pK_{a1}	1.60[d]	0.52[e]	1.85	2.497[f]	1.17[h]	2.21[i]			
pK_{a2}	6.62[d]	4.80[e]	7.4	7.51[g]	4.88[h]	5.93[i]			

4. pK_{a1} values of $XPO(OH)_2$ in water at 20°[j]

X	Me	$HOCH_2$	$ClCH_2$	OH	$CHCl_2$
pK_a	2.38	1.91	1.40	2.15[k]	1.14

5. pK_{a1} values of $XPO(OH)_2$ in 75% aqueous ethanol at 22°[l]

X	PhO	H	Ph	OH	*c*-C_6H_{11}
pK_a	3.13	3.15	3.96	4.34[k]	4.80

6. pK_a values of XZPO(OH) in water at 25°[m]

X, Z	Me, Me	Et, Et	Pr, Pr	*i*-Pr, *i*-Pr	Bu, Bu	*t*-Bu, *t*-Bu	Ph, Ph
pK_a	3.08	3.29	3.46	3.56	3.41	4.24	2.1[n]
X, Z	OH, OH	Et, OEt	OMe, OMe	OEt, OEt	OPr, OPr	OBu, OBu	
pK_a	2.622[o]	2.27[p]	1.29[d]	1.39[d]	1.59[d]	1.72[d]	

7. pK_a values of XZPO (OH) in 7% ethanol–water at 25°[a]

X, Z	MeO, MeO	EtO, EtO	PrO, PrO	PhO, OH	Me, Me	Bu, Bu	*i*-Bu, *i*-Bu
pK_a	1.25	1.37	1.52	1.76[q]	3.13	3.50	3.70
X, Z	Ph, Ph	Pr, Ph	*i*-Pr, Ph	C_2H_3, Ph	C_2H_3, C_2H_3		
pK_a	2.32	2.71[r]	2.82[r]	2.26[r]	2.54[r]		

8. pK_a values of XZPO(OH) in 50% ethanol–water at 25°[r]

X, Z	Pr, Ph	*i*-Pr, Ph	C_2H_3, OEt	C_2H_3, C_2H_3	C_2H_3, Ph
pK_a	4.15	4.28	3.18	3.59	3.53

9. pK_a values of XZPO(OH) in 80% ethanol–water at 25°[a]

X, Z	MeO, MeO	EtO, EtO	PrO, PrO	Me, Me	Bu, Bu	*i*-Bu, *i*-Bu	Ph, Ph
pK_a	3.01	3.15	3.29	5.15	5.63	5.63	4.14
X, Z	PhO, OH	PhO, PhO	C_2H_3, EtO	C_2H_3, Ph	C_2H_3, C_2H_3	Pr, Ph	*i*-Pr, Ph
pK_a	3.66	2.71	3.81	4.29	4.34	4.72	4.89

10. pK_a values of XMePO(OH) in water at 20°[j]

X	SPr	S(*i*-Pr)	O-*i*-Pr	OEt	4-C_6H_4Cl	Me	OH	F
pK_a	2.03	2.13	2.38	2.25	2.39	3.08	2.68[e]	1.94

11. pK_a values of X-*c*-$C_6H_{11}PO(OH)$ in 75% aqueous ethanol at 22°[l]

X	PhO	H	*c*-$C_6H_{11}O$	Ph	OH[e]	*c*-C_6H_{11}
pK_a	3.60	3.91	4.73	5.02	5.10	5.92

12. pK_a values of X-*c*-$C_6H_{11}PO(OH)$ in 95% aqueous ethanol at 22°[l]

X	PhO	H	*c*-$C_6H_{11}O$	Ph	OH[e]	*c*-C_6H_{11}
pK_a	4.19	4.55	5.42	5.60	5.95	6.64

13. pK_a values of X-*c*-$C_6H_{11}OPOP(OH)$ in 75% aqueous ethanol at 22°[l]

X	PhO	H	*c*-$C_6H_{11}O$	Ph	*c*-C_6H_{11}
pK_a	1.64	2.83	3.81	3.83	4.73

14. pK_a values of X-*c*-$C_6H_{11}OPO(OH)$ in 95% aqueous ethanol at 22°[l]

X	PhO	*c*-$C_6H_{11}O$	H	Ph	*c*-C_6H_{11}
pK_a	3.08	4.43	3.40	4.42	5.42

15. pK_a values of XPhOPO(OH) in 75% aqueous ethanol at 22°[l]

X	PhO	*c*-$C_6H_{11}O$	OH[e]	Ph	*c*-C_6H_{11}
pK_a	2.28	2.64	3.43	2.85	3.60

16. pK_a values of XPhOPO(OH) in 95% aqueous ethanol at 22°[l]

X	PhO	*c*-$C_6H_{11}O$	OH[e]	Ph	*c*-C_6H_{11}
pK_a	1.91	3.08	4.13	3.32	4.19

17. pK_a values of XPhPO(OH) in 75% aqueous ethanol at 22°[l]

X	PhO	H	*c*-$C_6H_{11}O$	OH[e]	Ph	*c*-C_6H_{11}
pK_a	2.85	3.11	3.83	4.26	4.10	5.02

18. pK_a values of XPhPO(OH) in 95% aqueous ethanol at 22°[l]

X	PhO	H	*c*-$C_6H_{11}O$	Ph	*c*-C_6H_{11}
pK_a	3.32	3.69	4.42	4.70	5.60

19. pK_a values of XHPO(OH) in 75% aqueous ethanol at 22°[l]

X	H	*c*-$C_6H_{11}O$	OH[e]	Ph	*c*-C_6H_{11}
pK_a	2.70	2.83	3.45	3.11	3.91

TABLE I (*Continued*)

20. pK_a values of XHPO(OH) in 95% aqueous ethanol at 22° [l]

X	H	c-$C_6H_{11}O$	OH[g]	Ph	c-C_6H_{11}
pK_a	2.94	3.40	4.31	3.69	4.55

21. Rate constants for the benzylation of $Na^+XZPS_2^-$ in ethanol at 25° [a]

X, Z	PhO, PhO	MeO, MeO	EtO, EtO	*i*-PrO, *i*-PrO	BuO, BuO	Ph, Ph	Me, PrO
−Log *k*	3.91	3.84	3.84	3.60	3.72	3.28	3.51
X, Z	Me, BuO	Et, Et	Pr, Pr	Bu, Bu	*i*-Pr, *i*-Pr		
−Log *k*	3.56	3.34	3.34	3.33	3.26		

22. pK_a values of $N_3P_3X_6$ in $PhNO_2$ at 25° [t]

X	EtO	$PhCH_2O$	EtS	$PhCH_2S$	PhS	Et	Ph	Me_2N
pK_a	0.20	−2.10	−2.75	−4.15	−4.80	6.40	1.50	7.60

23. pK_a values of $N_4P_4X_8$ in $PhNO_2$ at 25° [t]

X	EtO	Et	Ph	Me_2N	EtNH	MeNH
pK_a	0.60	7.60	2.20	8.30	8.10	8.20

[a] Reference 4. [b] W. J. Polestak and H. K. Zimmerman, *J. Phys. Chem.*, **60**, 787 (1956). [c] L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957). [d] W. D. Kumler and J. J. Eiler, *J. Amer. Chem. Soc.*, **65**, 2355 (1943). [e] L. N. Devonshire and H. A. Rowley, *Inorg. Chem.*, **1**, 680 (1962). [f] P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964). Includes a statistical factor of $\frac{2}{3}$. [g] K. S. Pitzer, *ibid.*, **59**, 2365 (1967). Includes a statistical factor of $\frac{1}{2}$. [h] F. Litman and L. C. Tuttle, *Arch. Biochem.*, **13**, 373 (1947). [i] D. C. Dittmer, O. B. Ramsay, and K. E. Spalding, *J. Org. Chem.*, **28**, 1273 (1963). [j] A. A. Neimysheva, V. I. Savchuk, and I. L. Knunyants, *Zh. Obshch. Khim.*, **36**, 500 (1966). [k] Includes statistical factor of $\frac{2}{3}$. [l] D. F. Peppard, G. W. Mason, and C. M. Andrejasich, *J. Inorg. Nucl. Chem.*, **27**, 697 (1965). [m] P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3379, 4903 (1953). [n] P. Lestauries and P. Rumpf, *Compt. Rend.*, **228**, 1018 (1949). [o] Reference *f*. Includes statistical factor of $\frac{1}{3}$. [p] A. I. Razumov and S. D. Khen, *Zh. Obshch. Khim.*, **26**, 2233 (1956). Includes statistical factor of $\frac{1}{2}$. [q] Reference 4. [r] M. I. Kabachnik, I. A. Mastryukova, and T. A. Melenteva, *Zh. Obshch Khim.*, **32**, 267 (1962); **33**, 382 (1963). [s] Includes statistical factor of $\frac{1}{2}$. [t] D. Feakins, W. A. Last, and R. A. Shaw, *Chem. Ind.* (London), 510 (1962); D. Feakins, W. A. Last, N. Neemuchwala, and R. A. Show, *ibid.*, 164 (1963).

TABLE II

SUBSTITUENT CONSTANTS FROM SOURCES OTHER THAN REF 6 AND 7

X	σ_I	Ref	σ_p	Ref	X	σ_I	Ref	σ_p	Ref
CH_2Cl			0.12	*a*	4-C_6H_4Cl	0.13	*b*	0.081	*b*
CH_2Br			0.12	*a*	SPr			0.06	*b*
CH_2I			0.09	*a*	O-*i*-Pr			−0.31	*b*
CH_2OH			−0.01	*a*	*c*-C_6H_{11}			−0.14	*c*
$CHCl_2$	0.31	*d*	0.185	*e*	*c*-$C_6H_{11}O$			−0.31	*b*
CCl_3	0.43	*d*	0.407	*e*	AcO	0.42	*f*		
BuS			0.04	*b*	PhO			−0.14	*b*
$PhCH_2O$	0.34	*g*	−0.23	*b*	$PhCH_2S$			0.07	*b*
PhS			0.075	*h*	MeNH	0.10	*i*		
Me_2N	0.10	*j*			*t*-$BuCH_2$			−0.17	*k*

[a] O. Exner and J. Jonas, *Coll. Czech. Chem. Commun.*, **27**, 2296 (1962). [b] Calculated as described in M. Charton, *J. Org. Chem.*, **28**, 3121 (1963). [c] Calculated from $\sigma_p = \sigma_I + \sigma_R$ assuming σ_R equal to that for *i*-Pr. [d] Calculated from $\sigma_I = \sigma^*/6.23$. [e] J. Hine and W. C. Bailey, Jr., *J. Amer. Chem. Soc.*, **81**, 2025 (1959). [f] C. D. Ritchie and W. Sager, Jr., ref 1. [g] σ_m was calculated as in *b*. σ_I was then obtained from $\sigma_I = (3\sigma_m - \sigma_p)/2$. [h] H. H. Szmant and G. Suld, *J. Amer. Chem. Soc.*, **78**, 3400 (1956). [i] Assumed equal to σ_I for NH_2 and Me_2N. [j] P. R. Wells, ref 1. [k] Calculated from $\sigma_{p,XCH_2} = m\sigma_{I,X} + c$. [l] Calculated from pK_a of XCH_2CO_2H. See ref 6.

of some substituted pentcovalent phosphorus compounds.

Phosphonic Acids.—Significant correlation is obtained for the first ionization constants of substituted phosphonic acids (set 2a). Omission of the value for X = CCl_3 improved the results (set 2b). The authors who reported this value have remarked that they consider it dubious. Exclusion of the value for X = $PhCH_2$ resulted in further improvement. A value of 2.3 has been reported for the pK_a of this compound; this value seems in better accord with our results. Results for this set are probably not so good as they possibly could be because of the difficulty of measuring reliable pK_a values in this range of acid strength. The results obtained for the second ionization constants of substituted phosphonic acids are excellent, particularly in view of the number of different sources for the data. Omission of the value for X = CCl_3 gave no meaningful difference in the results; we therefore conclude that the value of pK_a for this compound is reasonably good.

In set 2, β is significant at the 90% confidence level, in set 3 at the 99.9% confidence level. Again our results indicate a significant resonance effect. We have not included the value for X = H (pK_1, pK_2 of phosphorus acid) in either set 2 or set 3. The values cited in the literature (1.8 and 6.2, respectively) differ greatly from the calculated values (2.30 and 7.69, respectively).

Good correlation was obtained for the pK_a values of phosphonic acids in water at 20° (set 4). The correlation obtained for the phosphonic acids in 75% aqueous ethanol was not significant. Exclusion of the value for X = H gave a very good correlation (sets 5a and 5b).

Phosphinic Acids.—For our purposes we consider acids of the type XZPO(OH) as phosphinic acids. When Z is not constant the phosphinic acid sets have been correlated with eq 5 which assumes that the effect

TABLE III

RESULTS OF CORRELATIONS WITH EQ 3 AND EQ 4

Set	$-\alpha$	$-\beta$	h	R^a	E^b	r^c	s^d	$s_\alpha{}^d$	$s_\beta{}^d$	$s_h{}^d$	n^e	C.L.^{f}
1	−4.01	−0.760	−0.915	0.946	72.92	0.386	0.606	0.335	0.243	0.0670	20	99.9
2a	3.17	0.520	2.30	0.846	26.39	0.259	0.667	0.438	0.452	0.113	24	99.9
2b	3.56	0.796	2.26	0.878	33.73	0.341	0.679	0.436	0.431	0.104	23	99.9
2c	3.62	0.797	2.31	0.887	35.14	0.361	0.695	0.434	0.426	0.105	22	99.9
3	7.72	2.17	7.69	0.974	196.3	0.259	0.331	0.390	0.402	0.100	24	99.9
4	3.52	1.74	1.97	0.994	83.45	0.413	0.0795	0.299	0.179	0.0550	5	97.5
5a	7.20	4.01	3.81	0.800	1.779	0.883	0.623	3.82	2.39	0.417	5	<90.0
5b	6.83	2.76	4.34	0.99999	17730	0.850	0.00651	0.0400	0.0266	0.00586	4	99.0
6	5.64	1.98	2.54	0.946	42.40	0.947	0.959	1.04	0.724	0.262	13	99.9
7	3.45	0.395	2.98	0.942	35.21	0.922	0.816	0.891	0.570	0.154	12	99.9
8	5.74	1.58	4.27	0.997	170.8	0.874	0.458	0.428	0.284	0.0469	5	99.0
9	3.90	0.439	4.98	0.956	58.95	0.922	0.952	0.789	0.538	0.151	14	99.9
10	2.64	0.934	2.65	0.906	11.41	0.558	0.193	0.554	0.388	0.140	8	97.5
11a	8.84	4.30	4.79	0.781	2.343	0.899	0.683	4.14	2.45	0.453	6	<90.0
11b	8.46	2.81	5.48	0.996	134.7	0.864	0.102	0.618	0.388	0.0903	5	99.0
12a	9.99	5.07	5.41	0.820	3.070	0.899	0.667	4.05	2.40	0.443	6	<90.0
12b	9.61	3.61	6.09	0.998	201.0	0.864	0.0892	0.542	0.340	0.0792	5	99.5
13a	9.60	5.33	3.58	0.792	1.687	0.928	0.732	5.38	3.57	0.496	5	<90.0
13b	8.49	3.39	4.22	0.995	52.47	0.909	0.144	1.07	0.754	0.133	4	90.0
14a	10.8	5.93	4.18	0.814	1.971	0.928	0.764	5.61	3.72	0.518	5	<90.0
14b	9.62	3.92	4.85	0.994	40.82	0.909	0.183	1.36	0.957	0.168	4	<90.0
15	5.89	2.46	3.18	0.948	8.845	0.864	0.248	1.51	0.944	0.220	5	<90.0
16	10.4	4.52	3.64	0.968	15.03	0.864	0.328	2.00	1.25	0.292	5	90.0
17a	8.38	4.11	3.92	0.789	2.469	0.899	0.630	3.82	2.26	0.418	6	<90.0
17b	8.03	2.72	4.57	0.9993	686.6	0.864	0.0424	0.258	0.161	0.0376	5	99.5
18a	9.55	4.87	4.48	0.794	1.702	0.928	0.768	5.64	3.74	0.520	5	90.0
18b	8.39	2.83	5.16	0.997	81.12	0.909	0.127	0.945	0.666	0.117	4	90.0
19a	7.89	3.61	3.14	0.778	1.533	0.942	0.436	4.50	2.18	0.290	5	90.0
19b	7.28	2.68	3.49	0.976	9.868	0.924	0.177	1.84	0.927	0.158	4	90.0
20a	9.37	4.79	3.56	0.727	1.121	0.942	0.639	6.60	3.20	0.426	5	90.0
20b	8.52	3.48	4.06	0.927	3.049	0.924	0.347	3.60	1.82	0.310	4	90.0
21	0.212	−0.444	−3.21	0.946	38.05	0.937	0.238	0.257	0.197	0.0690	12	99.9
22	32.6	8.58	3.55	0.988	106.3	0.159	4.67	2.43	1.10	0.638	8	99.9
23	30.8	7.10	5.12	0.984	46.58	0.316	3.48	3.69	0.986	0.643	6	99.0

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient for σ_I with σ_R. [d] Standard errors of the estimate, α, β, and h. [e] Number of points in the set. [f] Confidence level for regression.

$$Q_X = \alpha\Sigma\sigma_I + \beta\Sigma\sigma_R + h \quad (5)$$

of multiple substituents is additive and ignores interaction terms. The results obtained for the XZPO(OH) in water (set 6), 7% aqueous ethanol (set 7), and 80% aqueous ethanol (set 9) are excellent; very good results were obtained for the pK_a values in 50% aqueous ethanol (set 8). Significant values of β were obtained for sets 6 and 8 but not for sets 7 and 9. The values of r show, however, that σ_I and σ_R are highly correlated for these sets and therefore the separation of the electrical effect into its components is difficult. All of the sets of XZPO(OH) in which Z is a constant substituent that included X = H as a substituent did not give significant correlations (sets 11a, 12a, 13a, 14a, 17a, 18a, 19a, and 20a). Exclusion of the value for X = H improved the results in all cases, significant correlations being obtained for sets 11b, 12b, 13b, 17b, and 18b. The remaining sets, 14b, 19b, and 20b, did not give significant correlations, owing at least in part to the small size of the set. When the constant substituent is Me, good correlation was obtained (set 10). When the constant substituent was PhO, the data in 75% aqueous ethanol (set 15) did not give a significant correlation; the data in 95% aqueous ethanol did (set 16).

Dithiophosphinates.—As excellent correlation is obtained for these data (set 21). It must be noted, however, that neither β nor, in particular, α have a high degree of significance. The results show that this reaction is essentially independent of substituent effects.

Phosphazenes.—Excellent (set 22) and very good (set 23) correlations were obtained for these sets. Values of β are significant in both sets.

Discussion

Of the 23 sets studied 19 gave significant correlations with eq 3 or 4. We conclude, therefore, that the effects of substituents bonded to pentacovalent phosphorus may be represented as a function of the σ_I and σ_R constants developed for substituents bonded to carbon. It is unnecessary to define new substituent constants.

Composition of the Electrical Effect.—To describe the composition of the electrical effects, we can make use of the parameter ϵ, defined as

$$\epsilon = \delta/\lambda \quad (6)$$

where any substituent constant may be written

$$\sigma = \lambda\sigma_I + \delta\sigma_R \quad (7)$$

Then from eq 1

$$Q_X = \rho\lambda\sigma_I + \rho\delta\sigma_R + Q_H \quad (8)$$

which is equivalent to eq 3 with $\alpha = \rho\lambda$, $\beta = \rho\delta$ and therefore

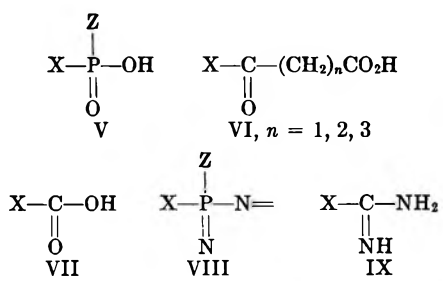
$$\epsilon = \beta/\alpha \quad (9)$$

TABLE IV
VALUES OF ϵ

Set	ϵ	Set	ϵ	Set	ϵ
1	0.191	9	0.113[a]	17b	0.339
2c	0.220	10	0.354	18b	0.337
3	0.281	11b	0.332	19b	[b]
4	0.494	12b	0.376	20b	[b]
5b	0.404	13b	0.400	21	[c]
6	0.351	14b	[b]	22	0.264
7	0.124[a]	15	[b]	23	0.230
8	0.278	16	0.435		

[a] β not significant. [b] Correlation not significant. [c] α not significant.

Values of ϵ for the sets studied are given in Table IV. The average value of ϵ for the phosphoric (V, Z = OH) and phosphinic (V) acids is 0.32 (for sets 2c–13b and 16b–18b). We have shown that ionization constants of acids of the type VI[8] and of carboxylic acids VII[2] are best correlated by the σ_m constants for which $\epsilon = 0.33$. Thus the composition of the electrical effect in V is comparable with that in VI and VII. For the substituted phosphazenes VIII, an average ϵ value of 0.25 is obtained. We have shown[3] that ionization constants of amidines, IX, are best correlated by the σ_m constants. Thus substituent effects upon pK_a values of phospazenes are comparable with those upon the pK_a values of amidines. It would seem that, to a good approximation, data for substituted pentacovalent phosphorus compounds can be correlated with the σ_m constants.



Magnitude of the Electrical Effect.—We may compare α for the ionization of substituted phosphonic acids in water at 25° with ρ for the ionization of substituted carboxylic acids under the same conditions; the values are 3.62 and about 8, respectively. Thus the phosphonic acids are decidedly less sensitive to substituent effects than are the carboxylic acids. This may well be due to molecular geometry. Owing to the larger covalent radius of phosphorus compared with carbon the ionizable proton is significantly further removed from the substituent in the phosphorus oxy acids than it is in the carboxylic acids.

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Substituent Effects at Elements Other than Carbon. II. Ionization Potentials

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Ionization potentials of XF, XCl, XBr, XI, X_2O, XOMe, XSH, XSMe, XSEt, X_3N, and X_3P were correlated with the extended Hammett equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$ with generally good results. For X_nY, $\alpha_Y = m\chi_Y + c$. For XY, $\alpha_Y = m\sigma_{I,Y} + c$; $\beta_Y = m'\sigma_{R,Y} + c'$. It is concluded that substituent effects on ionization potentials in compounds substituted at halogen, oxygen, sulfur, nitrogen, or phosphorus may be represented by substituent constants derived from compounds substituted at carbon.

In the first paper of this series[1] we have shown that rate and equilibrium data for P-substituted phosphorus oxy acids are correlated by the Hammett equation[2] in the extended form (eq 1). We consider in this paper

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (1)$$

the application of eq 1 to sets of ionization potentials for compounds of the type X_nY where Y is an element whose Pauling electronegativity is greater than 2.0 and where $n \leqq 3$. Successful correlation with eq 1 would permit us to determine the magnitude and composition of electrical substituent effects as a function of Y, and to compare the electrical substituent effect upon the ionization of n electrons with that observed for the ionization of π electrons in substituted benzenes and ethylenes.

A number of previous studies on the correlation of ionization potentials of substituted benzenes[3-6] and substituted pyridines[7] with the simple Hammett equation (2) have been reported. Correlations of ionization

$$Q_X = \rho\sigma_X + h \quad (2)$$

potentials of substituted benzyl radicals,[8] substituted phenoxy radicals,[9] and substituted alkyl radicals[10] with eq 2 have appeared. Ionization potentials of substituted ethylenes and substituted carbonyl derivatives have been correlated with eq 1.[11]

Many molecules possess two or more nonequivalent orbitals from which electrons are likely to be lost. In order for correlation with eq 1 to be meaningful, all of the members of the set must lose an electron from the same type of orbital on the same group. Specifically, in the sets studied here, all of the members of the set must lose an electron from a nonbonding orbital on the Y atom. In determining the orbital from which electron loss has occurred, we have assumed that electrons are lost most readily from π orbitals of benzene and ethylene, next from nonbonding orbitals, and least readily from σ orbitals. Thus, consider, for example, the series of compounds (ionization potentials are given in parentheses) PhF (9.20), C_2H_3 (10.37), MeF (12.80), and MeH (12.98). On the basis of this assumption we may now proceed to examine some of the sets studied. In set 1 all of the compounds have available only σ orbitals or nonbonding orbitals on F, and therefore the latter must suffer the loss of the electron. In set 2 all of those compounds which have available only σ orbitals or nonbonding Cl orbitals must lose the electron from the latter. A comparison of the ionization potentials of CF_3Cl and $C_3F_7CH_2Cl$ with that of CF_4 suggests that the electron in the former compounds is lost from a Cl n orbital. We have shown that, that for sets of XY where X is held constant and Y, an atom or group of atoms from which electron loss occurs, is varied[12]

$$I_{X,Y} = mI_{Me,Y} + c \quad (3)$$

where $I_{X,Y}$ is the ionization potential of XY and $I_{Me,Y}$ is the ionization potential of MeY. As I_{CNCl} and I_{ClCH_2CN} lie on the line for I_{CNY}, we conclude that electron loss must be from the n orbital on chlorine in these compounds. By means of arguments analogous to those used above, we may show that in the remaining sets electron loss does in fact occur from the same type of orbital on the same group.

The sets studied have been correlated with eq 1 by multiple linear regression analysis. The data used are reported in Table I. The substituent constants used are generally from the first paper in this series or from sources reported therein. Substituent constants from other sources are given in Table II.

In the correlation of sets of X_nY where $n > 1$ we have assumed that interaction terms may be neglected and therefore

$$Q_X = \sigma\epsilon\alpha_{I,X} + \beta\epsilon\sigma_{R,X} + h \quad (4)$$

Then

$$Q_X = \alpha n\sigma_{I,X} + \beta n\sigma_{R,X} + h \quad (5)$$

$$Q_X = \alpha'_{I,X} + \beta'_{R,X} + h \quad (6)$$

Correlations have been made with eq 6.

Results

Results of correlations with eq 1 are reported in Table III.

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(12) M. Charton, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, p S112.

TABLE I

IONIZATION POTENTIALS USED IN CORRELATIONS[a]

1. XF									
X	H	F	SF_5	Me	Et	CH_2F	CF_3	CHF_2	
IP	15.77[b]	15.7[b]	19.3[c]	12.80[d]	12.00[e]	12.55[d]	14.9[e]	13.84[d]	
2. XCl									
X	H	Cl	Me	Et	Pr	*i*-Pr	Bu	*s*-Bu	*i*-Bu
IP	12.74[b]	11.48[b]	11.28[b]	10.97[b]	10.82[b]	10.78[b]	10.67[b]	10.65[b]	10.66[b]
X-Bu	*t*-Bu	CF_3	$ClCH_2$	Cl_2CH	Cl_3C	CN	$ClCH_2CH_2$	CH_2CN	$CF_3CF_2CF_2CH_2$
IP	10.2[d]	12.8[b]	11.35[b]	11.42[b]	11.47[b]	12.49[e]	11.12[b]	12.2[b]	11.84[b]
3. XBr									
X	H	Br	Cl	Me	Et	Pr	*i*-Pr	Bu	*s*-Bu
IP	11.62[b]	10.55[b]	11.1[c]	10.53[b]	10.24[b]	10.18[b]	10.08[b]	10.13[b]	9.98[b]
X	CN	CF_3	$ClCH_2$	$BrCH_2$	$BrCH_2CH_2$	$ClCH_2CH_2$			
IP	11.95[c]	11.78[b]	10.77[b]	10.49[b]	10.30[c]	10.63[b]			
4. XI									
X	I	Cl^-	Br	H	Me	Et	Pr	*i*-Pr	Bu
IP	9.28[b]	10.31[c]	9.98[c]	10.38[b]	9.54[b]	9.33[b]	9.26[b]	9.17[b]	9.21[b]
X	*s*-Bu	*i*-Bu	*t*-Bu	CF_3CH_2	CF_3	CN	CF_3CF_2	ICH_2	$CF_3CF_2CF_2CH_2$
IP	9.09[b]	9.18[b]	9.02[b]	10.00[b]	10.40[b]	10.98[c]	10.36[b]	9.34[b]	9.96[b]
5. X_2O									
X	F	H	Me	Et	Pr	*i*-Pr	Bu	$ClCH_2CH_2$	
IP	13.7[c]	12.59[b]	10.00[b]	9.53[b]	9.27[b]	9.20[b]	9.18[b]	9.85[b]	
6. XOMe									
X	Me	CH_2OMe	Et	CH_2Cl	Cl_2CH	H			
IP	10.00[b]	10.00[b]	9.81[c]	10.25[b]	10.25[b]	10.85[b]			
7. XSH									
X	SH	H	Me	Et	Pr	Bu	*t*-Bu	MeS	EtS
IP	10.2[c]	10.46[b]	9.44[b]	9.29[b]	9.20[b]	9.14[b]	8.79[b]	8.8[c]	9.4[c]
8. XSMe									
X	H	Me	Et	Pr	*i*-Pr	MeS	CN		
IP	9.44[b]	8.69[b]	8.55[b]	8.80[c]	8.7[c]	8.46[b]	10.065[b]		
9. XSEt									
X	H	Me	Et	EtS	CN				
IP	9.29[b]	8.55[b]	8.43[b]	8.27[b]	9.89[b]				
10. X_3N									
X	H	Me	Et	Pr	CF_3CF_2	F			
IP	10.154[b]	7.92[b]	7.50[b]	7.23[b]	11.7[b]	12.9[d]			
11. X_3P									
X	H	CF_3	Cl	Me	Et				
IP	10.11[c]	11.31[c]	10.75[c]	8.60[c]	8.27[c]				

[a] R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications," Prentice-Hall, Englewood Cliffs, N. J. 1965, p 301. Ionization potentials are reported in electron volts. [b] Photoionization method. [c] Electron impact method. [d] Vacuum ultraviolet spectroscopy method. [e] R. W. Kiser and D. L. Hobrock, *J. Amer. Chem. Soc.*, **87**, 922 (1965).

TABLE II

SUBSTITUENT CONSTANTS[a,b]

X	σ_I	Ref	σ_R	Ref	X	σ_I	Ref	σ_R	Ref
C_3F_7	0.39	*c*	0.17	*c, d*	CH_2F	0.18	*e*	−0.04	*f*
$C_3F_7CH_2$			−0.05	*f*	CHF_2			0.03	*g*
CH_2CH_2Cl	0.05	*h*	−0.10	*f*	CH_2CN			−0.01	*i*
CH_2CH_2Br	0.05	*h*	−0.10	*f*	CH_2OMe			−0.03	*f*
CF_3CF_2	0.41	*c*	0.17	*c, d*	CHO	0.36	*j*	0.07	*k*
SF_5	0.55	*l*	0.11	*l*					

[a] From sources other than ref 1 or references cited therein. [b] σ_R values calculated from $\sigma_R = \sigma_p - \sigma_I$. References to source of σ_p. [c] W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965). [d] Calculated from $\sigma_R^0 = a\sigma_R + b$. [e] Calculated from $\sigma_{I,XCH_2} = a''\sigma_{I,X} + b''$. [f] Calculated from $\sigma_{p,XCH} = a'\sigma_{I,X_2} + b'$. [g] R. Pollet, R. van Poucke, and A. de Cat, *Bull. Soc. Chim. Belges*, **75**, 40 (1966). [h] Calculated from the pK_a of the corresponding substituted acetic acid. [i] O. Exner and J. Jonas, *Coll. Czech. Chem. Commun.*, **27**, 2296 (1962). [j] Calculated from $\sigma_I = (3\sigma_m - \sigma_p)/2$. [k] A. A. Humffray, J. J. Ryan, J. P. Warren, and Y. H. Yung, *Chem. Commun.*, 610 (1965). [l] W. A. Sheppard, *J. Amer. Chem. Soc.*, **84**, 3072 (1962).

Halogen Derivatives.—The correlations obtained for the fluorine compounds (set 1) are very poor. Exclusion of the point for X = H (set 1A) gave an improved correlation which remains very poor. Further exclusion of the point for X = F (set 1B) resulted in decreased correlation. By contrast, the correlations obtained for the chloro, bromo, and iodo compounds (sets 2, 3, and 4) are excellent. Exclusion of the value for X = H from these sets gave a very much improved correlation in all three cases (sets 2A, 3A, and 4A). Further exclusion of the value for X = Cl from the chloro compounds gave slightly improved results (set 2B). Further exclusion of the point for X = Br from the bromo compounds gave improved results (set 3B), whereas the exclusion of the point for X = I from the iodo compounds gave a very much improved

TABLE III
RESULTS OF CORRELATIONS

Set	α	β	h	R^a	F^b	r^c	$s_{estd}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$
1	6.54	2.63	12.21	0.717	2.649	0.019	1.96	2.95	4.01
1A	8.38	1.84	12.30	0.853	5.356	09031	1.61	2.61	3.32
2	1.39	5.21	11.56	0.809	14.27	0.400	0.476	0.586	1.51
2A	1.82	3.94	11.34	0.883	24.83	0.447	0.353	0.450	1.18
2B	1.02	6.26	11.56	0.898	27.11	0.816	0.343	0.734	2.06
3	1.68	3.51	10.73	0.860	17.03	0.182	0.425	0.425	1.00
3A	1.96	2.72	10.56	0.941	42.74	0.232	0.222	0.276	0.660
3B	2.26	1.97	10.49	0.958	55.91	0.451	0.198	0.289	0.699
4	1.66	2.02	9.59	0.818	15.18	0.271	0.361	0.400	0.859
4A	1.88	1.57	9.47	0.879	23.73	0.307	0.298	0.338	0.726
4B	2.17	1.15	9.44	0.942	51.30	0.349	0.214	0.255	0.533
5	17.2	15.7	11.82	0.917	13.27	0.924	0.818	4.17	6.00
5A	4.08	−5.60	8.99	0.981	52.26	0.978	0.380	3.57	5.61
6	0.624	4.77	10.47	0.692	1.377	0.114	0.339	1.09	2.95
6A	1.06	0.659	10.03	0.872	3.177	0.0664	0.130	0.432	1.49
7	3.22	9.06	10.37	0.953	29.87	0.579	1.99	0.585	1.19
7A	3.07	8.29	10.26	0.916	13.08	0.645	0.211	0.667	1.78
8	0.892	4.33	9.25	0.977	41.83	0.403	0.152	0.285	0.656
8A	1.08	3.75	9.14	0.990	73.45	0.513	0.108	0.220	0.536
9	0.651	4.99	9.15	0.984	19.94	0.437	0.174	0.354	0.837
9A	0.906	4.35	9.01	0.994	38.13	0.605	0.147	0.355	0.853
10	8.65	0.520	8.45	0.925	8.909	0.277	0.188	2.11	2.65
10A	9.36	−0.311	7.90	0.995	93.13	0.230	0.388	0.709	0.891
11	4.33	3.28	9.34	0.929	6.312	0.0163	0.693	1.32	2.56
11A	5.01	2.17	8.92	0.995	48.95	0.122	0.264	0.537	1.03

Set	$s_h{}^d$	n^e	C.L.^{f}	Set	$s_h{}^d$	n^e	C.L.^{f}
1	1.01	8	<90.0	6	0.250	6	<90.0
1A	0.961	7	90.0	6A	0.143	5	<90.0
2	0.190	18	99.9	7	0.150	9	99.9
2A	0.153	17	99.9	7A	0.239	8	97.5
2B	0.224	16	99.9	8	0.0926	7	99.5
3	0.142	15	99.9	8A	0.0831	6	99.5
3A	0.0978	14	99.9	9	0.123	5	95.0
3B	0.0944	13	99.9	9A	0.147	4	<90.0
4	0.129	18	99.9	10	0.583	6	90.0
4A	0.114	17	99.9	10A	0.222	5	97.5
4B	0.0818	16	99.9	11	0.413	5	<90.0
5	0.725	8	99.0	11A	0.196	4	<90.0
5A	0.729	7	99.5				

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient for correlation of σ_I with σ_R. [d] Standard deviations of the estimate, α, β, and h. [e] Number of points in the set. [f] Confidence level of regression.

correlation. We believe that the poor results obtained for the fluoro compounds are due largely to the small size of the set, and to a lack of variation in substituent type. The difficulty encountered in this set is that most of the functional groups which may be bonded to fluorine have n or π electrons which are more readily lost than are the n electrons on the fluorine atom.

Oxygen and Sulfur Derivatives.—Very good results were obtained for the X_2O (set 5). Exclusion of the value for X = H gave excellent results (set 5A). The high value of r indicates little separation into localized and delocalized effects. The correlation obtained for the XOMe is very poor (set 6). Although the results are improved by the exclusion of the point for X = H, they remain poor (set 6A). This is probably due to the small size of the set and to the low degree of variability in the substituent effects of the set members.

The correlation obtained for the substitued thiols (set 7) is excellent. It is of interest to note that exclusion of the point for X = H leads to poorer correlation (set 7A). The MeSX gave excellent results (set 8) which are improved by the exclusion of the unsubstituted compound (set 8A). Fair results were obtained for the EtSX (set 9). Elimination of the value for the unsubstituted compound may result in improvement (set 9A). Unfortunately, the set is too small to permit a definite conclusion.

Nitrogen and Phosphorus Derivatives.—A poor correlation was obtained for the X_3N (set 10). Exclusion of the value for X = H gave good results (set 10A). The X_3P gave a poor correlation (set 11), again, however, the results were improved by exclusion of the unstubstituted compound from the set, a good correlation being obtained (set 11A).

Discussion

Magnitude of the Electrical Effect.—In Table IV we have collected values of α, β, h, $\sigma_{I,Y}$, $\sigma_{R,Y}$, χ_Y, and I_{MeY}. Values obtained in previous work on the ionization potentials of substituted ethylenes and carbonyl derivatives[11] have been included for purposes of comparison.

Inspection of the values in Table IV suggests a linear

TABLE IV

VALUES OF α, β, h, $\sigma_{I,Y}$, $\sigma_{R,Y}$, χ_Y, AND I_{MeY}

Y	Set	α	β	h	$\sigma_{I,Y}$	$\sigma_{R,Y}$	χ_Y[a]	I_{MeY}
F	1A	8.38	*b*	12.30	0.52	−0.46	4.0	12.80
Cl	2A	1.82	3.74	11.34	0.47	−0.24	3.0	11.28
Br	3A	1.96	2.72	10.56	0.45	−0.22	2.8	10.53
I	4A	1.88	1.57	9.47	0.39	−0.12	2.5	9.54
OMe	6A	1.06	*b*	10.47	0.25	−0.52		10.00
SH	7A	3.07	8.29	10.26	0.25	−0.15		9.44
SMe	8A	1.08	3.75	9.14	0.25	−0.25		9.69
SEt	9A	0.906	4.35	9.01	0.25	−0.22		8.55
N	10A	3.12[c]	*b*				3.0	
P	11A	1.67[c]	0.723				2.1	
C_2H_3	*d*	1.32	2.51	9.85	0.09	−0.11		9.73
Ph	*d*	0.916	1.39	9.46	0.10	−0.11		8.82
HCO	*d*	3.87	1.34	10.31	0.36	0.07		10.21
Ac	*d*	3.01	0.589	9.60	0.29	0.21		9.69
Bz	*d*	2.42	*b*	9.29	0.29	0.17		9.27

[a] Pauling electronegativity. [b] β For this set is not significant. [c] Calculated from α' by dividing by n. [d] From ref 11.

TABLE V

RESULTS OF CORRELATIONS WITH EQ 7, 8, 9, AND 12

Set	m[a]	c[b]	r[c]	t[d]	$s_{est'd}$[e]	s_m[f]	n[g]	C.L.[h]
A1	3.64	−7.42	0.887	3.851	1.35	0.945	6	98.0
A2	9.16	−0.351	0.595	2.455	1.59	3.73	13	95.0
A2A	9.49	−0.548	0.614	2.462	1.73	3.85	12	95.0
B1	−8.05	2.11	0.536	1.795	1.99	4.48	10	80.0
B1A	−7.03	1.67	0.842	4.129	0.753	1.70	9	99.0
H1	0.799	2.12	0.935	8.734	0.350	0.0915	13	99.9
H1A	0.823	1.83	0.954	10.10	0.308	0.0815	12	99.9

[a] Slope. [b] Intercept. [c] Correlation coefficient. [d] Student "t" test. [e] Standard error of the estimate. [f] Standard error of the slope. [g] Number of points in the set. [h] Confidence level.

relationship between α and χ_Y in X_nY (eq 7). Correlation of α with χ gives good results (set A1, Table V).

$$\alpha_Y = m\chi_Y + c \tag{7}$$

Where Y is a group as in XY, the eq 8 is roughly obeyed.

$$\alpha_Y = m\sigma_{I,Y} + c \tag{8}$$

Fair results are obtained for this correlation (set A2). Exclusion of the value for Y = SH gives only slight improvement (set A2A).

The values of β seem to follow eq 9. The correlation

$$\beta_Y = m'\sigma_{R,Y} + c' \tag{9}$$

obtained is not significant (set B1). Exclusion of the value for Y = SH gives very good results, however (set B1A).

Composition of the Electrical Effect.—We characterize the composition of the electric effect by eq 10. From

$$\epsilon = \beta/\alpha \tag{10}$$

eq 8 and 9, we obtain eq 11.

$$\epsilon = (m'\sigma_{R,Y} + c')/(m\sigma_{I,Y} + c) \tag{11}$$

The Intercept h as a Function of Eq. 3.—Equation 3 relates $I_{X,Y}$ to I_{MeY}. The intercept h obtained in correlation with eq 1 is equivalent to the ionization potential of reference substituent X°. Then h should be correlated by eq 12. This relationship is in fact

$$h = mI_{Me,Y} + c \tag{12}$$

observed (set H1, Table V). The correlation is excellent. The results are improved by the exclusion of the value for Y = SH.

Applicability of Eq 1.—Of the eleven sets studied we have obtained excellent results in five (set 2A, 3A, 4A, 5A, and 8A), very good results in two (sets 7A and 10A), and poor but significant results in one (set 1A). Although very poor correlation (with regard to the confidence level) was obtained for the other three sets, in two there were only four members in the set (sets 9A and 11A) and in the third only five. We believe that better results would have been obtained had more data been available. We conclude, therefore, that substituent effects on ionization potentials in compounds bearing the substituent on halogen, oxygen, sulfur, nitrogen, and phosphorus may be represented by substituent constants derived from compounds bearing the substituent on carbon.

It should be noted that, in general, the value for X = H deviates significantly from the set. This phenomenon has also been observed for many correlations of substituted carbon compounds.

Photosensitized Fragmentation of a Bicyclo[4.2.0]octa-2,4-diene Derivative. Preparation of the Isomeric 1,2-Diacetoxyethylenes

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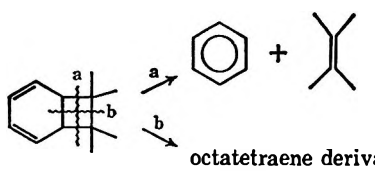
Photosensitized reactions of *trans*-7,8-diacetoxybicyclo[4.2.0]octa-2,4-diene (1) lead to the isomeric diacetoxyethylenes and benzene in good yield and to a cycloadduct dimer of 1 as a minor product. The results contrast sharply with the results of direct irradiation of 1. Both *cis* and *trans* isomers of diacetoxyethylene are formed as primary products, though 1 is known to be cleanly a *trans* compound. Mechanisms which will account for the stereochemical result are discussed; one possibility is the fragmentation of triplet 1 to benzene and triplet diacetoxyethylene, a reaction of theoretical significance.

The photochemical behavior of bicyclo[4.2.0]octa-2,4-diene derivatives has been of interest to several groups.[1-3] Two general modes of reaction has been observed. Thus, the well-known bullvalene synthesis[1]

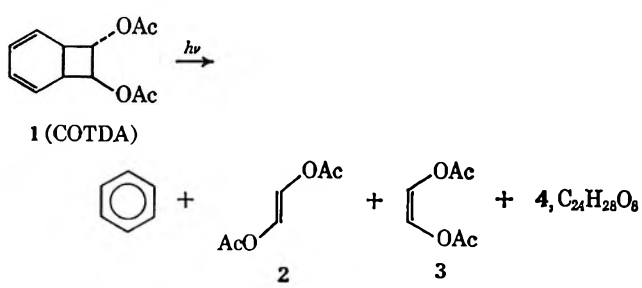


octatetraene derivatives

involves a type a fragmentation of a dimer of cyclooctatetraene. The benzonitrile–trimethylethylene photoadduct undergoes both types of cleavage,[2] while only type b cleavage has been reported for *trans*-7,8-diacetoxybicyclo[4.2.0]octa-2,4-diene (1).[3] We have investigated the photochemistry of 1 in the presence of photosensitizers and find, in contrast, evidence only for the type a process. This paper describes the products arising from the triplet state of 1 and discusses possible mechanisms for their formation.

Results

Irradiation of 1 in ether in the presence of benzophenone, thioxanthone, or fluorenone as photosensitizer at wavelengths longer than 3000 Å led to benzene and the isomeric 1,2-diacetoxyethylenes 2 and 3 as the major products in 50–80% yield. Since the only previous



report[4] of 2 and 3 gave minimal structure evidence, a thorough spectral investigation seemed appropriate. The high-resolution mass spectrum confirms $C_6H_8O_4$ as the molecular formula. For each isomer, the nmr shows two singlets in the ratio of 6:2 in the acetyl and vinyl regions, respectively. Assignment of geometry follows from the observation of a C=C stretch in the ir of the higher melting *cis* isomer but not in the *trans*. Observations of the olefinic H–H coupling constant from the C^{13} satellite peaks (J_{H-H} = 11 Hz, *trans*; 4 Hz, *cis*.) confirms the isomer assignment[5] and eliminates vinylidene acetate as a possibility.

Concentration of the ether solution afforded a 5–10% yield of 4, mp 209–211.5° after recrystallization from toluene. The structure of this material has not been established in detail, but the molecular weight, mass spectral fragmentation pattern, and nmr show it to be a cycloadduct dimer of 1. There is ample analogy for photosensitized dimerization of cyclohexadienes.[6]

A quantitative study of the fragmentation reaction has been carried out. The reaction can be sensitized in either ether or benzene by fluorenone, thioxanthone, or benzophenone with substantially the same results. Interestingly, both 2 and 3 are primary photoproducts though the starting material 1 is exclusively *trans*. The quantum yields (at 3660 Å) for 2 and 3 add to about 0.3 at 0.02 *M* 1 (see Table I). The ratio of quantum yields ϕ_2/ϕ_3 is 1.22 ± 0.02 in ether and 1.48 ± 0.02 in benzene, invariant to sensitizer. The ratio is independent of the extent of conversion in the early stages of the reaction for all sensitizers; however, prolonged irradiation of the benzene solutions leads to changes in the *cis–trans* ratio for benzophenone and thioxanthone due to a subsequent photosensitized isomerization of the diacetoxyethylenes. This effect was not observed with fluorenone.

The reaction has been studied as a function of the concentration of 1. The sum of the quantum yields of 2 and 3, $\phi_2 + \phi_3$, diminishes markedly as the concentration of 1 increases though no change in the ratio ϕ_2/ϕ_3 is observed outside of experimental error. This observation is expected for a unimolecular fragmentation to give 2 and 3 which must compete with the bimolecular dimerization reaction. These data lead to the mechanism outlined below (eq 1–6).

$$S \xrightarrow{h\nu} S^1 \xrightarrow{\phi_{ic}} S^3 \quad (1)$$

$$S^3 + \text{COTDA} \longrightarrow S + \text{COTDA}^3 \quad (2)$$

$$\text{COTDA}^3 \xrightarrow{k_2} C_6H_8 + \textit{trans}\text{-AcOCH=CHOAc} \quad (3)$$

$$\text{COTDA}^3 \xrightarrow{k_3} C_6H_6 + \textit{cis}\text{-AcOCH=CHOAc} \quad (4)$$

$$\text{COTDA}^3 \xrightarrow{k_D} \text{COTDA} \quad (5)$$

$$\text{COTDA}^3 + \text{COTDA} \xrightarrow{k_{DIM}} 4 \quad (6)$$

(1) G. Schröeder, *Chem. Ber.*, **97**, 3140 (1964).

(2) J. G. Atkinson, D. E. Ayer, G. Büchi, and E. W. Robb, *J. Amer. Chem. Soc.*, **85**, 2257 (1963).

(3) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959).

(4) M. F. Shostakovskii, V. N. Kuznetzof, and C.-M. Yang, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 710 (1962).

(5) The isomers were incorrectly assigned in ref 4.

(6) D. Valentine, N. J. Turro, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 5202 (1964).

Table I

Yields of Diacetoxyethylenes from Sensitized Photolyses of COTDA (1)

Solvent	(1), M	Sensitizer	E_T	% 2[a]	% 3[a]	ϕ_2[b]	ϕ_3[b]	ϕ_2/ϕ_3
Ether	0.055	Fluorenone	53	32	26	0.13	0.10	1.22 ± 0.02
Ether	0.022	Fluorenone	53	40	32	0.16	0.13	1.24 ± 0.02
Ether	0.012	Thioxanthone	65	44	37	0.25	0.21	1.21 ± 0.02
Benzene	0.021	Benzophenone	69	16.5	22	0.18	0.12	1.50 ± 0.05
Benzene	0.022	Fluorenone	53	43.5	30.6	0.17	0.12	1.48 ± 0.02
Benzene	0.030	Thioxanthone	65	28.8	35.7	0.18	0.125	1.47 ± 0.02

[a] Over-all yield. [b] Quantum yield at 5–15% reaction.

This mechanism leads readily to the following kinetic expression (eq 7). Here $\phi_F = \phi_2 + \phi_3$ = the total

$$\frac{\phi_{ic}}{\phi_F} = 1 + \frac{k_D}{k_F} + \frac{k_{DIM}}{k_F}(\text{COTDA}) \qquad (7)$$

fragmentation quantum yield, $k_F = k_2 + k_3$ = the sum of the fragmentation rate constants, and COTDA (cyclooctatetraene diacetate) stands for **1**. A fit to eq 7 is observed, with $k_D/k_F = 1.55 \pm 0.1$ and $k_{DIM}/k_F = 36\ M^{-1}$ in benzene (Figure 1).

Discussion

Multiplicity.—Compound **1** represents the first bicyclo[4.2.0]octa-2,4-diene derivative for which data are available both for direct[3] and sensitized irradiation. We have repeated the direct irradiation and, in a preliminary experiment, find no evidence for the formation of **2** or **3**. We conclude that, for **1** at least, the type a fragmentation is a triplet-state process while the type b process must be essentially exclusively a singlet-state process. This in accord with observations on cyclohexadiene itself, where ring opening to hexatriene occurs from the singlet state,[7] but the triplet-state chemistry exclusively involves dimerization.[6]

An attractive, though speculative, conclusion is that all type a processes occurring upon direct irradiation[1,2] involve intersystem crossing to the triplet. The competing conrotatory ring-opening process allowed photochemically by the Woodward–Hoffmann rules[8] would lead to the strained *trans,cis,cis*-cyclooctatriene derivative and therefore might be relatively slow in the bicyclo system. Intersystem crossing then might compete, even though it appears not to in the cyclohexadiene–hexatriene conversion.

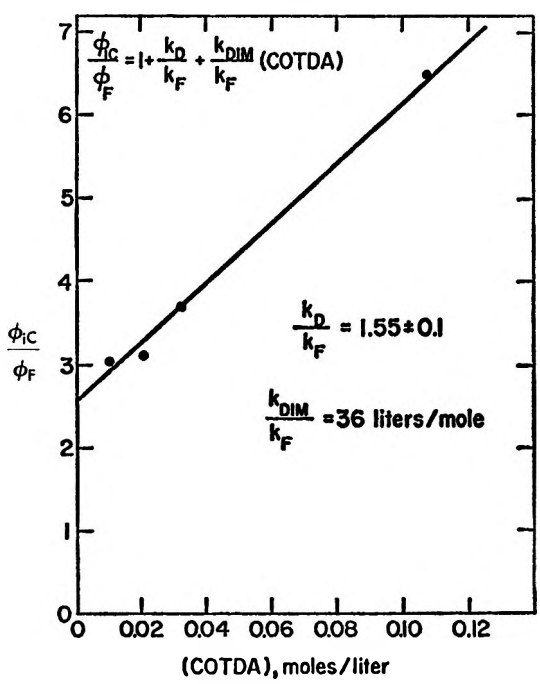


Figure 1.—Plot of the reciprocal fragmentation quantum yield for COTDA *vs.* COTDA concentration.

Kinetic Results.—Figure 1 allows determination of the ratio k_{DIM}/k_D as 23 M^{-1}. This may be compared with the results of Hammond and Vesley referred to by Lam, Valentine, and Hammond[9] who determined that, for dimerization of cyclohexadiene sensitized by benzophenone, $1/\phi = 1 + 0.028/(\text{cyclohexadiene})$. This leads to $k_{DIM}/k_D = 36\ M^{-1}$ for cyclohexadiene. Comparison of the results for **1** is gratifying. For **1**, dimerization appears to be slowed down relative to decay by a factor of two or so, quite consistent with what one would have expected on the basis of the increased steric hindrance on the one face of the cyclohexadiene ring. One may therefore conclude that the lifetime of the triplet state of **1**, k_D^{-1}, probably is close to that for cyclohexadiene. There appears to be no very efficient anomalous decay process, analogous to that suggested for ketones which may undergo the Norrish II reaction,[10] dominant in the present case.

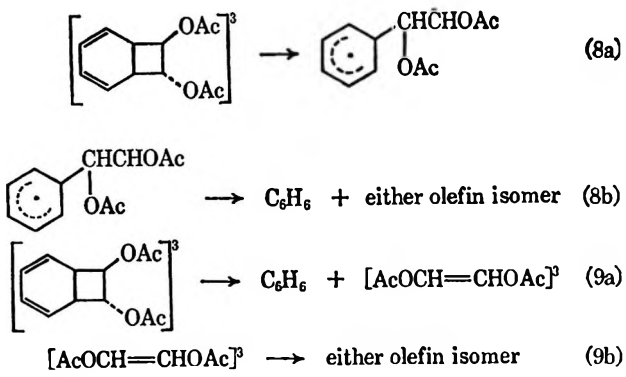
The rate constant k_F for total type a fragmentation must be no larger than about 10^8 sec^{-1}, since k_{DIM} must be less than or equal to the rate constant for diffusion in benzene, about $5 \times 10^9\ M^{-1}$ sec^{-1}. Since the only estimate available for a dimerization reaction between a diene triplet and a ground-state diene molecule is a *maximum* value of about $5 \times 10^6\ M^{-1}$ sec^{-1} for isoprene,[11] k_F may be considerably less. One may conclude that the rate constant for fragmentation is probably somewhere in the range of 10^5–10^8 sec^{-1}: fast, but no means extremely fast for a unimolecular reaction of a triplet state.

Details of the Fragmentation.—Either a stepwise or a concerted process for the fragmentation, eq 8 and 9 will explain the data. The observation that *both* olefins are primary photoproducts demands a mechanism that can account for the loss of stereochemistry. In reaction 8, loss of stereochemistry arises from rotation about a single bond in the biradical intermediate. In reaction 9, it arises from the partitioning of the (presumably twisted) olefin triplet between decay to *trans* isomer and *cis* isomer.

Distinguishing between eq 8 and 9 is an extremely important point, since a reaction such as 9a is of considerable theoretical significance. There are no proven examples of photochemical fragmentations of

(7) R. Srinivasan, *Advan. Photochem.*, **4**, 113 (1966), and references contained therein.

(8) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).
(9) E. Y. Y. Lam, D. Valentine, and G. S. Hammond, *ibid.*, **89**, 3482 (1967).
(10) P. J. Wagner, *ibid.*, **89**, 5898 (1967).
(11) R. S. H. Liu, N. J. Turro, and G. S. Hammond, *ibid.*, **87**, 3406 (1965).



(8a)

(8b)

(9a)

(9b)

large organic molecules which give electronically excited fragments. However, the reasonable supposition that chemical reactions of an initially formed molecule may lead to intermediate or product molecules containing electronic excitation is an integral part of one of the more successful schemes for rationalizing photochemical mechanisms.[12] Indeed, Zimmerman[13] has raised very similar questions in a recent communication dealing with the photorearrangement of 6,6-disubstituted bicyclo[3.1.0]hex-3-en-2-ones.

We feel that organic photochemistry needs direct evidence relating to the question of the timing of the loss of electronic excitation, if only for a few simple systems such as the present one, in view of the theoretical importance of the question. It might be noted that the present example might be particularly favorable for the occurrence of a reaction such as 9a since (1) it is a retro [2 + 2] cycloaddition which is allowed[14] to occur photochemically, (2) Woodward–Hoffmann correlation diagrams for [2 + 2] cycloadditions correlate excited-state reactants *with excited-state products*, and (3) reaction 9a should be exothermic[15] and is therefore energetically feasible.

The experimental distinction between reactions 8 and 9 rests on the determination of the decay ratio for triplet diacetoxyethylene. If reaction 9 is correct, the decay ratio should be precisely equal to the observed initial product ratio, ϕ_2/ϕ_3. Unfortunately, determination of the decay ratio by photosensitized isomerization experiments[16] has proved extraordinarily difficult. Such experiments have led to the conclusion that there must be some interaction between a benzophenone or propiophenone triplet and diacetoxyethylene which leads neither to any observable new photoproduct nor to diacetoxyethylene triplet.[17]

Further experiments in this system, and on related derivatives for which quantitative evidence pertinent to eq 9 may be more easily obtained, are in progress. We are also investigating the photosensitized isomerization of the diaxetoxyethylenes and related compounds.

(12) H. E. Zimmerman, *Advan. Photochem.*, **1**, 183 (1963).

(13) H. E. Zimmerman and J. O. Grunewald, *J. Amer. Chem. Soc.*, **89**, 3354 (1967).

(14) R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 2046 (1965).

(15) Assuming 20 kcal of strain for the cyclobutane ring, all π bonds as 60 kcal, all σ bonds as 80 kcal, the resonance energy of the benzene ring as 36 kcal, and the E_T values (at the potential minimum) for **1** and **2** as 54 and 60 kcal, the estimated $\Delta H°$ for reaction 9a is −9 kcal/mol.

(16) For details of this technique, see (a) G. S. Hammond, *et al.*, *J. Amer. Chem. Soc.*, **86**, 3197 (1964); (b) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965); (c) R. B. Cundall and Davies, *Proc. Roy. Soc.*, **A290**, 563 (1966).

(17) R. A. Caldwell, unpublished results.

Experimental Section

trans-7,8-Diacetoxybicyclo[4.2.0]octa-2,4-diene (**1**) was prepared by the method of Cope, *et al.*[18] It was purified by recrystallization from hexane, sublimation at 10^{-3} mm and one further recrystallization from hexane; mp 60–61.8, lit.[18] 60–61°. The material was homogeneous to tlc and showed two nonequivalent acetates in the nmr spectrum, requiring that the acetates be *trans*. The chemical[18] and spectral[19] observations thus leave no doubt that the stereochemistry of **1** is correct as drawn. The uv of **1** showed one maximum, λ_{max} 269 mμ (ε 3900).

Other Compounds.—Sensitizers were twice recrystallized and sublimed. Mallinckrodt anhydrous ether was suitable for preparative use as received. Dodecane was used as an internal standard in all quantitative work. Commercial dodecane (Aldrich Chemical Corp.) was shaken five times with its own volume of cold concentrated sulfuric acid, five times with distilled water, dried over P_2O_5, and distilled, bp 95° (*ca.* 10 mm). Vpc analysis showed the presence of 0.2% impurity, but other experiments[17] showed that the impurity did not quench benzophenone triplets detectably.

Benzene for quantitative photochemical work was shaken with its own volume of cold concentrated sulfuric acid until the washings were almost colorless (four or five times). It was washed with distilled water, dried over P_2O_5, and distilled from P_2O_5.

Preparative-Scale Photolysis of 1.—Fluorenone (0.9 g), **1** (5.00 g), and 1 l. of ether were stirred in a standard 1-l. photochemical reaction vessel, equipped with a Pyrex immersion well, and purged with a slow stream of nitrogen. After 30 min, the reaction mixture was irradiated with a Hanovia 450-W medium-pressure mercury lamp. Results were identical for irradiation times from 2 to 40 hr.

Four such reaction mixtures were combined and concentrated to 200 ml. A solid material (**4**) (1.05 g) precipitated and was collected. The remainder of the material was distilled on a Teflon spinning-band distillation column to afford (1) ether, (2) a fraction, bp 26.5° (100 mm), identified by vpc retention time and infrared spectrum as predominantly benzene, and (3) three fractions of diacetoxyethylene isomers (**2** and **3**) totaling 8 g (62%), bp 96.5–99.5° (23 mm). The most careful distillations performed gave 50% of the total as better than 90% pure *trans*, about 15% as an approximately equimolar mixture, and the remaining 35% as better than 95% pure *cis*, which solidified in the receiver. Further purification of the two isomers could be accomplished by preparative gas chromatography on a Carbowax 20M column or, better, by several low-temperature recrystallizations from cyclohexene for the *trans* isomer **2**, mp 23°, or for the *cis* isomer **3**, mp 42.6–43.8°, trituration as a melt with an equal volume of hexane during solidification.

Spectral data for **2** were as follows: ir, 3080, 1770, 1440, and 1375, no absorption between 1600 and 1700 cm^{-1}; nmr (CCl_4), δ 7.33 (2 H), 2.10 (6 H), $J_{C^{13}-H}$ = 192 Hz for the vinyl protons. Fine structure to the C^{13} satellite of the vinyl protons gives J_{H-H} as 11 Hz. Spectral data for **3** were as follows: ir, 3100, 3020, 1770, 1690, 1620, 1440, 1375, and 1360 cm^{-1}; nmr (CCl_4), δ 6.7 (2 H), 2.15 (6 H), $J_{C^{13}-H}$ = 195 Hz for vinyl protons, J_{H-H} 4 Hz. The mass spectra of the two isomers were very similar, showing major fragments at 102 (M − ketene), 60, 44, 43 (base), 42 for both. Parent peaks were at 144.0416 for **2** and 144.0427 for **3** ($C_6H_8O_4$ requires 144.0422).

Compound **4** showed a weak parent peak in the mass spectrum at 444.1808 ($C_{24}H_{28}O_8$ requires 444.1784), fragments corresponding to the loss of up to four acetate or acetyl or ketene or acetic acid moieties, and major fragments at 222.0893 ($C_{12}H_{14}O_4$ requires 222.0892), 144, 102, and 43. Metastable peaks for 222 → 144 and 144 → 102 were observed. The molecular weight measured by vapor-pressure osmometry was 454. The nmr spectrum in $CDCl_3$ showed 2 H (approximate triplet) at δ 6.4, 2 H (broad singlet) at 5.7, 4 H (multiplet) at 4.6–5.1, and 20 H at 1.8–3.2, including 9 H (broad singlet) at 2.05 and 3 H at 2.1. No uv absorption attributable to a conjugated diene was observed.

Quantitative photochemical experiments were performed in 13-mm Pyrex ampoules. The tubes were necked down for sealoff

(18) A. C. Cope, N. A. Nelson, and D. A. Smith, *J. Amer. Chem. Soc.*, **76**, 1100 (1954).

(19) R. Anet, *Tetrahedron Lett.*, 720 (1961).

under vacuum and connected through grease traps to 14/35 joints, which could then be connected to a vacuum manifold through a cow. Reaction mixtures, containing a known amount of purified dodecane, were added to the sample tube *via* a calibrated syringe, and the samples were subjected to five freeze–thaw outgassing cycles on the vacuum manifold at an ultimate pressure of about 10^{-4} mm. After sealoff, the tubes were irradiated for the desired period of time in a "merry-go-round" rotating sample stage apparatus, with a Hanovia 450-W medium-pressure mercury lamp whose output was filtered (Corning C.S. Number 7-83) to pass only the 3660-Å region.

Actinometry was carried out with potassium ferrioxalate in the standard manner.[20] Reproducibility of quadruplicate (or more) samples throughout the period of a run was ±2% in general and often ±0.5%.

(20) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1960, p 785.

Yields of **2** and **3** measured gas chromatographically relative to dodecane were corrected for differences in detector response. Analyses were performed on 0.25 in. × 6 ft Carbowax 20M columns, 5–10% on either Chromosorb P or Chromosorb W. It was shown that both isomers were stable to the analysis conditions and that **1** did not give **2** and **3** by pyrolysis during analysis.

Registry No.—**1**, 7698-06-8; **2**, 19191-10-7; **3**, 19191-11-8.

Acknowledgment.—I wish to thank Research Corporation for funds used for the purchase of a gas chromatograph, the Petroleum Research Fund for support of this work through Grants 519-G-1 and 3031-A-4, Mr. G. W. Sovocool for assistance with actinometry, and Dr. Stephen Shrader for mass spectrometric analyses and helpful discussions.

Homogeneous Catalytic Deuteration of Olefinic Double Bonds[1]

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The specific deuteration of olefins using tris(triphenylphosphine)rhodium(I) chloride (A) as a homogeneous catalyst has been investigated. Seventeen *n*-monoolefins were deuterated and the distribution and the vicinal positions of the deuterium atoms were located by mass spectrometry. Deuterium adds specifically across the double bonds in *n*-monoolefins and the reaction proceeds to completion in a reasonable time. The mass spectral fragmentation patterns for the deuterioalkanes formed by this specific labeling technique can be used to locate the deuterium atoms and thus to determine the position of the double bond in the original olefin.

For some time, we have been interested in the location of double bonds in olefins for characterization of olefin fractions of shale-oil distillates. About one-third of Green River shale-oil middle distillate (C_{12}–C_{20}) consists of olefins. Knowledge about the type of olefins and the positions of the double bonds in the olefins would be an aid in their utilization.

Young and coworkers[2a] have demonstrated the connection between the formation of a hydride intermediate and homogeneous hydrogenation by using a new compound, tris(triphenylphosphine)rhodium(I) chloride (A). They state that the compound can be used as a catalyst for the reduction of compounds containing double or triple bonds. In a later article, Osborn and coworkers[2b] studied the properties and reactions of A and proposed a mechanism for the hydrogenation of olefins and acetylenes. Birch and Walker[3,4] used A as a homogeneous catalyst for hydrogenation and deuteration. They found that cyclohexene, methyl oleate, methyl linoleate, and ergosterol were deuterated without introduction of additional deuterium. Djerassi[5] and Bielmann[6] have used A as a homogeneous catalyst for the deuteration of steroids, and Zeeh[7] used this homogeneous catalyst to deuterate hydrindanones.

This homogeneous catalytic research is of interest because the heterogeneous, catalytic deuteration of straight-chain olefins is an unsatisfactory method for the selective introduction of deuterium.[8] Heterogeneous catalysts cause double-bond migration and/or exchange reactions between the chemisorbed olefin and the adsorbed deuterium resulting in unspecific labeling.[9,10] For example, Nguyen and Ryhage[11] reported the deuteration of methyl oleate using Adam's platinum catalyst. Their mass spectral results showed a series of molecular ion peaks whose intensities decrease with increasing mass number, due to unspecific labeling.

This paper reports the specific deuteration of 17 *n*-monoolefins using deuterium and A as a homogeneous catalyst. Mass spectrometry was used to determine the location of the deuterium in the alkanes formed.

Monoolefins are readily deuterated using deuterium and A as a homogeneous catalyst to give the corresponding dideuterioalkanes. For example, 1-tridecene was deuterated without difficulty in less than 2 hr at room temperature and slightly above atmospheric pressure. Examination of the mass spectra of the deuterated tridecane showed the addition of two deuteriums to the monoolefin with little evidence of unspecific labeling.

When a heterogeneous catalyst, such as platinum black, was used for the deuteration of 1-tridecene,

(1) Presented at the Midwest Regional Meeting of the American Chemical Society, Manhattan, Kan., Oct 31–Nov 1, 1968.

(2) (a) J. F. Young, J. A. Osborn, J. H. Jardine, and G. Wilkinson, *Chem. Commun.*, No. 7, 131 (1965); (b) J. A. Osborn, J. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc., A*, 1711 (1966).

(3) A. J. Birch and K. A. M. Walker, *J. Chem. Soc., C*, 1894 (1966).

(4) A. J. Birch and K. A. M. Walker, *Tetrahedron Lett.*, 4939 (1966).

(5) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966).

(6) J. F. Bielmann and H. Liesenfelt, *Bull. Soc. Chim. Fr.*, 4029 (1966).

(7) B. Zeeh, G. Jones, and C. Djerassi, *Chem. Ber.*, **100**, 3204 (1967).

(8) H. Budzikiewiez, C. Djerassi, D. H. Williams, "Structural Elucidation of Natural Products by Mass Spectrometry. I. Alkaloids," Holden-Day Inc., San Francisco, Calif., 1964, Chapter 2.

(9) T. I. Taylor in "Catalysis," Vol. 5, P. H. Emmett, Ed., Reinhold Publishing Corp., New York, N. Y., 1957, Chapter 5.

(10) G. V. Smith and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **84**, 925 (1962).

(11) N. Dinh Nguyen and R. Ryhage, *Acta Chem. Scand.*, **13**, 1032 (1959).

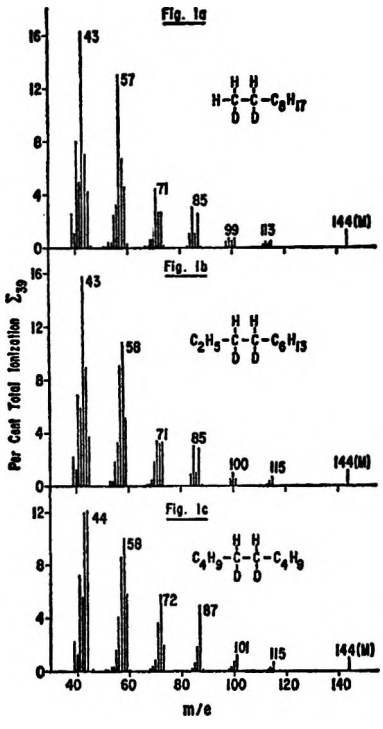

Figure 1.—Mass spectra of vicinal dideuteriodecanes: (a) decane-1,2-d_2, (b) decane-3,4-d_2, and (c) decane-5,6-d_2.

unspecific labeling occurred. Mass spectrometry showed the product to contain from zero to as many as 17 deuterium atoms per molecule.

Some of the olefins deuterated using the tris(triphenylphosphine)rhodium(I) chloride catalyst are as follows: *cis*-2-decene, *trans*-2-decene, *cis*-3-decene, *cis*-4-decene, *cis*-5-decene, *trans*-5-decene, and all the α olefins from decene through eicosene inclusively. In each case, the corresponding dideuterioalkane was the product obtained.

The ability to locate the position of the double bonds in olefins requires that two deuteriums per double bond be added and that the deuterium add specifically to each carbon atom originally joined by the double bond. Mass spectrometry showed that two deuterium atoms per double bond were added when the homogeneous catalyst A was used.

That the deuterium adds specifically to the carbon atoms originally joined by the double bond can be shown by examination of the mass spectra of selected, deuterated decenes. Figure 1 shows the mass spectra of the products from the homogeneous deuteration of 1-decene, *cis*-3-decene, and *cis*-5-decene. If the deuterium adds specifically to the double bond in each of these decenes, these are the spectra of decane-1,2-d_2, decane-3,4-d_2, and decane-5,6-d_2, respectively. This will be demonstrated later.

For correlation of the mass spectra of these vicinal dideuterio-*n*-alkanes with their structure, we will assume that fragment ions are formed by simple carbon–carbon bond cleavage of the parent ion. Using this assumption, the fragmentation peaks expected from the three selected deuterated decanes are as follows: for decane-1,2-d_2 (C_8) 113, 115, (C_7) 99, 101, (C_6) 85, 87, (C_5) 71, 73, (C_4) 57, 59, (C_3) 43, 45; for decane-3,4-d_2 (C_8) 115, (C_7) 100, 101, (C_6) 85, 87, (C_5) 71, 73, (C_4) 57, 59, (C_3) 43, 44; for decane-5,6-d_2 (C_8) 115, (C_7) 101, (C_6) 87, (C_5) 72, (C_4) 57, (C_3) 43.

Comparison of the peaks shown in Figure 1 with the expected peaks listed above shows the assumptions to be correct for some regions of the mass spectra. For example, in the spectra of the deuterated products, the fragment peaks having six, seven and eight carbon atoms, shown in Figure 1, occur where the above list predicts they should. Also, they occur either singly or in pairs just as the assumption of simple carbon–carbon bond cleavage would predict. Thus the C_6 ions for decane-1,2-d_2 and for decane-3,4-d_2 occur equally at *m/e* 85 and *m/e* 87, whereas the C_6 ions for decane-5,6-d_2 occur only at *m/e* 87. Similar observations and conclusions are possible for the fragments occurring at the C_7 and C_8 regions in these three spectra. Because cleavage should occur from either end of the molecule with equal ease, peaks such as 100 and 101 in Figure 1b should be of equal size. Examination of the Figure 1b shows that this is not the case. The fragment ion peak from the decane-3,4-d_2 having a mass of 101 has as its source the fragment produced by cleavage between the 7 and the 8 carbon atoms. The fragment ion peak of mass 100 has two sources: the fragment produced by cleavage between the 3 and 4 carbon atoms and the fragment produced from the 101 fragment ion by hydrogen loss. Therefore, the peak at *m/e* 100 is larger than the peak at *m/e* 101. The peak at *m/e* 99 is produced by hydrogen loss from the fragment ion of mass 100. Hydrogen loss from the major fragment peaks accounts for peaks such as those at *m/e* 84, 86, 98, 100, 112, and 114 in Figure 1a, and peaks 84, 86, 99, part of 100, and 114 in Figure 1b, etc. Peaks produced by hydrogen loss occur in the mass spectra of alkanes. For example, in the mass spectra of *n*-decane, simple carbon–carbon bond cleavage accounts for the peak at *m/e* 113, 99, etc., but the peaks at *m/e* 112 and 98, etc., are produced from the 113 and 99 fragment ions, respectively, by hydrogen loss. Although, for the fragment ions with five or less carbons, the ratios of fragment ion peaks cannot be predicted by simple carbon–carbon bond cleavage, the fragment ion having more than half the carbon atoms (C_6–C_8 fragment ions) are sufficient to locate the deuterium atoms.

The conclusiveness of the data for locating the deuterium atoms for the other deuterated alkanes prepared is as positive as that shown for the three dideuteriodecanes whose spectra are shown in Figure 1.

Additional evidence for the specificity of the deuteration reaction when using the homogeneous catalyst A can be obtained from the nmr spectra of the deuterated alkanes. Calculations made from the nmr spectra of the decane-1,2-d_2 showed the presence of only five methyl hydrogens indicating that one of the deuteriums was located on one of the terminal carbon atoms. Similar calculations made on the spectra of decane-2,3-d_2, decane-3,4-d_2, and decane-4,5-d_2 showed the presence of six methyl hydrogens indicating no deuteriums present on the terminal carbon atoms.

Examination of the relative rates of the reaction of the *cis* and the *trans* olefins should suggest a possible mechanism for homogeneous catalytic reduction. That a faster reaction rate was observed for the *cis* olefin

suggests that the rate-determining step may be the formation of the olefin complex as suggested by Osborn.[2b] He proposed that the initial step is the formation of $RhCl(PPh_3)_2H_2$ (solvent), displacement of the solvent by the olefin, and stereospecific *cis* transfer of the bound hydrogen to the olefin in an actual intermediate or in an activated complex.[12] He postulated that the rate-determining step in the reaction is the displacement of the solvent from the complex and the complexing of the olefin. If the olefin in the complex occupies a position *cis* to both rhodium–hydrogen bonds as Osborn suggests we suggest that the *trans*-olefins probably do not form the complex as readily as the *cis* isomers. We suggest that the formation of the complex with the *trans* olefins is slower because of the orientation of the bulky groups of the *trans* isomers and possibly a suitable alignment of these groups with respect to the double bond may be necessary to form the complex.

The specific labeling of the double-bonded carbons of olefins is a potentially useful device in an analytical scheme for characterizing mixtures of olefins. Present indications are that mass spectra of the alkane-d_2 compounds reflect the location of the deuterium atoms so that characterization of single compounds or simple mixtures is possible. Work is proceeding on the development of a method for the analysis of olefins using homogeneous deuteration and mass spectrometry.

Experimental Section

The deuteration equipment was similar to the hydrogenation apparatus described by Joshel.[13] A Teflon-coated[14] magnet driven by an external motor was used as a stirrer. The reaction flask was equipped with a side arm that was fitted with a silicone-rubber plug which enabled the withdrawal of samples with a syringe during deuteration.

Gas chromatographic separations were performed on an Aerograph Autoprep Model A-700 instrument using a 0.25 in. × 30 ft column of 15% Tween 20 on Chromosorb P. All mass spectra of the deuterioalkanes were obtained on a Consolidated Electrodynamics Model 21-103 mass spectrometer at an ionization voltage of 70 eV. Nuclear magnetic resonance spectra on selected deuterioalkanes were obtained on a Varian HA-100.

The homogeneous catalyst tris(triphenylphosphine)rhodium(I) chloride was prepared from rhodium chloride trihydrate and triphenylphosphine as described by Young.[2a] The deuterium used at first was 98 mol %, but later deuterations were performed using 99.5 mol % deuterium. The olefins were of 98% or better purity as determined by gas–liquid partition chromatography.

The heterogeneous catalysts such as platinum black and palladium were prepared from chloroplatinic acid and palladium chloride, respectively, by reduction with sodium borohydride in the reaction flask just prior to use.

About 0.40 g of the olefin was weighed into the reaction flask and diluted with 20 ml of benzene. Catalyst A was added in the amount of 15 wt % of the olefin to be reduced. The deuteration apparatus was connected to a manifold and the system was alternately evacuated and filled four times with deuterium gas, at which time the magnetic stirrer was turned on. Pressure was maintained at slightly above atmospheric pressure (positive pressure of about 10 mm).[15] The deuteration was monitored periodically by withdrawing a small sample of the solution with a syringe and analyzing the solution by gas–liquid partition chromatography. The heterogeneous catalytic deuteration was performed using similar conditions as the homogeneous catalytic deuteration.

Registry No.—Decane-1,2-d_2, 19165-56-1; decane-3,4-d_2, 19165-57-2; decane-5,6-d_2, 19165-58-3; tris(triphenylphosphine)rhodium(I) chloride, 14694-95-2.

Acknowledgment.—The work upon which this report is based was done under a cooperative agreement between the Bureau of Mines, U. S. Department of the Interior, and the University of Wyoming.

(12) J. F. Bielmann and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968)
(13) L. M. Joshel, *Ind. Eng. Chem.*, **15**, 590 (1943).
(14) References to trade names are made for information only and do not imply endorsement by the Bureau of Mines.
(15) Atmospheric pressure at this altitude is approximately 585 mm.

Ozonolysis. Steric Effects in the Aldehyde

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The ozonolysis of 1-olefins results in little or no cross-ozonide formation. Ozonolysis of 3,3-dimethylbutene-1 in the presence of added aldehydes with varying substituent size indicates that both aldehyde substituent size and concentration have a pronounced effect on the ozonide *cis–trans* ratio in the new ozonide produced. Larger substituent size and lower aldehyde concentration lead to a higher percentage *cis*-ozonide. The effect of substituent size on the ozonide *cis–trans* ratio is essentially the same whether the substituent is located in the olefin or the aldehyde.

A number of experimental facts which suggest that some modification to the Criegee[2] mechanism of ozonolysis should be considered have now been reported. Perhaps the most striking of these observations is the dependence of cross-ozonide *cis–trans* ratios on olefin stereochemistry.[3–6] These observations have stimulated several new suggestions regarding the mechanism. One, in the form of a working hypothesis, has as its

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(2) R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957).
(3) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *J. Amer. Chem. Soc.*, **88**, 3143 (1966).
(4) F. L. Greenwood, *ibid.*, **88**, 3146 (1966).
(5) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *ibid.*, **89**, 2429 (1967).
(6) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *ibid.*, **90**, 1822 (1968).

TABLE I

SUMMARY OF OZONIDE EXPERIMENTAL DATA

Ozonide	Yield, %	Calcd, % C	Calcd, % H	Calcd, % O	Found, % C	Found, % H	Found, % O	Solvent	Nmr, τ (multiplicity)[a]	Wt ratio
4-Methylpentene	80	54.53	9.15	36.32	54.26	9.00	36.69	CCl_4	4.87 (s), 4.91 (t), 5.05 (s), 7.90–8.60 (m), 9.04 (d)	1:1:1:3:6
Hexene-1	78	54.53	9.15	36.32	54.67	9.02	36.16	C_6H_6	4.97 (t), 5.15 (s), 5.25 (s), 8.32–8.9 (m), 9.2 (t)	1:1:1:6:3
3-Methylbutene-1	92							CCl_4	4.88 (s), 5.04 (s), 5.19 (s), 7.9–8.6 (m), 9.03 (d)	1:1:1:1:6
Butene-1	85							CCl_4	4.90 (s), 4.97 (t), 5.04 (s), 8.0–8.6 (m), 9.07 (t)	1:1:1:2:3
3,3-Dimethylbutene-1	88	*b*						CCl_4	4.85 (s), 5.09 (s), 5.30 (s), 9.07 (s)	1:1:1:9

[a] τ values are relative to external tetramethylsilane. Abbreviations used are s, singlet; d, doublet; t, triplet, m, multiplet. [b] R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).

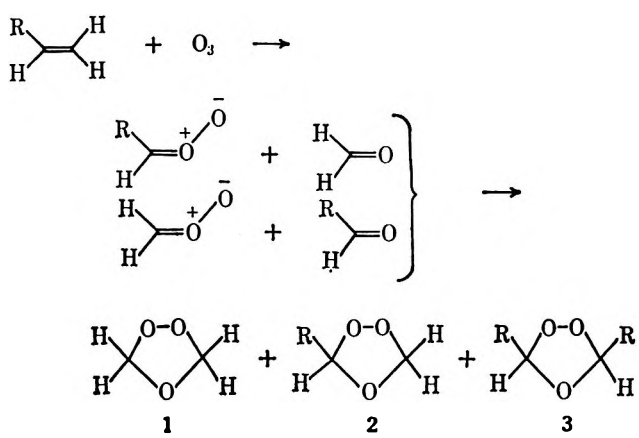
basis the proposal that there may be a competing path to ozonide formation which involves direct interaction of aldehyde and molozonide.[5,7] Some support for this proposal has been obtained in one case by means of an ^{18}O tracer technique.[8] Application of a similar technique in another case was interpreted to indicate predominance of the Criegee mechanism or perhaps a modified version of the molozonide–aldehyde mechanism.[9] Finally, a modified version of the Criegee mechanism has been suggested[6] the essence of which is that initial ozonides may stereoselectively decompose to give mixtures of *syn* and *anti* zwitterions which then stereoselectively recombine with aldehydes to give the final ozonides.

All of the various mechanistic pathways which have been proposed have in common the reaction of an aldehyde with some other species whether it be the molozonide, zwitterion, or a mixture of *syn* and *anti* zwitterions. Because of this essential nature of the aldehyde to all of the mechanistic proposals we decided to study the effect of aldehyde substituent size on ozonide *cis–trans* ratio. That is, we would hopefully determine what specific demands, if any, the aldehyde brings to the ozonide-forming reaction. The observation of ozonide *cis–trans* ratios and the dependence of these ratios on various reaction conditions has been amply demonstrated as an important probe with which to study the mechanism.

The desired results were obtained by ozonizing a 1-olefin in the presence of a series of aldehydes in which the substitutent size was varied. The ozonide *cis–trans* ratios in the new ozonides produced were then examined. The ozonide *cis–trans* ratios produced in this manner are the result of various aldehydes reacting with the same precursor to ozonide formation, whatever that precursor or precursors may be.

In addition to examining steric effects in the aldehyde we have, as an outgrowth of this work, also begun a corollary study of the ozonolysis of 1-olefins with emphasis on the mechanistic consequences of the results. As shown in Table I these 1-olefins give high yields of ozonides. In this respect they are like *cis*-olefins and unlike *trans*-olefins.[5,6] Also, the ozonolysis of 1-olefins leads to little or no cross-ozonide formation. Formally, at least, these ozonolyses ought to give two zwitterions and two aldehydes which upon random combination ought to give three ozonides, namely, ethylene ozonide, **1**, the parent olefin ozonide, **2**, and a third symmetrical ozonide, **3** (Scheme I).

SCHEME I



Obviously other factors must be superimposed on this simple scheme. Thus it may be that the 1-olefin does not cleave in a statistical manner, but that formation of formaldehyde, for example, is highly favored. While, in the case of styrene, the reported[10–13a] data indicate about a 50/50 split between the possible modes of decomposition of the molozonide, little quantitative data is available for other 1-olefins. In addition the methods used to assay the direction of split are complicated by the possibility of bimolecular reaction between reactive solvent and molozonide as opposed to the generally assumed reaction between reactive solvent and zwitterion, with the latter formed as a result of prior decomposition of the molozonide.

Vrbaski and Cvetanovic[13b] have reported the formation of small amounts (10% of the main ozonide) of ethylene ozonide in the ozonolysis of isobutene and 1-butene at −78° in ethyl chloride. It may be that in this more polar solvent the direction of initial adduct cleavage is altered somewhat.

(7) P. R. Story, R. W. Murray, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **88**, 3144, (1966).

(8) P. R. Story, C. E. Bishop, J. R. Burgess, R. W. Murray, and R. D. Youssefyeh, *ibid.*, **90**, 1907 (1968).

(9) S. Fliszar, J. Carles, and J. Renard, *ibid.*, **90**, 1364 (1968).

(10) S. Fliszar, *Can. J. Chem.*, **44**, 2351 (1966).

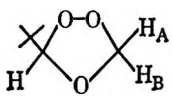
(11) W. P. Keaveney, M. G. Berger, and J. J. Pappas, *J. Org. Chem.*, **32**, 1537 (1967).

(12) E. Briner, S. Fliszar, and M. Ricca, *Helv. Chim. Acta*, **42**, 749 (1959).

(13) (a) E. Briner, C. Christol, S. Fliszar, and G. Rossetti, *ibid.*, **46**, 2249 (1963); (b) T. Vrbaski and R. J. Cvetanovic, *Can. J. Chem.*, **38**, 1063 (1960).

Nevertheless, our results in the case of 3,3-dimethyl-1-butene for example, indicate that even when ozonolysis is carried out at fairly high olefin concentration (2.0 *M*), the ratio of parent ozonide to the cross-ozonide, di-*t*-butylozonide, is at least 20/1. The other expected cross-ozonide, ethylene ozonide, would probably not survive even the mild glpc conditions used.

Two other aspects of the 1-olefin ozonolysis work are worth mentioning before going on to consider the results obtained with added aldehyde. The nmr spectra of the resultant ozonides (Table I) indicate that the ring methylene protons, H_A and H_B, as in 3,3-dimethyl-1-butene ozonide (**4**), for example, appear as separate singlets. That is, these geminal protons have a coupling constant, $J \cong 0$ Hz. This is consistent with similar observations in 1,3-dioxolans where it has been found that introduction of the oxygen atoms increased the value of J from a large negative value in cyclopentane to values close to 0 for 1,3-dioxolan itself.[14]

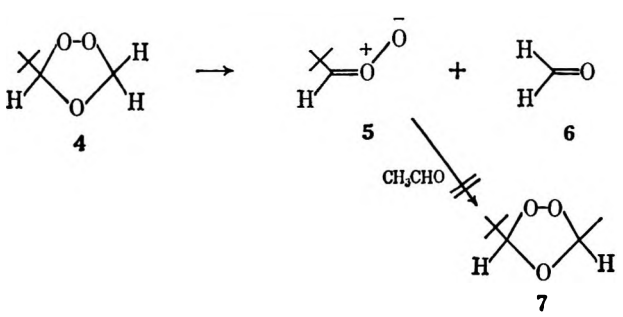


4

This same ozonide, **4**, was found to be relatively unstable. It slowly decomposed upon standing overnight at room temperature whereas all of the other ozonides involved in this work were completely stable under these conditions. In fact there are not many cases known where an ozonide has been isolated and subsequently found to decompose at room temperature. One other such case is that of 2,3,3-trimethylbutene-1 ozonide reported by Criegee, Kerckow, and Zinke.[15] These two examples suggest that, at least in the case of 1-olefins, the instability may be due to steric crowding on one side of the ozonide ring.

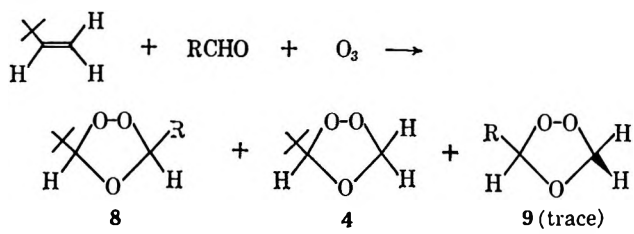
We have attempted to take advantage of this decomposition behavior to test for the possibility of reversible ozonide formation. Thus if **4** were to decompose into fragments **5** and **6** which presumably represent one of the two possible combinations leading to its formation, then it ought to be possible to intercept zwitterion **5** by adding an excess of a different aldehyde (Scheme II).

SCHEME II



We have tested this possibility by storing pure ozonide **4** in the presence of a threefold excess of acetaldehyde. While considerable decomposition of **4** occurred over a 24-hr period, no evidence for 4,4-dimethylpentene-2 ozonide (**7**) or any other new ozonide, could be found using glpc analysis. There are numerous instances now reported where an added aldehyde is allegedly reacting with a zwitterion intermediate to give a new ozonide incorporating the aldehyde. The results found here would seem to indicate, therefore, that the decomposition of **4** does not involve production of zwitterion **5** or of the other possible zwitterion, namely, formaldehyde carbonyl oxide.

Added Aldehyde Experiments.—The results of adding various aldehydes to the ozonolysis of 3,3-dimethylbutene-1 are shown in Figure 1. The aldehydes were also added in different concentrations which provided a separate aldehyde concentration effect result. In each case the ozonide of 3,3-dimethylbutene-1 is formed along with a new ozonide, **8**, which incorporates the added aldehyde. While, theoretically, there are two such new ozonides possible, only one is formed in appreciable yield. This one is that which formally is the adduct between the added aldehyde and pivalaldehyde carbonyl oxide. The other predicted ozonide, **9**, which represents the adduct between the added aldehyde and formaldehyde carbonyl oxide is present in a glpc detectable amount, but is estimated to be formed in less than one-tenth of the amount of **8**. As with the earlier



observation that 1-olefins give little or no cross-ozonides, this result again suggests that the direction of cleavage of the initial olefin–ozone adduct is heavily in favor of the path which leads to formaldehyde and pivalaldehyde carbonyl oxide. This point will be examined further in a separate study.

Ozonides **8** can exist as *cis–trans* pairs and should reflect the sensitivity of ozonide precursor to steric effects in the added aldehyde. As shown in Figure 1 there is indeed a pronounced and regular sensitivity to steric bulk in the aldehyde. As the size of the aldehyde substituent is increased from ethyl to isopropyl to *t*-butyl, the percentage of *cis*-ozonide in ozonide **8** increases sharply. Since the nonaldehyde reacting partner in all of these cases is the same, the stereochemical effects transmitted to ozonide **8** must be due to the aldehyde. These results indicate that proposals for the mechanism must give adequate weight to requirements in the aldehyde.

The ozonide-producing reaction is also sensitive to the concentration of the added aldehyde. Above an aldehyde concentration of approximately 1.0 *M* the *cis–trans* ratio produced in ozonide **8** is constant. Below this aldehyde concentration the *cis–trans* ratio is very sensitive to aldehyde concentration and is altered drastically in favor of more *cis*-ozonide at low added aldehyde concentrations. The effect is so pronounced that in the case of added pivalaldehyde ozonide **8** produced is almost completely the *cis* isomer at 0.125 *M* added aldehyde concentration (Figure 1).

In order to study further the effect of steric bulk on

(14) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron Suppl.*, No. 7, 355 (1966).

(15) See Table I, footnote *b*.

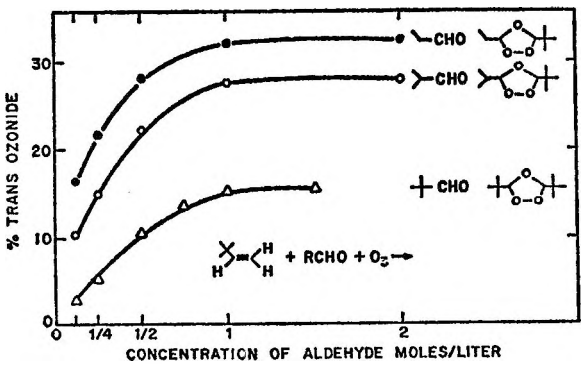


Figure 1.—The percentage of *trans*-ozonide obtained as a function of added aldehyde concentration in the ozonolysis of 3,3-dimethylbutene-1.

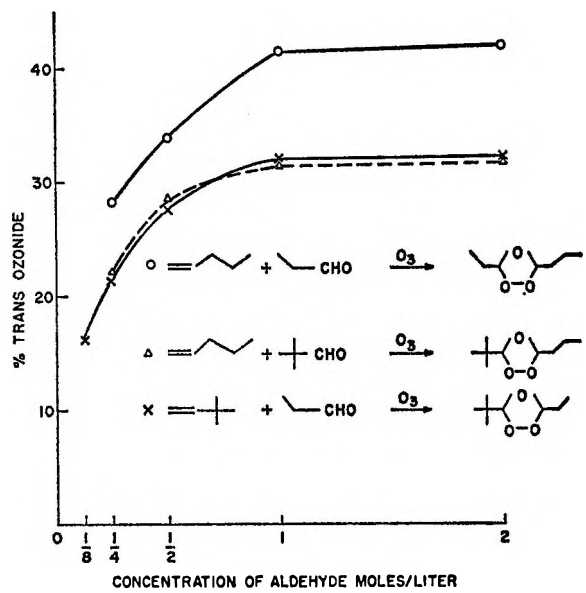


Figure 2.—The percentage of *trans*-ozonide obtained as a function of added aldehyde concentration in the ozonolysis of 3,3-dimethylbutene-1 and pentene-1.

the *cis–trans* ratio in ozonide **8** we have attempted to determine whether the steric effect is felt the same way depending upon whether the same steric requirement is present in either the olefin or the aldehyde. Thus pentene-1 was ozonized in the presence of added pivalaldehyde so that the *cis–trans* ratio in the new ozonide produced, **10**, could be compared with that in ozonide **8** in the case of the ozonolysis of 3,3-dimethylbutene-1 in the presence of propionaldehyde. In addition pentene-1 was also ozonized in the presence of propionaldehyde to determine whether this olefin reffected a sensitivity to aldehyde steric requirements comparable to that already seen in 3,3-dimethylbutene-1. The results of these experiments are shown in Figure 2. As seen in the uppermost curve pentene-1 does respond to aldehyde steric effects as reflected in the *cis–trans* ratio in the ozonide formed by diversion of intermediate by propionaldehyde. In this case the constant ozonide *cis–trans* ratio achieved has the expected higher percentage *trans*-ozonide presumably because of an over-all reduced steric requirement.

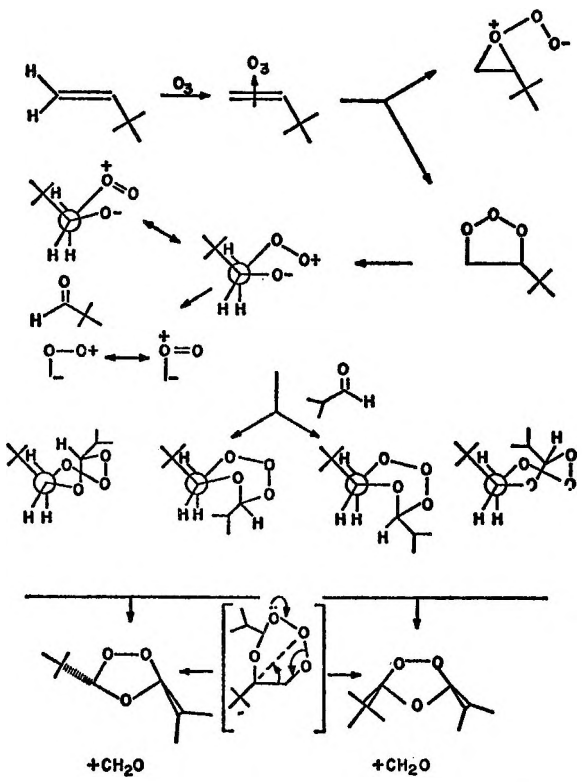


Figure 3.—Schematic of possible mechanism of ozonide formation for 3,3-dimethylbutene-1 with added aldehydes.

The remaining two curves in Figure 2 demonstrate a rather remarkable result. As reflected in the ozonide *cis–trans* ratios produced, the ozonide-forming process demonstrates exactly the same sensitivity to steric bulk *whether that bulk is present in the olefin or the aldehyde*, and this observation is true over a wide range of aldehyde concentrations.

The results in Figures 1 and 2 indicate a regular and significant effect of aldehyde substituent size on ozonide *cis–trans* ratio. The meaning of these results in terms of the mechanism problem is still not completely clear. In a general way the results appear to be somewhat consistent with the mechanistic proposals made earlier[5,7] in which it is suggested that aldehyde may react with molozonide to provide another path to ozonide formation. An application of this approach to the reaction of added aldehydes with 3,3-dimethylbutene-1 is shown schematically in Figure 3 with isobutyraldehyde used for illustration. A detailed analysis of the operation of this scheme will not be given here since it has been discussed earlier.[5,7,16] The scheme does predict that *cis*-ozonide would be formed preferentially in this pathway since only a precursor to *cis*-ozonide suffers only H–H nonbonded repulsions. Other precursors have somewhat less desirable steric interactions. Likewise this preference for *cis*-ozonide should be enhanced as the substituent size in the aldehyde is increased.

Results of a similar application of the molozonide–aldehyde pathway scheme to the case where the probing substituent can be either in the olefin or the aldehyde are shown in Figure 4. Here again the scheme predicts

(16) R. W. Murray, *Trans. N. Y. Acad. Sci.*, **29**, 854 (1967).

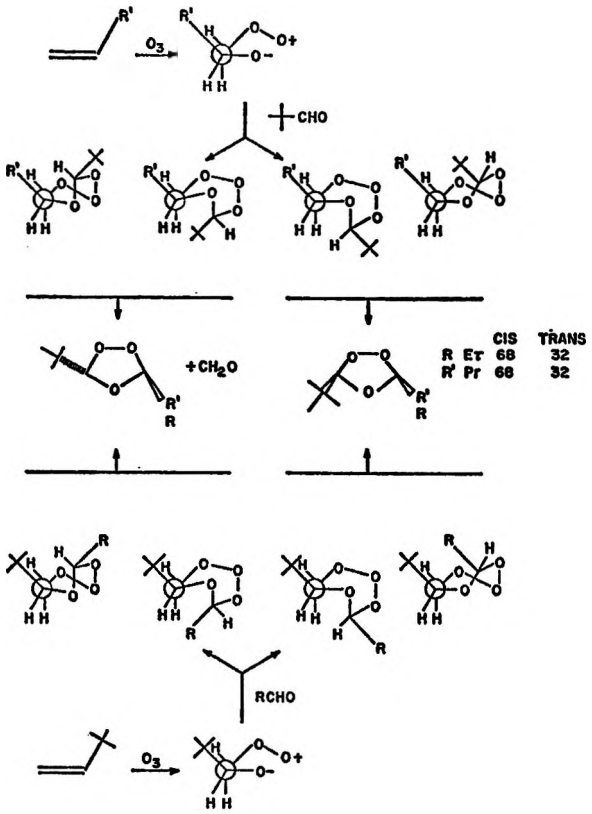


Figure 4.—Schematic showing influence of substituent size in olefin and aldehyde on ozonide formation.

a predominance of *cis*-ozonide. More importantly such a mechanistic path would seem to permit substituent bulk to have a similar influence on ozonide *cis–trans* ratio whether it is located in the olefin or the aldehyde, in keeping with the experimental results.

Interpretation of the aldehyde concentration dependence results is even more difficult—the shapes of the curves in Figures 1 and 2 suggest that what may be happening is that at higher aldehyde concentrations a shorter lived ozonide precursor may be intercepted to give a particular ozonide *cis–trans* ratio. When the aldehyde concentration is sufficiently high this path might be expected to dominate so a constant ozonide *cis–trans* ratio would be produced. The lower aldehyde concentrations would then represent a transition period in which another path which gives a different ozonide *cis–trans* ratio is still influencing the final ozonide *cis–trans* ratio. This other path could be the zwitterion–aldehyde path or some other path.

The results may also be consistent with the modified Criegee mechanism recently suggested by Bailey, *et al.*[16] Thus larger substituents might be expected to lead to more *anti* zwitterion and therefore, according to this scheme, more *cis*-ozonide.

At this point these attempts to provide a mechanistic explanation of the results are meant to be purely speculative. The results themselves are striking and in our opinion are important to those interested in stereochemical control in the ozonolysis reaction. Final resolution of the mechanism problem involved will probably require use of one of the labeling techniques recently described.[8,9]

Experimental Section

Procedures and Equipment.—A Welsbach Model T-23 ozonator was used as a source of ozone. The sample stream output of the ozonator was used with ozone delivery of 0.4 mmol of O_3/min. All ozonolyses were carried out to 75% of theory, in pentane solvent (total volume 25 ml), and at −70°. The reaction mixtures were analyzed by glpc on a Varian-Aerograph Model 700 gas chromatograph. In most cases a 10 ft 10% XE-60 cyanosilicone column was used. Maximum column temperature was 50° and maximum detector temperature was 88°. Direct on column injection was used. Quantitative data were obtained with an Aerograph Model 471 digital integrator. The ozonide *cis–trans* ratios reported are the result of an least five separate integrations of the glpc peak areas. The integrations were done on samples which were determined to be pure by nmr. Yields were obtained by calibrating glpc peak areas using pure samples and under conditions where no ozonide decomposition was detectable. A summary of yield, analytical data, and nmr data is given in Table I. Nmr spectra were run on a Varian A-60 high resolution nmr spectrometer.

In the added aldehyde experiments the olefin was present in 0.5 *M* concentration. The aldehyde concentration varied as shown in Figure 1. In the pure olefin runs the olefin concentration was 1.0 *M*, except as otherwise noted.

The assignment of ozonide *cis* and *trans* configurations was based on glpc, infrared, and nmr data and the correlation of these data with the unequivocal assignment made in the case of diisopropylozonide.[17] Elemental analyses are by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377.

Materials.—All olefins (Chemical Samples Co.) were at least 99% pure. All aldehydes were distilled immediately before use.

Ozonolysis of 3,3-Dimethylbutene-1.—Solutions of the olefin up to 2.0 *M* were ozonized according to the general procedure given above. Even at the highest concentration used there was insufficient cross-ozonide produced to permit their glpc peak areas to be integrated. It is estimated that a ratio of cross-ozonide to normal ozonide of 1/20 would have permitted this integration.

The normal ozonide was somewhat unstable. In order to collect a pure sample, glpc column and detector temperatures of 40 and 60°, respectively, had to be used. Pure ozonide deposited a white solid upon standing overnight. This material was not further identified.

When a solution of this ozonide in pentane was stored with a threefold excess of acetaldehyde at room temperature for 24 hr, no 2,2-dimethylpentene-3 ozonide was formed as determined by glpc. Thus the decomposition of 1-olefin ozonide was probably not occurring through the free pivalaldehyde carbonyl oxide.

Ozonolysis of 1-Olefins with Added Aldehyde.—The general procedure given above was followed using varying concentrations of propionaldehyde, isobutyraldehyde, and pivalaldehyde with 3,3-dimethylbutene-1, and varying concentrations of propionaldehyde and pivalaldehyde with pentene-1. The results are shown in Figures 1 and 2. Yields of the new ozonide incorporating the added aldehyde and pivalaldehyde carbonyl oxide were generally about one-third those of the 1-olefin ozonide. Only trace quantities of the other possible ozonide expected in the presence of added aldehyde, that is, the ozonide incorporating the added aldehyde and formaldehyde carbonyl oxide, could be detected.

Registry No.—4-Methylpentene-1, 691-37-2; ozonide of 4-methylpentene-1, 18963-59-2; 1-hexene, 592-41-6; ozonide of 1-hexene, 767-09-9; 3-methylbutene-1, 563-45-1; ozonide of 3-methylbutene-1, 18963-61-6; 1-butene, 106-98-9; ozonide of 1-butene, 18963-62-7; 3,3-dimethylbutene-1, 558-37-2; **4**, 18963-63-8.

(17) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *J. Amer. Chem. Soc.*, **88**, 3655 (1966).

The Ozonolysis of Deuterium-Labeled 1-Olefins

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The ozonolysis of either *cis*- or *trans*-1-deuteriohexene-1 gives a 50/50 mixture of *cis*- and *trans*-1-deuteriohexene-1 ozonide. Ozonolysis of 1,1-dideuteriohexene-1 in the presence of a fivefold excess of formaldehyde leads to only 39% incorporation of the formaldehyde in the hexene-1 ozonide. Ozonolysis of an equimolar mixture of 1,1-dideuteriohexene-1 and heptene-1 leads to hexene-1 and heptene-1 ozonides containing 80.3 and 27% dideuterio ozonide, respectively.

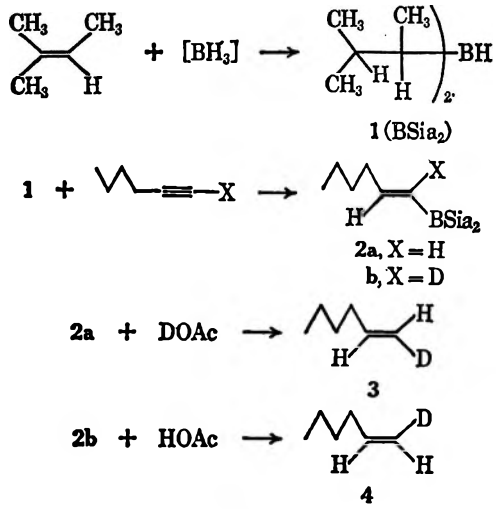
As part of our over-all approach to the problem of the mechanism of ozonolysis we have begun a study of the behavior of 1-olefins in this reaction.[2] These 1-olefin ozonolyses are characterized by a high yield of ozonide in monosubstituted cases,[2] little or no cross-ozonide formation,[2] and, when appropriately substituted, the formation of high yields of epoxides or other products derived from partial cleavage of the double bond.[3-6] Bailey and Lane[5] have shown that the competition between partial and complete cleavage of the double bond is quite sensitive to the size of the olefin substituents.

The formation of high yields of ozonides by monosubstituted 1-olefins is reminiscent of the behavior found in *cis*-olefins and contrasts with that observed in *trans*-olefins.[6,7] It has also been observed that the high yield of ozonide in the case of *cis*-olefins may be accompanied by a predominance of *cis*-ozonide and that this stereoselectivity is more pronounced as substituent size increases.[6,7] It was of interest, therefore, to devise a means of studying the stereochemistry of the olefin to ozonide conversion in the case of a 1-olefin which gave a high yield of ozonide.

This goal was achieved by suitably substituting an olefin with deuterium and then following the stereochemical course of the reaction by means of nmr. The required olefins were synthesized through the use of the hydroboration technique of Brown and Zweifel.[8,9] The reaction of 2-methylbutene-2 with diborane was used to prepare bis-3-methyl-2-butylborane (disiamylborane), **1**. Because of its large steric requirements only monohydroboration occurred when **1** was treated with 1-hexyne or d_1-1-hexyne to give **2a** or **2b**, respectively. The monohydroboration products **2a** and **2b** are then treated with d_1-acetic acid or acetic acid to give *trans*-1-olefin **3** or *cis*-1-olefin **4**, respectively. A variation of this synthesis was also used to prepare 1,1-dideuteriohexene-1, **5** (Scheme I).

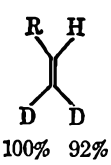
The assignment of configuration to the deuterated olefins is aided by the nmr spectra (Figure 1). The spectra are those of the vinyl protons only. The vinyl proton coupling constants in the *cis*- and *trans*-d_1-hexene-1 isomers are 10 and 18 Hz, respectively. These

SCHEME I



values are typical of those expected for *cis* and *trans* isomers[10] and follow the expected $J_{cis}/J_{trans} \sim 0.5$ correlation.[10] In each case the vinyl proton doublets have a further minor triplet splitting with $J \sim 1.0$ Hz due to the geminal deuterium atom. Here again, the observed coupling is reasonable for the assigned structure since one expects[11] the deuterium–hydrogen geminal coupling to be approximately one-seventh of the value for the corresponding geminal hydrogen–hydrogen coupling (~12–15 Hz[10]).

In the case of the 1,1-dideuteriohexene-1 the vinyl proton nmr spectrum shown in Figure 1 has several implications regarding the structural assignments. First of all it is obvious from the top two spectra in Figure 1 that the resonances on the right are those due to the terminal vinyl protons since these are the ones which are reduced by deuterium exchange. It is also clear that the proton exchange with deuterium was not 100% complete. The spectrum for the dideuterated material suggests that deuterium exchange was 100% complete for the terminal proton *trans* to the 2-vinyl proton and ~92% complete for the terminal proton *cis* to the 2-vinyl proton since the residual proton coupling is characteristic of the *cis* geometry (Figure 1).



100% 92%

(1) (a) To whom inquiries should be addressed at the Chemistry Department, The University of Missouri at St. Louis, St. Louis, Mo. 63121. (b) Chemistry Department, The University of Adelaide, Adelaide, Australia.

(2) R. W. Murray and G. J. Williams, *J. Org. Chem.*, **34**, 000 (1969).

(3) P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955).

(4) R. Criegee, "Advances in Chemistry Series," No. 21, American Chemical Society, Washington, D. C., 1959, p 133.

(5) P. S. Bailey and A. G. Lane, *J. Amer. Chem. Soc.*, **89**, 4473 (1967).

(6) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *ibid.*, **89**, 2429 (1967).

(7) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *ibid.*, **90**, 1822 (1968).

(8) H. C. Brown and G. Zweifel, *ibid.*, **81**, 1512 (1959).

(9) H. C. Brown and G. Zweifel, *ibid.*, **83**, 3834 (1961).

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 87.

(11) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 61.

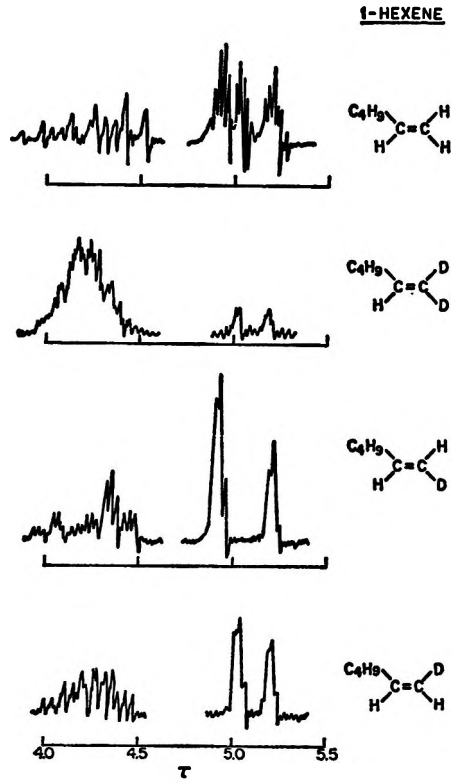


Figure 1.—Vinyl proton nmr spectra of various 1-hexenes.

Ozonolysis of both **3** and **4** gives the same ozonide mixture, the nmr spectrum of which indicates that it is a 50/50 mixture of the ozonide isomers (Figure 2). Only the spectra of the ring protons are shown. In the nondeuterated ozonide (upper spectrum) the methine proton has the expected triplet splitting due to the adjacent methylene group. The geminal methylene protons appear as separate singlets; *i.e.*, the geminal coupling constant is approximately zero. This observation appears to be typical for 1-olefin ozonides and is consistent with the observed change in the value of this coupling constant from a large negative value in cyclopentane to approximately zero for 1,3-dioxolan.[12]

The splitting pattern for the monodeuterated ozonides is the same (lower spectrum) only now the integrated intensities for the three ring protons has changed from

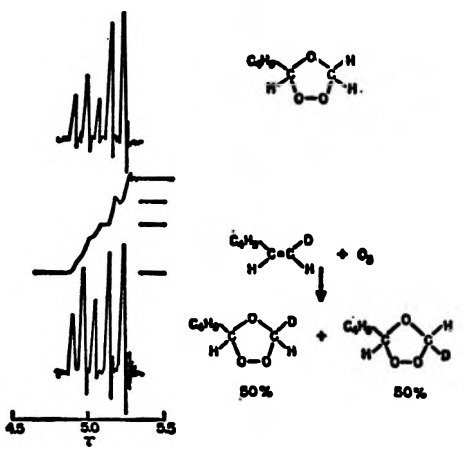


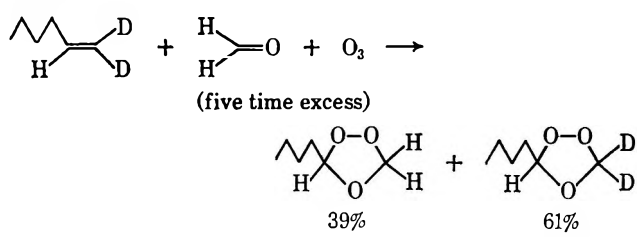
Figure 2.—Nmr spectra of ring protons in ozonides from olefins **3** and **4**.

(12) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron Suppl.*, No. 7, 355 (1966).

a 1:1:1 ratio in the undeuterated ozonide to a ratio of 2:1:1 for the monodeuterated ozonide (Figure 2, center) indicating that this ozonide must be a mixture of the *cis* and *trans* isomers. The 50:50, *cis–trans* ozonide distribution was found not to be dependent upon the extent of ozonolysis nor the concentration of olefin used. It seems fairly certain, therefore, that this ratio is representative of the dominant ozonolysis reaction, and is not the result of a fortuitous combination of separate reaction pathways. Likewise the nmr spectra of the recovered olefins showed that they were not isomerized under the reaction conditions. Thus the loss of stereochemistry was taking place in the ozonolysis reaction.

It seems clear, therefore, that while these ozonolyses are proceeding in high yield, they are also proceeding with complete loss of olefin stereochemistry. These results would seem to rule out any concerted, stereospecific path as being largely responsible for the high yield. Apparently the ozonide-forming fragments are produced and recombine rapidly, perhaps in a solvent cage, with little chance for side reactions. This would also be consistent with the view of Greenwood and coworkers[13,14] that ozonide yield is in large part dependent upon the stability of the molozonide and that 1-olefins are expected to have molozonides with stabilities intermediate between those of *cis*- and *trans*-olefins.[15]

In order to learn more about the ozonide-forming reaction in these cases we have ozonized 1,1-dideuteriohexene-1 in the presence of a large excess of added formaldehyde. This kind of experiment tests the accessibility of the ozonide precursor to diversion by the added aldehyde. It was found that even with a fivefold excess of added formaldehyde only 39% of the hexene-1 ozonide produced had been diverted to the nondeuterated material.

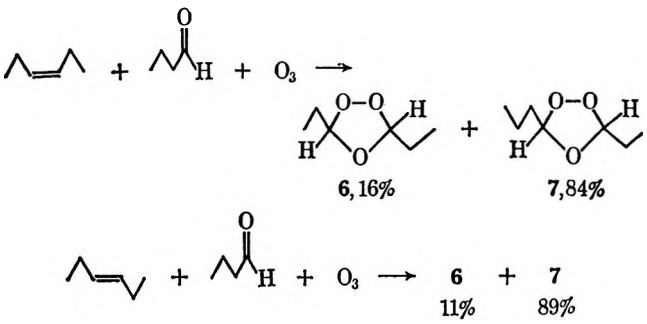


This result is to be contrasted with the cases of the internally unsaturated olefins, *cis*- and *trans*-hexene-3, where ozonolysis in the presence of a fivefold excess of added butyraldehyde led to 84 and 89% diversion of the intermediate, respectively.[16]

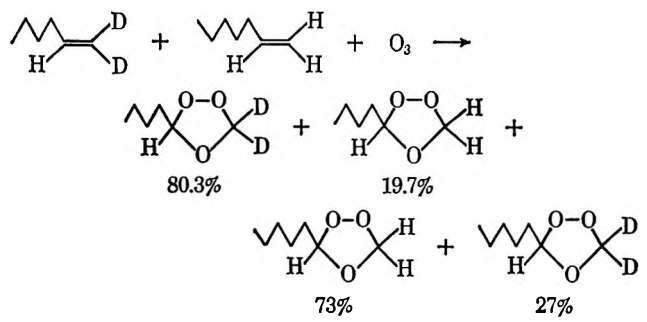
Again these results indicate a striking difference between the ozonolysis of 1-olefins and internally unsaturated olefins. In the 1-olefin cases the ozonide precursor is particularly difficult to divert to a new ozonide by the added aldehyde technique.

Evidence that 1-olefin ozonolyses do allow for some fragment interchange comes from the ozonolysis of a mixture of 1,1-dideuteriohexene-1 and heptene-1. Here an nmr analysis of the hexene-1 and heptene-1 ozonides produced indicates a fair amount of fragment

(13) F. L. Greenwood and H. Rubinstein, *J. Org. Chem.*, **32**, 3369 (1967).
(14) L. J. Durham and F. L. Greenwood, *ibid.*, **33**, 1529 (1968).
(15) F. L. Greenwood, *ibid.*, **30**, 3108 (1965).
(16) R. W. Murray and G. J. Williams, "Advances in Chemistry Series", American Chemical Society, Washington, D. C., No 77, Vol. III, p 32.



exchange. The hexene-1 ozonide consists of 80.3% dideuterated material and 19.7% undeuterated ozonide. The heptene-1 ozonide has a 73% undeuterated fraction and a 27% dideuterated fraction.



The combined observations of high yield, loss of stereochemistry, and relative inaccessibility of intermediate suggest a mechanism in which the molozonide is rather unstable and undergoes fairly rapid cleavage to the Criegee zwitterion and aldehyde fragments[17] and then recombination to ozonide. The entire process is not entirely intramolecular, however, since some exchange recombination occurs. At present it is not known whether these latter reactions involve a Criegee[17] zwitterion, or the molozonide, or some combination of both. What is certain is that this reaction is quite sensitive to the steric requirements of the aldehyde.[2]

Experimental Section

Procedures and Equipment.—The general procedure and equipment used in this study is the same as that described earlier.[2]

Bis(3-methyl-2-butyl)borane (Disiamylborane).—Into a three-necked flask was placed 2-methylbutene-2 (16.8 g, 0.24 mol) in 100 ml of dry ether. The flask was immersed in an ice bath and diborane, generated by the addition of boron trifluoride etherate (17 g, 0.12 mol) to lithium aluminum hydride (4.6 g, 0.12 mol) in 100 ml of dry ether, was introduced into the olefin solution. The resulting disiamylborane was used in the following preparations.

***trans*-d_1-Hexene-1.**—To disiamylborane at 0° was added dropwise 1-hexyne (8.2 g, 0.1 mol). After the reaction mixture had stood for 1 hr at 0°, d_1-acetic acid was added dropwise to the cold reaction solution. This solution was allowed to stand at room temperature overnight and 100 ml of ice water was added. The organic layer was washed first with a sodium carbonate solution, then water, and then dried ($MgSO_4$). Distillation through a spinning band column gave a mixture of 2-methylbutene-2, 1-hexyne, and product. The product was purified by glpc using a 20 ft, 20% cyanosilicone column. The yield was 4.1 g (48.2%). The nmr (neat) of the pure material had a multiplet at 4.2 (1 H) a doublet (J = 18 Hz) of triplets ($J \sim 1.0$ Hz) at 4.92 and 5.22 (1 H), and multiplets at 7.9 (2 H), 8.7 (4 H) and 9.1 (3 H). These absorptions are assigned to the 2-vinyl, 1-vinyl, 3-methylene, 4- and 5-methylene, and methyl protons of *trans*-d_1-1-hexene, respectively.

***cis*-d_1-Hexene-1.**—The procedure given for the *trans* compound was repeated except using d_1-hexyne-1 (8.2 g, 0.1 mol) and normal acetic acid. The yield after glpc purification was 3.8 g (44.6%). The nmr (neat) of the pure material had a multiplet at 4.25 (1 H), a doublet (J = 10 Hz) of triplets ($J \sim 1.0$ Hz) at 5.04 and 5.20 (1 H), and multiplets at 7.95 (2 H), 8.7 (4 H), and 9.1 (3 H). These absorptions are assigned to the 2-vinyl, 1-vinyl, 3-methylene, 4- and 5-methylene, and methyl protons of *cis*-d_1-hexene-1, respectively.

1,1-Dideuteriohexene-1.—The procedure given for *trans*-d_1-hexene-1 was repeated except that now both d_1-hexyne-1 and deuterioacetic acid were used. The yield of glpc purified product was 3.9 g (45.8%). The nmr spectrum had a multiplet at 4.25 (1 H), a weak doublet (J = 10 Hz) at 5.0 and 5.17, and multiplets at 7.9 (2 H), 8.7 (4 H) and 9.1 (3 H). These absorptions can be assigned to the 3-vinyl, residual 1-vinyl, 3-methylene, 4- and 5-methylene, and methyl protons of 1,1-dideuteriohexene-1, respectively. The weak doublet is due to residual 1-vinyl hydrogen which is estimated to be 8% of the initial value and must be *cis* because of the coupling (J = 10 Hz) observed.

Ozonolysis of 1-Deuterio Olefins.—The olefins were ozonized in various concentrations and to various conversions in pentane at −70°, and the resulting *cis*-*trans* distribution determined from the nmr spectra. In all cases this ratio was 50/50. The *cis*-d_1-hexene-1 was ozonized to 75% conversion and at concentrations of 0.5 and 0.25 M. *trans*-d_1-Hexene-1 was ozonized to 15, 50, and 75% conversion and at concentrations of 0.25 and 0.125 M. The nmr spectra of the recovered olefins indicated that no isomerization had occurred. The nmr spectrum of the ozonide mixture had a triplet (J = 5 Hz) at 4.97 (1 H), a singlet at 5.14 (0.5 H), a singlet at 5.25 (0.5 H), and a complex envelope between 8.2 and 9.3 (9 H). Average yield of ozonide was 80%.

Ozonolysis of 1,1-Dideuteriohexene-1 with Added Formaldehyde.—To the olefin (0.54 g, 6.25 mmol) in pentane (0.25 M) was added formaldehyde from the decomposition of 0.5 g (17.9 mmol) of paraformaldehyde. The reaction solution was ozonized to 75% conversion at −70°. The nmr spectrum of the ozonide produced showed a 37% incorporation of formaldehyde. When the same reaction was carried out using 0.9 g (32.1 mmol) of paraformaldehyde, the recovered ozonide showed a 39% incorporation of formaldehyde.

Ozonolysis of *cis*- and *trans*-Hexene-3 with Added Butyraldehyde.—These experiments were described earlier.[16] The ozonolyses were carried out on solutions of the olefins in pentane. The olefins were present at 0.5 M concentration and the butyraldehyde at 3.0 M concentration. The ozonolyses were continued to 75% conversion at −70°.

1-Deuteriohexyne-1.—To magnesium (8.5 g, 0.354 mol) in 250 ml of dry ether was added dropwise 44.3 g (0.31 mol) of methyl iodide. The reaction mixture was stirred for 2 hr and then 20.5 g (0.25 mol) of hexyne-1 was added dropwise. The reaction mixture was refluxed for 0.5 hr and then allowed to cool to room temperature. To the cooled solution was added with stirring 6.6 g (0.33 mol) of deuterium oxide. The reaction mixture was stirred for 0.5 hr and the product distilled out. After drying ($MgSO_4$) the product was redistilled to give 18.4 g (89%) with bp 72–73°. The nmr spectrum showed no acetylenic proton absorption.

Ozonolysis of 1,1-Dideuteriohexene-1 and Heptene-1.—A pentane solution which was 0.5 M in both 1,1-dideuteriohexene-1 and heptene-1 was ozonized at −70° to 75% conversion. The ozonides were collected by glpc and their deuterium content determined from the nmr spectra. The hexene-1 ozonide consisted of 80.3% dideuterated material and 19.7% undeuterated ozonide. The heptene-1 ozonide contained a 73% undeuterated fraction and a 27% dideuterated fraction.

Registry No.—**3**, 18963-98-9; ozonide of **3**, 18963-13-8; **4**, 18963-99-0; ozonide of **4**, 18963-12-7; 1,1-dideuteriohexene-1, 18963-11-6; 1-hexene, 592-41-6; ozonide of 1-hexene, 767-09-9.

(17) R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957).

Angularly Substituted Octahydrophenathrenes. I. The Synthesis of Hexahydrofluorenone Intermediates

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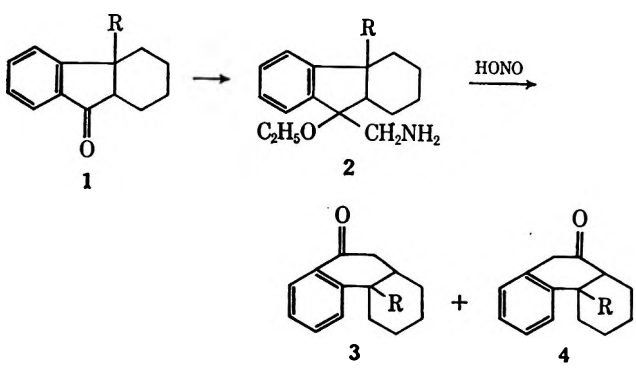
An improved procedure for the preparation of 1,2,3,4-tetrahydrofluoren-9-one (**5**), which affords the ketone free of double-bond position isomers, is described. The reactions of **5** with hydrogen cyanide, with anions derived from *t*-butyl malonate, malononitrile, and ethyl cyanoacetate, and with organocopper derivatives have been shown to provide high yields of a new class of angularly substituted hexahydrofluoren-9-ones of type **1**. These compounds are of interest as intermediates for the preparation of angularly substituted octahydrophenanthrenes and the morphinan ring system.

The reaction sequence shown in Scheme I, which has been described[3] for the case where R = H, offers an attractive synthetic procedure for the preparation of angularly substituted octahydrophenathrenes (**3** and **4**) and derivatives of the morphinan[4] and isomorphinan ring systems. The ultimate success of this proposed synthetic route to such compounds is, however, contingent upon the evolution of a convenient synthesis of the new class of angularly substituted hexahydrofluoronenones of type **1**. In this regard, 1,2,3,4-

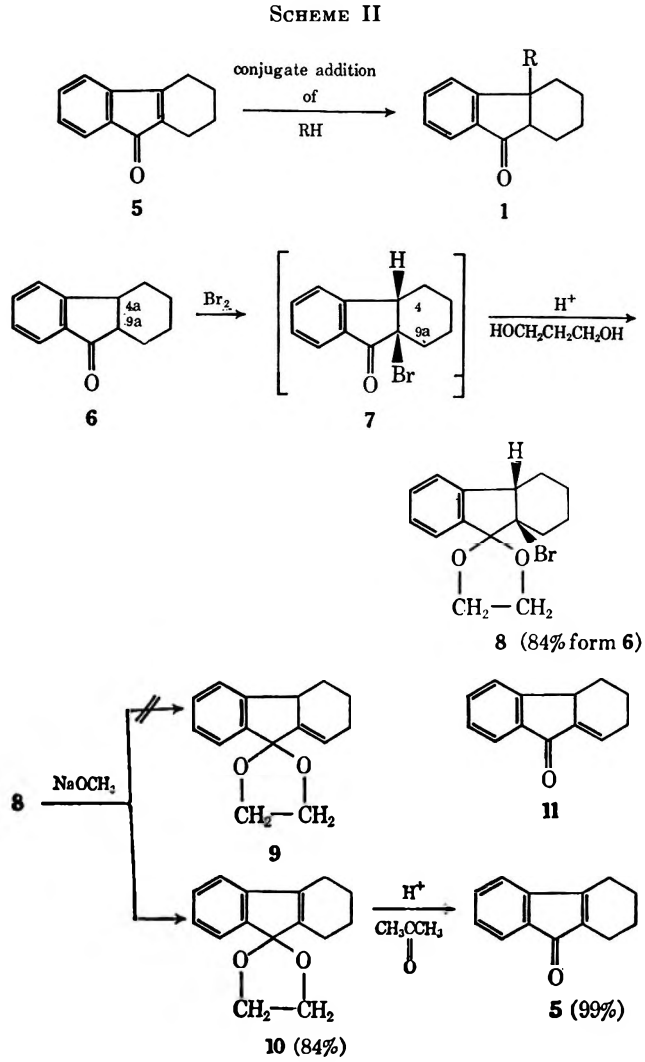
SCHEME I



tetrahydrofluoren-9-one (**5**) has proved to be a useful precursor to a variety of such angularly substituted ketones, as shown at the top of Scheme II, and the synthesis of **5** and a study of its reactions with nucleophilic reagents constitute the subject of this report.

Preparation of 1,2,3,4-Tetrahydrofluoren-9-one (5).—The desired ketone **5** was prepared by a new procedure from **6** as shown in Scheme II. This sequence of reactions is preferable to direct dehydrohalogenation of **7**,[5] since the latter process gives a mixture containing approximately 40% **11** and 55% **5**. Bromo ketal **8** was obtained in 84% yield from **6** and was assigned the *cis*

SCHEME II



relative configuration at carbon atoms C-4a and C-9a based on the configuration previously established for **7**.[5] The facile E2 elimination of hydrogen bromide from **8** to give only **10** is consistent with the *cis* configuration assigned to **8**, and was expected from both kinetic[6] and thermodynamic considerations. The absence of **9** as a product of dehydrohalogenation of **8** was demonstrated, since no vinyl hydrogen was observed in the nmr spectrum of the crude reaction product. Conversion of ketal **10** to **5** was accomplished in essentially quantitative yield, and without any isomerization of the double

(1) From the Ph.D. Thesis of L. J. Czuba, The University of Minnesota, 1967.

(2) Financial assistance is gratefully acknowledged for a Sinclair Oil Co. Fellowship (1965-1966) and for summer fellowships or assistantships from the Du Pont Co., the Sun Oil Co., and the Smith Kline and French Laboratories. Part of this work was also supported (1966-1967) by the National Science Foundation (GP-6169X).

(3) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

(4) Derivatives of type **1** in which R = CH_2COOH (**22**) are particularly attractive as intermediates for the synthesis of morphinans and isomorphinans [*cf.* J. Hellerbach, O. Schnider, H Besendorf, and B. Pellmont, "Synthetic Analgesics, Part II(a), Morphinans," Pergamon Press, London, 1966, for a review of procedures for the preparation of morphinan and isomorphan systems].

(5) H. O. House, V. Paragmian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1457 (1960).

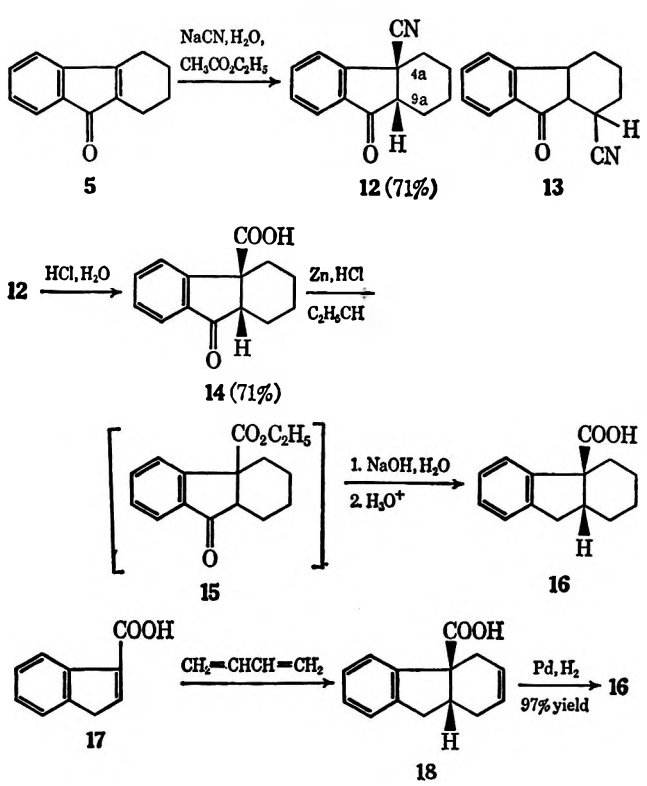
(6) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).

bond, by ketal interchange using dry acetone and *p*-toluenesulfonic acid. The nmr spectrum of the ketone **5** showed no vinyl hydrogen which excluded the presence of isomer **11**.

Conjugate Addition Reactions.—While conjugate addition reactions to give quaternary carbon atoms do not generally proceed in high yields,[7] geometric considerations together with several recently reported synthesis[7d-h] of this type suggested that such reactions should proceed satisfactorily with the unsaturated ketone **5**. This conclusion was confirmed by studies of the reaction of **5** with hydrogen cyanide, with derivatives of malonic acid and malononitrile, and with organocopper compounds.

1. With Hydrogen Cyanide.—The reaction of **5** with hydrogen cyanide, generated *in situ* by the method of Koelsch,[8] afforded a crystalline product in 71% yield which was subsequently shown to be 1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-carbonitrile (**12**) as shown in Scheme III. Spectral data (uv, ir, and nmr) for this

SCHEME III



product were consistent with the assigned structure **12**; however, these data did not exclude structure **13**, which could form from **11** derived by isomerization of **5** under the conditions of the reaction. The structure of the nitrile **12**, and the derived acid **14**, were confirmed by the independent synthesis of **16**, as shown in Scheme III.

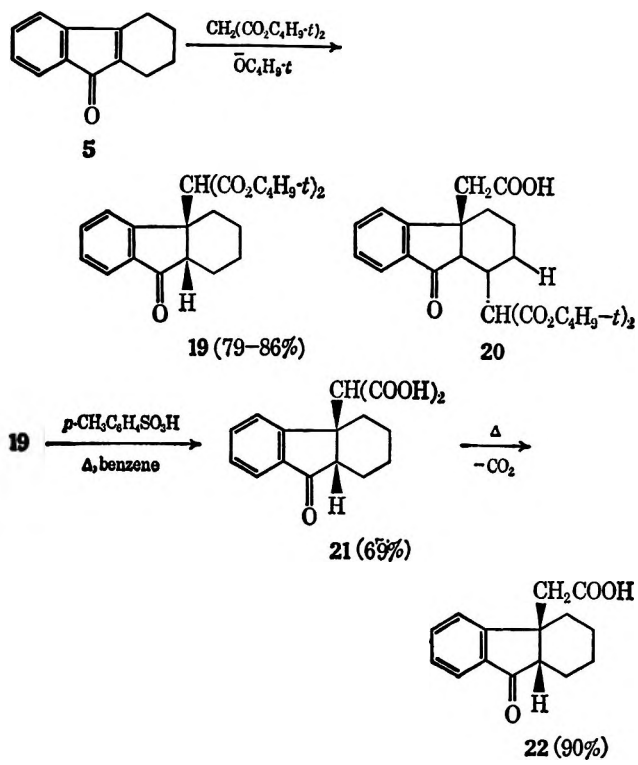
(7) (a) S. Patai and Z. Rapport in "The Chemistry of Alkenes," S. Patai Ed., Interscience Publishers, New York, N. Y., 1964, pp 469, 483, 504; (b) E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959). (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 694; (d) C. F. Koelsch, *J. Org. Chem.*, **25**, 2088 (1960); (e) E. Campaigne, G. F. Bulenko, W. E. Kreighbaum, and D. R. Maulding, *J. Org. Chem.*, **27**, 4428 (1962); (f) K. Jori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (Tokyo), **28**, 241 (1964); *Chem. Abstr.*, **61**, 9539 (1965); (g) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); (h) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **33**, 840 (1968).

(8) C. F. Koelsch, private communication.

The stereochemistry of the two angularly substituted hexahydrofluorenones (**12** and **14**) is dependent upon the relative thermodynamic stabilities of the two diastereomers in each case, since enolization of the ketone functions could result in epimerization at C-9a. The isolation of a single diastereomer in high yield in both cases, under conditions where enolization of the ketone function is expected, established a thermodynamic preference for one diastereomer in each case. House[5] and coworkers have shown that the diastereomer of **6** with the *cis* relative configuration at the bridging carbon atoms C-4a and C-9a is considerably more stable than the *trans* isomer (*cis*:*trans* ratio is 86:14 at equilibrium). On this basis **12** and **14** are tentatively assigned *cis* relative configurations at C-4a and C-9a.

2. With Di-*t*-butyl Malonate.—The Michael adduct **19** was prepared in 79–86% yield by reaction of **5** with di-*t*-butyl malonate in *t*-butyl alcohol containing a catalylic amount of potassium *t*-butoxide (Scheme IV).

SCHEME IV



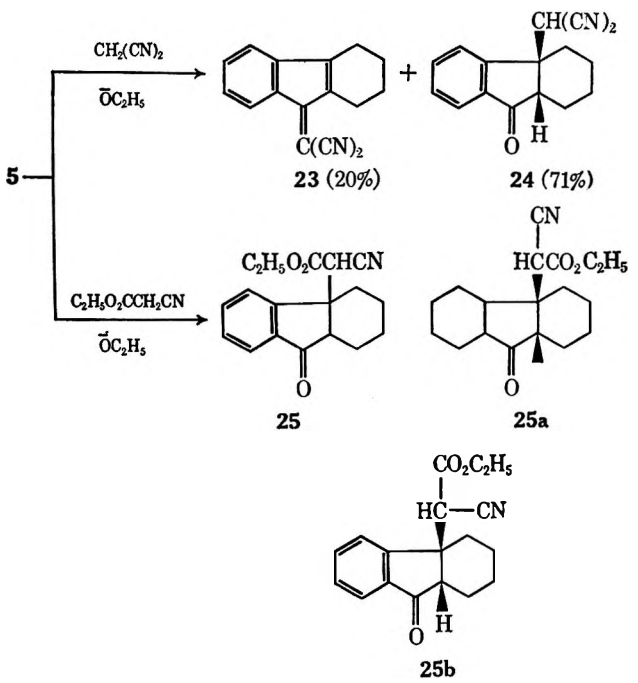
The crude product contained **5**, di-*t*-butyl malonate and the Michael adduct **19** (79–86% yield of **19** by nmr); however, attempts to isolate **19** pure by crystallization or column chromatography were unsuccessful. The nmr spectrum of the crude product did, however, exclude the possible presence of the isomeric adduct **20**, which could have formed by isomerization of **5** to **11** prior to the Michael addition reaction. The nmr spectrum of **19** showed methine hydrogen adjacent to the ester functions only as a sharp singlet. Methine hydrogen in **20** would appear as a doublet due to splitting by hydrogen β to the ester function.

Treatment of crude **19** with a small amount of *p*-toluenesulfonic acid in boiling benzene gave the dibasic acid **21** in 69% yield as a white crystalline powder, melting at 160–161° with gas evolution. The ir spectrum of the product was consistent with that

expected for a dibasic acid, and the composition was in reasonable agreement (±0.4%). The dibasic acid **20** was hygroscopic, and attempts to remove the last traces of water were accompanied by decarboxylation (see Experimental Section). It was surprising, in view of previous reports,[9] that the dibasic acid did not decarboxylate under the conditions of its formation; fusion of **21** at 170–180° gave 1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-ylacetic acid (**22**) in 90% yield. The angularly substituted hexahydrofluorenones **19–22** are tentatively assigned the *cis* configurations for reasons analogous to those described above for **12** and **14.**

3. With Malononitrile and Ethyl Cyanoacetate.—The products of reaction of **5** with malononitrile in ethanol containing sodium methoxide were 1,2,3,4-tetrahydrofluoren-9-ylidinemalononitrile (**23,** 20% yield) and 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylmalononitrile (**24,** 71% yield) as shown in Scheme V.

SCHEME V



The assignment of structures **23** and **24** were made on the basis of composition and spectral data; the tentative stereochemical assignment by analogy to that discussed for **12, 14,** and **19–22.** The nmr spectrum of **24** showed a sharp singlet at τ 5.62 due to the methine proton in the angular malononitrile function.

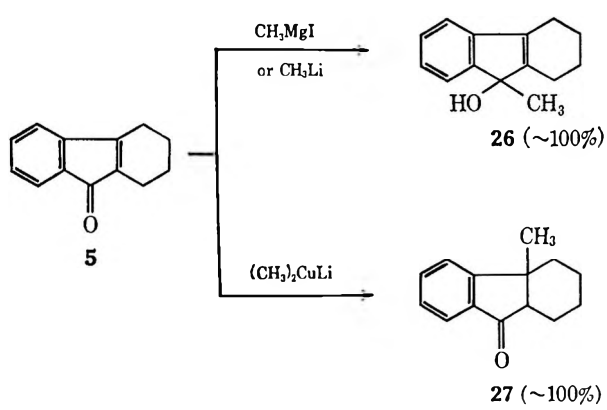
The composition of the product mixture was not changed appreciably when reaction times of 30 min to 2 hr at 25° were employed; however, when the reaction time was increased to 20 hr a more complex mixture was obtained and the amount of **23** increased (35% yield) while the amount of **24** decreased (34% yield). Thus adduct **24** is formed rapidly and is converted into other products after prolonged reaction times. Ylidenemalononitrile **23** was shown not to be a precursor of **24** by its recovery unchanged after treatment with malononitrile in ethanol containing sodium ethoxide.

Similarly, the reaction of **5** with ethyl cyanoacetate gave a mixture containing ethyl 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylcyanoacetate (**25**) in 66% yield (by nmr). The 1,4 adduct was obtained pure by distillation, and nmr spectral data of the crude and pure product showed hydrogen α to nitrile only as a sharp singlet (τ 5.94). This observation was consistent for angular substitution but inconsistent for position isomers related to **20.** The nmr spectrum of **25** indicated that it was a mixture of diastereomers with two nonequivalent ester groups (see Experimental Section). On the basis of the rationale offered for the stereochemistry of other angularly substituted hexahydrofluorenones discussed above, it seems reasonable that **25** is a mixture which is epimeric with respect to the asymmetric center in the angular substituent, and that the relative configurations at C-4a and C-9a are *cis* as shown in **25a** and **25b.**

4. With Organometallics.—Studies of the reaction of **5** with methylmagnesium iodide, methyllithium, and derivatives of methylcopper suggests that either exclusive 1,2 addition or exclusive 1,4 addition of organometallic reagents can be achieved. Thus reaction of **5** with methylmagnesium iodide in ether gave an 81% isolated yield of the 1,2-addition product **26.** Alcohol **26** was also obtained (98% yield) by reaction of **5** with methyllithium in ether. The nmr spectrum of the crude products obtained from both of these reactions showed a single methyl hydrogen atom absorption at τ 8.62 which confirmed the absence of any 1,4-addition product **27** (singlet, τ 8.56).

By contrast, the reaction of **5** with lithium dimethyl copper, which is readily prepared from methyllithium and cuprous iodide, gave a 95% isolated yield of 4a-methyl-1,2,3,4,4a,9a-hexahydrofluoren-9-one (**27**) (Scheme VI). The nmr spectrum of the crude

SCHEME VI



product showed only angular methyl absorption at τ 8.56 and the complete absence of absorption at τ 8.62 required if **26** were present. The ir spectrum of the crude product supported the conclusion that this reaction gave exclusively the 1,4-addition product.

The reaction of **5** with the complex[10] derived from tetrakis[iodo(tri-*n*-butylphosphine)copper(I)][11] and methyllithium gave, exclusively, the 1,4-addition product **27**; however in this case ketone **27** (82% yield) was difficult to separate from tri-*n*-butylphosphine. The use of these copper reagents for conjugate addition

(9) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.* **66,** 1286 (1944).

(10) H. O. House, W. L. Repress, and G. M. Whitesides, *J. Org. Chem.* **31,** 3128 (1966).

(11) G. B. Kaufman and L. A. Teter, *Inorg. Syn.* **7,** 9 (1963).

reactions were recently described by House, Repress, and Whitesides,[10] and their application in reactions with **5** offers an exceptionally promising route for the syntheses of angular alkyl-substituted hexahydrofluoren-9-ones of type **1**.

It is interesting to note that the reaction of **5** with methylmagnesium iodide in tetrahydrofuran containing cupric acetate[12,13] gave a mixture of **27** (34%) and **26** (56%), and reaction of **5** with methylmagnesium iodide in ether containing cupric acetate gave the alcohol **26** in 78% yield with no evidence of 1,4 addition. The high selectivity of the organocopper reagents in their reactions with **5**, which afford only 1,4 adduct **27**, is surprising in view of the failure of the copper-catalyzed Grignard reactions to give predominant 1,4 addition. House and coworkers[10] have proposed that the enhancement of the 1,4 addition of Grignard reagents in the presence of catalytic amounts of copper salts occurs becuase the reaction rates for both the formation of organocopper intermediate and the subsequent reaction of this intermediate with the substrate, in a conjugate manner, are much faster than 1,2 addition of the Grignard reagent to the substrate. In the present case, the rate of 1,2 addition of the Grignard reagent to **5** may be fast enough to compete with the rate of formation of the copper intermediate or, alternatively, the rate of 1,4 addition of organocopper reagent to **5** may be of the same order of magnitude as the rate of 1,2 addition of Grignard reagents to **5**.

Experimental Section

Melting points were determined on a calibrated Fisher-Johns hot stage. All melting points were corrected and boiling points were not corrected. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 spectrometer using 1–2% tetramethylsilane as an internal standard. Mass spectra were obtained by Mr. A. Swanson and his assistant(s) at the University of Minnesota on a Hitachi-Perkin-Elmer RMU-6D mass spectrometer.

9a-Bromo-1,2,3,4,4a,9a-hexahydrofluoren-9-one Ethylene Ketal (8).—Crude bromo ketone **7** (lit.[5] 87% yield, mp 58–59°), obtained from bromine (30.4 g, 0.19 mol) and **6** (35.5 g, 0.019 mol), was treated with a mixture of *p*-toluenesulfonic acid (1.0 g), ethylene glycol (15 ml), and benzene (300 ml). The resulting solution was heated at the reflux temperature for 48 hr during which time 7 ml of water–glycol was separated with a Dean–Stark trap. The resulting mixture was washed with brine and dried (Na_2SO_4). The brown oil (55 g), obtained subsequent to removal of solvent, was crystallized from methanol to give 34.3 g (58.7% yield, mp 94–95°) of **8**. The brown oil, obtained by concentration of the mother liquor, was retreated with *p*-toluenesulfonic acid, and ethylene glycol in benzene as described above. There was obtained an additional 14.91 g (25.6%, mp 94–95°) of **8** (total yield 84.3%). The product melted at 94.5–95.5° after recrystallization from methanol; nmr (32% in $CDCl_3$) showed τ 2.55–3.07 (m, 4, C_6H_4), 5.51–6.12 (m, 4, ketal CH_2), 6.32–6.52 (m, 1, benzylic CH), 7.77–9.23 (m, 7.9, CH_2).

Anal. Calcd for $C_{15}H_{17}BrO_2$: C, 58.26; H, 5.54; Br, 25.85. Found: C, 58.00; H, 5.72; Br, 26.04.

1,2,3,4-Tetrahydrofluoren-9-one Ethylene Ketal (10).—Sodium methoxide powder (27 g, 0.50 mol) was added in one portion to a well-stirred solution of bromo ketal **8** (66.7 g, 0.197 ml) in dimethyl sulfoxide (300 ml) under a dry nitrogen atmosphere. After 30 min the temperature rose to 60° and stirring was continued with no external temperature control for 3 hr. The mixture was diluted with ice–water (700 ml) and then was extracted with three 150-ml portions of ether, and the ether extract was dried and concentrated to give 43.7 g (97% yield) of crude **10** as oily orange crystals. This material was crystallized from methanol to give 37.9 g (84% yield of which 4% was recovered from mother liquor) of **10** (mp 71.5–72°): uv (95% EtOH); λ_{max} mμ (log ϵ) 219 (4.49), 225 (4.45), 277 (3.68); nmr (20% in CCl_4) τ 2.74–3.28 (m, 4, C_6H_4), 5.87–6.14 (m, 4.1, ketal CH_2), 7.60–8.07 (m, 4, allylic CH_2), 8.07–8.48 (m, 4, CH_2).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.21; H, 7.05.

1,2,3,4-Tetrahydrofluoren-9-one (5).—A solution of ketal **10** (35.64 g, 0.156 mol), *p*-toluenesulfonic acid (1.0 g), and dry acetone (200 ml) was heated to reflux with stirring for 15 min. The mixture was then aged for 30 min at room temperature, poured into water (500 ml), and the resulting mixture was extracted with three 125-ml portions of petroleum ether (bp 30–68°). The organic extract was washed successively with aqueous sodium bicarbonate and with brine and was then dried (Na_2SO_4) and concentrated. The crude ketone (28.6 g, 99% yield, yellow crystals, mp 39.5–40.5°) was recrystallized from *n*-pentane to give bright yellow crystals of pure **5** (mp 41–42°, lit.[5] mp 41.5–42.5°): ir (CCl_4) 1705 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 236 (4.06), 243 (4.67); nmr (20% CCl_4) τ 2.58–3.30 (m, 4, C_6H_4), 7.50–8.03 (m, 4, allylic CH_2), 8.03–8.43 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 85.08; H, 6.85.

Reaction of 5 with Hydrogen Cyanide.—The following is an adaptation of an unpublished procedure by Professor C. F. Koelsch (University of Minnesota). A mixture of ketone **5** (2.00 g, 10.9 mmol), sodium cyanide (0.69 g, 14 mmol), ethyl acetate (1.8 g, 20 mmol), water (6 ml) and 95% ethanol (9 ml) was heated at the reflux temperature for 1.5 hr and was then poured into cold water (100 ml). The mixture was extracted with four 50-ml portions of ether and the ether extract was then washed with saturated sodium bicarbonate and was dried (Na_2SO_4) and concentrated. The crude light yellow oily solid (2.26 g, 99% yield) was recrystallized from ethanol–water to give 1.62 g (71% yield, mp 74.6–75.3°) of **1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-carbonitrile (12)**: ir (CCl_4), 1720 (C=O), 2250 cm^{-1} w (C≡N); uv (95% EtOH) λ_{max} mμ (log ϵ) 244 (4.09), 283 (3.24), 288 (3.24); nmr (25% in $CDCl_3$) τ 2.10–2.63 (m, 4, C_6H_4), 6.79–7.02 (m, 1, bridgehead CH), 7.35–9.19 (m, 8.8, CH_2).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.31; H, 6.18; N, 6.49.

1,2,3,4,4a,9a-Hexahydro-9-oxofluorene-4a-carboxylic Acid (14).—A mixture of **12** (1.16 g, 5.5 mmol) and concentrated hydrochloric acid (30 ml) was heated on a steam bath for 16 hr. The resulting mixture was diluted with water (150 ml) and extracted with three 50-ml portions of ether. The ether extract was washed with water and with brine, and was then dried (Na_2SO_4) and concentrated to give an oil which crystallized on standing to give light tan prisms (1.23 g, 97% yield, mp 121–126°). The crude acid was recrystallized from benzene–petroleum ether (bp 60–68°) to give **14** as a white powder (0.90 g, 71% yield, mp 136.4–136.6°): ir (halocarbon–Nujol) 1690 and 1712 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 242 (4.04), 290 (3.32); nmr (14% in $CDCl_3$) τ −2.00 (s, 1, acid OH), 2.16–2.78 (m, 4, C_6H_4), 6.57–6.78 (s, 1, bridgehead H), 7.29–9.06 (m, 7.9, CH_2).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.07; H, 6.24.

2,3,4,4a-*cis*-9,9a-*cis*-Hexahydro-1H-fluorene-4a-carboxylic Acid (16). 1. From 14.—A mixture of granulated zinc metal (0.75 g), mercuric chloride (0.08 g), water (2 ml), and two drops of concentrated hydrochloric acid was stirred for 5 min and the solution was decanted from the zinc amalgam. Water (1 ml), concentrated hydrochloric acid (3 ml), and a solution of keto acid **14** (293 mg, 1.27 mmol) in 95% alcohol (10 ml) was added to the zinc amalgam and the mixture was stirred and heated at the reflux temperature for 24 hr. Additional hydrochloric acid (after 6 hr, 2 ml, and after 12 hr, 2 ml) was added during the reflux period. The mixture was diluted with water (100 ml) and the organic material was extracted with two 40-ml portions of ether. The ether extract was washed with water

(12) M. S. Karasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, Inc., New York, N. Y., 1954, p 219.

(13) House and coworkers (see ref 10) have proposed that the enhancement of 1,4 addition by cupric acetate in tetrahydrofuran relative to ether is due to the low solubility of cupric acetate in ether.

and was dried (Na_2SO_4) and concentrated. The crude product contained appreciable unconverted **14** and was reduced again exactly as described above. Chromatography of the crude yellow oil, thus obtained, on 100–200 mesh silica (20 g) gave as the first fraction by elution with chloroform slightly impure ester (**15**, ir and nmr identical with those of authentic **15**, see below; but showing impurity bands at 1265 and 1220 cm^{-1} and sharp bands near the methyl triplet at τ 8.78 and small peaks at τ 3.57 and 6.34). A mixture of the slightly impure ester (157 mg) and 10% ethanolic potassium hydroxide (25 ml) was heated at the reflux temperature, and the cooled mixture was extracted with ether. The basic solution was acidified (concentrated HCl) at 0° and the dry oil (71.8 mg) obtained was chromatographed on 100–200 mesh silica gel (20 g). Acid **16** (57 mg) was eluted with 300 ml of chloroform and was recrystallized from ethanol–water to give pure **16** (47 mg, mp and mmp 107.5–108°). The ir spectrum of the product was identical with that obtained from **16**.

2. From 17.—Acid 18[14] (22.6 g) was reduced with hydrogen (4 atm) in a Parr apparatus using 95% ethanol (250 ml) as solvent and 10% palladium on carbon powder (0.5 g) as catalyst. The yield of **16** (22.08 g from ethanol–water, mp 108.6–109.5°) was 97%: ir (Nujol) 1695 cm^{-1} (C=O); nmr (25% in $CDCl_3$), τ −2.13 (s, 1, acid OH), 2.53–3.00 (m, 4, C_6H_4), 6.80–8.83 (m, 11, benzylic CH_2, bridgehead CH and CH_2).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.47; H, 7.41.

Acid **16** (3.00 g, 0.014 mol) was further characterized by esterification (with ethanol and sulfuric acid) to ester **15** [3.11 g, 92% yield, bp 98–102° (0.15 mm), $n^{28}D$ 1.5259]: ir (neat) 1720 cm^{-1} (C=O); nmr (32% in $CDCl_3$) τ 2.63–3.04 (m, 4, C_6H_4), 5.88 (q, J = 7 Hz, 2, OCH_2), 6.81–7.47 (m, 3, benzlic CH_2 and bridgehead CH), 7.60–8.98 (t, J = 7 Hz, CH_3 superimposed on a m, CH_2, total wt 11).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.33; H, 8.44.

Reaction of 5 with Di-*t*-butyl Malonate. 1,2,3,4,4a,9a-Hexahydro-9-oxofluoren-4a-ylmalonic Acid (21).—A mixture of **5** (2.00 g, 0.011 mol), di-*t*-butyl malonate[15] (3.0 g, 0.014 mol), and potassium *t*-butoxide (from 0.10 g, 0.0025 g-atom of potassium) and anhydrous *t*-butyl alcohol was heated with stirring at 60° under a dry nitrogen atmosphere for 3 hr, and was then aged for 16 hr at room temperature. The resulting mixture was treated with acetic acid (0.3 ml) and poured into cold water (100 ml). The aqueous mixture was extracted with four 50-ml portions of petroleum ether (bp 30–60°) and the ether extract was washed with cold water and with brine and was dried (Na_2SO_4) and concentrated. An nmr spectrum of the crude product showed $CH(CO_2R)$ only as a singlet (τ 6.30) and analysis of the peak area (*i.e.*, area of the singlet at τ 6.30 relative to that of the multiplet at τ 2.23–2.85 due to the aromatic protons) suggest 86% conversion into **19**. The crude product was chromatographed on 100–200 mesh silica gel (100 g) and the column was eluted with chloroform to give a mixed fraction of **5** and di-*t*-butyl malonate (0.49 g), a mixed fraction of **19** and di-*t*-butyl malonate (2.04 g), and a fraction of slightly impure **19** (2.33 g). The composition of the fractions was determined by tlc on Stahl silica gel G, developed with benzene. Attempts to crystallize pure samples of **19** were unsuccessful: nmr (32% in CCl_4) showed τ 2.27–2.86 (m, 4, C_6H_4), 6.30 [s, 1, $CH(CO_2R)_2$], 6.61–6.85 [m, 1, C(=O)CH], and 7.40–9.20, (two singlets at τ 8.58 and 8.83 due to nonequivalent *t*-butyl groups superimposed on the multiplet due to CH_2, total 26).

An impure sample of ester (4.68 g, containing 79% of **19**) was dissolved in benzene (100 ml) and the mixture was heated at the reflux temperature with continuous water separation for 30 min to ensure dryness. Dry *p*-toluenesulfonic acid was added and the mixture was heated at the reflux temperature for 2 hr. The cooled mixture was diluted with water (50 ml) and with ether (100 ml) and the organic phase was separated, washed with water (50 ml) and with brine (50 ml) and was dried (Na_2SO_4) and concentrated. The yellow solid (2.94 g), thus obtained, was suspended in boiling benzene (75 ml) and the mixture was cooled and filtered. The white crystalline powder residue was recrystallized from ethanol to give **21** as white crystals which melted at 160–161° with gas evolution: ir (halocarbon–Nujol) 1730, 1710, 1680, 1655 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 67.05; H, 5.42.

The analytical sample had been dried for a short period under vacuum at 100°. This sample was shown to be hydroscopic (by ir) and attempts to remove the last trace of water under vacuum at 60° were unsuccessful. Longer periods of drying at 100° were accompanied by slow decarboxylation and a gradual rise in the carbon content of the residue.

1,2,3,4,4a,9a-Hexahydro-9-oxofluoren-4a-ylacetic Acid (22).—The dibasic acid **21** (1.91 g, 6.63 mm) was heated for 10 min (until gas evolution ceased) at 170–180° under nitrogen. The resulting glassy product was recrystallized from benzene–petroleum ether (bp 60–68°) to give **22** as white crystals (1.46 g, 90% yield, mp 77–81°). Recrystallization of the product produced no change in melting point. The product was ground to a fine powder and was heated under vacuum for 24 hr at 56° and for 48 hr at 80° with only small weight loss, to give pure **22** as a white crystalline powder: mp 102–102.5°; ir (halocarbon–Nujol) 1723 and 1673 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 245 (4.06), 291 (3.36); nmr (32% in $CDCl_3$) τ −1.30 (s, 1, acid OH), 2.23–2.88, 4, C_6H_4), 6.89–7.24 (AB, q, J_{AB} = 15 Hz, τ_A 7.07, τ_B 7.17, superimposed on m at τ 6.89–7.24, due to angular CH_2 and proton at C-9a, total wt 3).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.60, H, 6.69.

The product described above which melted at 77–81° appears to be **22** with 0.166 mol of benzene of crystallization (nmr shows singlet at τ 2.72 superimposed on the multiplet due to C_6H_4 at τ 2.22–2.88, total wt 5).

Anal. Calcd for $C_{15}H_{16}O_3 \cdot 0.166C_6H_6$: C, 74.68; H, 6.66. Found: C, 74.89; H, 6.96.

An attempt to remove the *t*-butyl groups from **19** by reaction in acetic acid and acetic anhydride containing two drops of 85% phosphoric acid at 130° for 2 hr gave acid **22** (20% yield) and a product assumed to be the enol acetate of **22** (16% yield). The two products were separated by a column chromatography and the latter showed: mp 145.2–145.6°; ir (nujol) 1660 m, 1695 s, 1755 cm^{-1} s (C=O); nmr (14% in $CDCl_3$) τ −1.71 (s, 1, acid OH), 2.53–3.10 (m, 4, C_6H_4), 6.96–9.23 (ABQ, J_{AB} = 14 Hz, τ_A 7.14, τ_B 7.47 and s, 7.73 and all superimposed on m, angular CH_2 and CH_3CO superimposed on CH_2); mass spectrum *m/e* (relative intensity) 286 (18, M^+, calcd 286.3 for $C_{17}H_{18}O_4$), 43 (3, CH_3CO), 226 (22, loss of H_2O and CH_3CO), 244 (100, loss of CH_3CO), metastable peak centered on *m/e* 209.3 which corresponds to the 244 → 226 fragmentation.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.35; H, 6.62.

Reaction of 5 with Malononitrile.—A solution of ketone **5** (2.00 g, 0.0109 mol) and malononitrile (1.98 g, 0.030 mol) in absolute ethanol (15 ml) was added to a solution of sodium ethoxide prepared from sodium (0.07 g, 0.003 g-atom) and absolute ethanol. The red solution was allowed to stir for 30 min at room temperature under an atmosphere of dry nitrogen and was then diluted with cold 10% aqueous sodium chloride (100 ml). The mixture was extracted with four 50-ml portions of ethyl acetate and the organic extract was washed with brine (100 ml), dried (Na_2SO_4) and was concentrated. The oily solid residue (3.12 g) was chromatographed on 100–200 mesh silica gel (80 g) and chloroform was used as eluent. The deep red solid, which was eluted first was 1,2,3,4-tetrahydrofluoren-9-ylidenomalononitrile (**23**, 500 mg, 20% yield, mp 207–209° dec). The melting point of a sample of **23** obtained by sublimation of this product, 90° (0.2 mm), was 208–209.5° dec: ir (Nujol), 2240 cm^{-1} (CN); uv (95% EtOH) λ_{max} mμ (log ϵ) 251 (4.29), 290 (4.24), 353 (4.03); nmr (7% in $CDCl_3$) τ 1.88–2.06 (m, 1, CH), 2.57–3.12 (m, 3, C_6H_3), 7.18–7.70 (m, 4, allylic CH_2), 8.07–8.33 (m, 4, CH_2).

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.86; H, 5.56; N, 12.08.

The second component obtained from the chromatography was recrystallized from benzene–petroleum ether (bp 60–68°) and was 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylmalononitrile (**24**, 1.8 g, 70% yield, mp 122–124°). A sample of **24** was purified further by sublimation of this product at 90° (0.05 mm): mp 126–127°; ir (Nujol) 2250 (C≡N), 1703 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 243 (4.11), 203 (3.26), 289

(14) E. F. Godefroi and L. H. Simanyl, *J. Org. Chem.*, **28**, 1112 (1963).

(15) G. S. Fonken and W. S. Johnson, *J. Amer. Chem. Soc.*, **74**, 831 (1952).

(3.26); nmr (25% in $CDCl_3$) τ 2.04–2.68 (m, 4, C_6H_4), 5.62 (s, 1, angular CH), 7.05–7.29 (m, 1, bridgehead H), 7.61–9.14 (m, 9, CH_2).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.70; N, 11.15.

Reaction of 5 with Ethyl Cyanoacetate.—The reaction of **5** (200 g, 0.0109 mol) with ethyl cyanoacetate was carried out for 18 hr at 60° essentially as described above for the reaction with malononitrile. The mixture was treated with acetic acid (0.5 ml) and the crude oil (3.45) obtained after processing as described above was chromatographed on 80 g of 100–200 mesh silica gel. The first compound removed from the column with chloroform was recovered **5** (0.49 g, 25% crude recovery). The second product eluted was shown to be **25** contaminated with ethyl cyanoacetate (tlc). Analysis of this mixture by nmr showed it to be 74.5% **25**, which corresponds to an over-all yield of 66% of **ethyl 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylcyanoacetate** from **5**. The Michael adduct was obtained pure by short-path distillation: bp 175–180° (0.7 mm); $n^{27}D$ 1.5462; ir (neat) 2240 (C≡N), 1735 (C=O), and 1712 cm^{-1} (C=O); nmr (25% in $CDCl_3$) τ 2.10–2.75 (m, 4, C_6H_4), angular CH superimposed on two nonequivalent ester CH_2's (s, τ 5.94 superimposed on q, J = 7 Hz, 5.96 and q, J = 7 Hz, 6.03, total wt 3), 6.74–7.01 (m, 1, bridgehead H), 7.43–9.15 (t, J = 7 Hz, 8.94 and t, J = 7 Hz, 8.99 superimposed on m, CH_2, total wt ~11).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44: N, 4.71. Found: C, 72.52; H, 6.29; N, 4.80.

Reaction of 5 with methylmagnesium iodide in ether was carried out in a conventional manner to give the crude 1,2 adduct (**9-methyl-1,2,3,4-tetrahydrofluoren-9-ol, 26**), 97% yield (2.10 g, mp 101–122°). An nmr spectrum of this crude product confirmed the absence of **27**. The crude alcohol was recrystallized from ethanol–water to give pure **26**: white needles, 1.75 g; 81% yield; mp 142–143°; ir (Nujol) 3305 (OH) cm^{-1}; uv (95% EtOH) λ_{max} mμ (log ϵ) 272 (3.83), 276 sh (3.85); nmr (19% in $CDCl_3$) τ 2.58–3.13 (m, 4, C_6H_4), 7.60–7.95 (m, 4, allylic CH_2), 8.08 but varied with concentration (s, 1, OH), 8.13–8.38 (m, 4, CH_2), 8.62 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.72; H, 7.80.

Reaction of 5 with methyllithium[16] in ether gave 2.15 g (98% yield) of **26** (mp 141–143°).

(16) Obtained from the Foote Mineral Co.

Reaction of 5 with Lithium Dimethylcopper.—A solution of methyllithium[16] in ether (1.4 *M*, 34 ml, 0.048 mol) was added dropwise, with stirring, under dry nitrogen to a slurry of cuprous iodide (4.76 g, 0.025 mol) in anhydrous ether at 0°. The solution was aged for 30 min and the ketone **5** (2.00 g, 0.0109 mol) in anhydrous ether (40 ml) was then added dropwise. The resulting mixture was aged for 30 min at 0° and was then poured into cold 20% ammonium chloride (100 ml) with vigorous mixing. The dry faintly yellow oil (2.21 g, 100% yield) obtained from the organic extract was essentially pure **4a-methyl-1,2,3,4,4a,9a-hexahydrofluoren-9-one (27)**; spectral analysis (ir and nmr) confirmed the absence of any alcohol (**26**). Short-path distillation of this crude product gave pure **27** (2.08 g, 95% yield): bp 94–98° (0.2 mm); $n^{26}D$ 1.5580; ir (neat) 1715 (CO) cm^{-1}; uv (95% EtOH) λ_{max} mμ (log ϵ) 245 (4.03), 290 (3.35); nmr (32% in CCl_4) τ 2.29–2.90 (m, 4, C_6H_4), 7.62–9.03 (s, 8.56, CH_3, superimposed upon m, CH_2, total wt 12).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.14.

The **2,4-dintrophenylhydrazone of 27** (82% yield) was recrystallized from ethanol–ethyl acetate and obtained as bright red needles melting at 209–210.6°.

Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.54; N, 14.50.

Ketone 27 was also obtained by reaction of **5** with the complex of methyllithium and tetrakis[iodo(tri-*n*-butylphosphine)copper(I)]. The reaction was carried out as described for similar reactions by House, *et al.*[10] The crude product contained no alcohol **26** (nmr), and a mixture of **27** and tri-*n*-butylphosphine was obtained by distillation. The mixture thus obtained was treated in ether with excess methyl iodide to precipitate methyl tri-*n*-butyl-phosphonium iodide. Distillation of the residual oil gave 1.79 g (82% yield) of 27, bp 103–106° (0.7–0.6 mm), $n^{25}D$ 1.5585, which still contained a trace of tri-*n*-butylphosphine.

Registry No.—**5**, 634-19-5; **8**, 19459-37-1; **10**, 19462-82-9; **12**, 19459-38-2; **14**, 19459-39-3; **15**, 19459-40-6; **16**, 19459-41-7; **21**, 19459-42-8; **22**, 19459-43-9; **22** (enol acetate), 19459-44-0; **23**, 19462-83-0; **24**, 19459-45-1; **25**, 19459-46-2; **26**, 19462-84-1; **27**, 19462-85-2; **27** (2,4-dinitrophenylhydrazone), 19462-86-3.

The Synthesis of 4-Bromophenanthrene[1]

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Two routes by which 4-bromophenanthrene (**1**) has been synthesized are described in detail. In one 4-phenanthrenecarboxylic acid (**2**) is treated with mercuric acetate in N-methylpyrrolidone at 100°. The resulting solution is treated with pyridinium hydrobromide perbromide (or with bromine) to give **1** in 55% yield. The second route involves conversion of diphenic acid (**3**) in seven steps to **1** in 11% over-all yield.

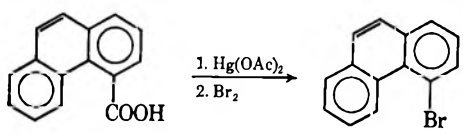
The objective of the work herein described was to develop a good synthesis for 4-bromophenanthrene (**1**). This compound was desired for use in the contemplated synthesis of helicenes by the route developed in this laboratory.[2] Since further synthetic work in this area

(1) This work was supported in part by Grants 5552 and 6624 from The National Science Foundation and in part by Grant DA-ARO(D)-31-124-G206 from the U. S. Army Research Office (Durham).

(2) M. S. Newman and D. Lednicer, *J. Amer. Chem. Soc.*, **78**, 4765 (1956).

is not contemplated because of the success of the photochemical route[3] the description of two routes by which **1** has been prepared is given herein.

One route starts from tetralin. By an eight-step synthesis, 4-phenanthrenecarboxylic acid (**2**) can be made in about 40–45% over-all yield.[4] Although **2** was converted into 4-aminophenanthrene in good yield[4] we have never been able to find proper conditions for the preparation of **1** from the amine. Evidently the steric factors involved interfere not only with ordinary diazotization–replacement reactions but also with the von Schwechten method.[5] However, on treatment of **2** with mercuric acetate in N-methylpyrrolidone at 100° 1 equiv of carbon dioxide is evolved to yield a solution which, on treatment with pyridinium hydrobromide perbromide[6] (or 2 equiv of bromine), yields 4-bromophenanthrene (**1**) in good yield.

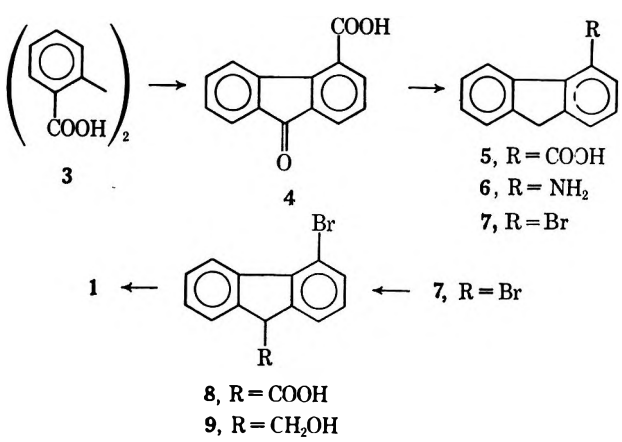


2 **1**

This method of conversion of an aromatic acid to the corresponding bromo compound apparently works well only with **2** as no 2-bromonaphthalene or bromobenzene was obtained on similar treatment of 2-naphthoic and benzoic acids. We were unable to prepare **1** from **2** by Cristol and Firth's procedure.[7] The modification of this method which uses $CBrCl_3$ [8] instead of CCl_4 was also tried without success.

The second route to **1** involved a multistep synthesis from diphenic acid (**3**) as shown in Scheme I. The

SCHEME I



yield in each step is approximately 90% except for the conversion of **6** into **7** (66%) and **9** into **1** (47%).

Relatively little work has been done in attempts to improve the yield of **1** from **9** as we tried only the conditions used by Collins and coworkers which worked well on similar rearrangements.[9]

The structure of **1** was confirmed by formation of the corresponding lithium derivative by exchange with butyllithium, followed by reaction with carbon dioxide to form pure 4-phenanthroic acid. In one experiment **1** yielded 4-phenanthrylmagnesium bromide (80% by titration) on treatment with magnesium in ether using ethylene dibromide to initiate reaction.[10]

All attempts to prepare 4-chlorophenanthrene by reaction of 4-keto-1,2,3,4-tetrahydrophenanthrene with phosphorus pentachloride followed by treatment of the product with dehydrogenating agents failed to give much 4-chlorophenanthrene. As mixtures containing mainly phenanthrene were obtained this route to 4-chlorophenanthrene was abandoned.

Several attempts at photolysis[11] of *m*-bromo-*trans*-stilbene[12] failed to give any **1**.

The nmr spectrum of **1** was interesting in that one hydrogen appeared as a multiplet centered at τ −0.25. This is unusually low for an aromatic hydrogen.[13] Interestingly, the nmr spectrum of 1-bromobenzo[*c*]-phenanthrene[14] showed no hydrogen at lower field than τ 1.67.

Experimental Section[15]

Fluorenone-4-carboxylic Acid (4).—To 3 kg of polyphosphoric acid (PPA) well stirred and heated to 150° was added 300 g of diphenic acid in five equal portions during 1.5 hr. After a further 3 hr at 150° the cooled mixture was poured into 10 l. of ice water. The dark solid was collected, washed with water, and dissolved in 2 l. of 30% sodium hydroxide. This hot solution was decolorized with charcoal (Norit) then acidified to yield 250 g of crude **4**. Recrystallization from methanol afforded 220 g (80%) of pure **4**, mp 225–226°.[16]

Fluorene-4-carboxylic Acid (5).—By a typical modified Huang-Minlon Wolff–Kishner reduction **4** was converted into **5**, mp 193–195°, in 90% yield (pure **5**).[17] The nitrogen evolution was complete in 1.5 hr at 155°. The over-all yields of pure **5** from **3** were somewhat better when pure **4** was used than when crude **4** was reduced.

4-Aminofluorene (6).—To a solution of the acid chloride of **5** (prepared in quantitative yield from 60.0 g of **5** as described[17]) in 1 l. of acetone at −5 to 0° was added a solution of 38 g of sodium azide in 120 ml of water so that the temperature never

(3) (a) M. Flammang-Barbieux, J. Nasielski, and R. H. Martin, *Tetrahedron Lett.*, 743 (1967); (b) R. H. Martin, M. Flammang-Barbieux, J. P. Cosyn, and M. Gelbcke, *ibid.*, 3507 (1968).

(4) K. G. Rutherford and M. S. Newman, *J. Amer. Chem. Soc.*, **79**, 213 (1957).

(5) M. S. Newman and P. H. Wise, *ibid.*, **63**, 2847 (1941).

(6) Obtained from Arapahoe Chemical Co.; see also L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 967.

(7) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(8) F. W. Baker, H. D. Holtz, and L. M. Stock, *ibid.*, **28**, 514 (1963).

(9) C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, **75**, 1644 (1953), and references therein.

(10) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

(11) C. S. Wood and F. B. Mallory, *ibid.*, **29**, 3373 (1964).

(12) J. I. G. Cadogan, E. G. Duell, and R. W. Inward, *J. Chem. Soc.*, 4164 (1962).

(13) (a) B. V. Cheney [*J. Amer. Chem. Soc.*, **90**, 5386 (1968), and references therein] discusses magnetic deshielding of protons due to intramolecular interactions with hydrogens. Evidently, bromine is more effective. (b) K. D. Bartle and S. A. S. Smith [*Spectrochim. Acta*, **23A**, 1689, 1715 (1967)] show that hydrogens in the 4 and 5 positions in substituted phenanthrenes absorb in the τ 1.0–1.5 region.

(14) M. S. Newman and D. K. Phillips, *J. Amer. Chem. Soc.*, **81**, 3667 (1959).

(15) All melting and boiling points are uncorrected. The term "worked up in the usual way" means that an ether–benzene solution of the organic products of reaction was washed with aqueous acid and/or base, with saturated salt solution, and filtered through a cone of anhydrous magnesium sulfate. The solvent was then stripped and the residue used as described. Analyses by Galbraith Laboratories, Knoxville, Tenn. All experiments described were repeated at least once with comparable results. Often many other less successful variations were tried.

(16) We also obtained **4** in 83% yield on a 20-g run in sulfuric acid as described by E. H. Huntress, K. Pfister, III, and K. H. T. Pfister, *J. Amer. Chem. Soc.*, **64**, 2845 (1942).

(17) E. Sawicki, F. E. Ray, and V. Glocklin, *J. Org. Chem.*, **21**, 243 (1956).

exceeded 0° (15 min). After 30 min this solution was poured into 2 l. of ice water. The tan azide was collected, washed with water and dried in a vacuum desiccator at room temperature *without a drying agent.*[18] The dried azide was dissolved in 800 ml of dry benzene. On warming nitrogen evolution started and was complete after 1 hr at 70°. To this solution at 70° was added 100 ml of absolute ethanol. The solution was then concentrated on a rotary evaporator to yield the corresponding urethane, mp 98.5–101.5°, quantitatively. A pure sample, mp 115.0–115.5°, was obtained by recrystallization from methylene chloride–hexane after chromatography over Florisil. Since there was very little loss in this purification, the lower melting point of the crude material was undoubtedly a polymorphic form. In this run, as in all subsequent runs, the crude urethan was immediately hydrolyzed to **6**.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 6.0; N, 5.5. Found: C, 75.7; H, 5.7; N, 5.3.

A mixture of 72 g of urethan and 300 ml of 30% KOH was heated at gentle reflux overnight during which time the amine separated as an orange solid. After the usual work-up 48 g of **6**, mp 109–110°, was obtained.[19] Sublimation under 1-mm pressure yielded 47 g (91%) of pure **6**, mp 112.6–113.5°.

4-Bromofluorene (7).—A solution of 85 g of **6** in 300 ml of pyridine[20] was added during 2.5 hr to a solution at −20° of nitrosylsulfuric acid prepared by adding 49 g of sodium nitrite to 570 ml of 23 *N* sulfuric acid at −20°. The resulting solution was cooled to −20° and a solution of 90 g of sodium bromide and 90 g of mercuric bromide[5] in 300 ml of water added. The yellow solid was collected and washed with water and 300 ml of acetone. On drying 215 g of yellow solid was at hand. This was suspended in 1.5 l. of toluene and heated to 80° when the evolution of the theoretical amount of nitrogen ceased after 1.5 hr. The solvent was removed on a rotary evaporator and the residue triturated with warm hexane. Filtration and removal of hexane from the filtrate yielded a dark oil which on distillation yielded 75.5 g (66%) of **7**, mp 53–56°. Chromatography of 4 g over 30 g of alumina using hexane yielded 3.9 g, mp 56.5–57.5°, homogeneous by tlc.[21] On exposure to light this colorless material yellowed after several days. The above procedure of heating in toluene gave better yields than heating the dry complex with added sodium bromide.[21,22] Alternatively, **7** was obtained once in 53% yield by a Huang-Minlon reduction of 4-bromofluorenone[16] but this reaction was not reliable.

4-Bromofluorene-9-carboxylic Acid (8).—To a solution of 60 g of **7** in 200 ml dry ether (all dry ether used was distilled from Grignard reagents) was added a 200 ml of 1.26 *N* phenyllithium in ether (freshly prepared). The dark red mixture was stirred for 1 hr then forced with dry nitrogen onto powered CO_2. After treatment with water the products were worked up as usual. From the neutral fraction was isolated 16.5 g (27.5%) of **7** and from the acid fraction 51 g (72%) of **8**, mp 227–229°. Recrystallization from tetrahydrofuran–benzene yielded a colorless analytical sample of **8**, mp 227–229°, with little loss.

Anal. Calcd for $C_{14}H_9BrO_2$: C, 58.2; H, 3.1; Br, 27.6. Found: C, 58.2; H, 3.3; Br, 27.8.

The methyl ester of **8**, mp 66.0–67.5°, was prepared by heating **8** with methanol and HCl.

Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.4; H, 3.7. Found: C, 59.7; H, 3.8.

4-Bromofluorene-9-methanol (9).—Attempts to prepare **9** by $LiAlH_4$ reduction of **8** or its methyl ester failed to yield appreciable amounts of **9**. However, reduction of the acid chloride worked well. The acid chloride was prepared in essentially quantitative yield by treatment of **8** with thionyl chloride in THF at room temperature for 24 hr or similarly with phosphorus pentachloride. A solution of the acid chloride prepared from 22.0 g of **8** in 200 ml of ether was added dropwise to a stirred mixture of 6 g of $LiAlH_4$ in 200 ml of ether at 0°. After treatment with water the usual work-up afforded 16.0 g (97%) of yellow oil which contained no carbonyl (infrared) and was used for rearrangement to **1**. Chromatography over alumina yielded a colorless solid which was crystallized from hexane to yield pure **9**, mp 87–89°.

Anal. Calcd for $C_{14}H_{11}BrO$: C, 61.1; H, 4.0; Br, 29.0. Found: C, 61.3; H, 3.9; Br, 28.8.

4-Bromophenanthrene (1).—To a rapidly stirred solution of 5.0 g of **9** in 150 ml of dry xylene at reflux was added 6 g of phosphorus pentoxide. After 30 min the xylene solution was decanted from a tan residue and concentrated to yield an oil which was chromatographed on 80 g of alumina (Woelm I) using benzene–hexane (1.4). After a small amount of phenanthrene (0.1 g), 2.5 g of a yellow oil was obtained which slowly crystallized. Recrystallization from hexane at −20° yielded 1.8 g (47%) of colorless **1**, mp 48.5–50.0°, homogeneous by vpc. Despite several other attempts no higher yield, and occasionally a much lower yield, was obtained.

Anal. Calcd for $C_{14}H_9Br$: C, 65.4; H, 3.5; Br, 31.1. Found: C, 65.6; H, 3.7; Br, 30.9.

The tetranitrofluorenone[23] complex, mp 191.5–192.5°, separated as red needles from acetone–ethanol.

Anal. Calcd for $C_{27}H_{13}BrN_4O_9$: C, 52.5; H, 2.1; Br, 12.9; N, 9.1. Found: C, 52.7; H, 2.2; Br, 12.7; N, 9.2.

A solution of 10.0 g of 4-phenanthrenecarboxylic acid and 14.5 g of mercuric acetate in 30 ml of N-methylpyrrolidone[24] was heated at 80–100° (mostly at 100°) for 6 hr in a small flask during which time 1 equiv of carbon dioxide was evolved. To the resulting yellow solution cooled to 50° was added 18.0 g of pyridinium perbromide (or 2 equiv of bromine). The cooled dark mixture was diluted with 200 ml of water. The organic product, isolated by hexane extraction, consisted of 7.0 g of a yellow oil which by vpc analysis contained about 5% each of phenanthrene and an unidentified substance and 90% **1**. By formation of the red tetranitrofluorenone complex above described followed by chromatography over alumina there was isolated 4.4 g (38%) of pure **1**, mp 48–49°. In another similar run a 55% yield of **1**, mp 41–45°, was obtained by direct crystallization. This material was only slightly contaminated with phenanthrene.

A solution of 0.5 g of **1** in 20 ml of ether was treated with a slight excess of butyllithium. The resulting solution was carbonated to yield 0.3 g of **2**. Identity with an authentic sample was established by mixture melting point and infrared spectra.

A mixture of 0.5 g of magnesium turnings, 2.45 g of **1**, 5 ml of ether, 5 ml of benzene, and 0.3 ml of ethylene dibromide was left at room temperature. After 30 min an exothermic reaction occurred. After 1 hr more titration of the orange solution showed that about an 80% yield of Grignard reagent had been found.

Registry No.—**1**, 19462-79-4; **4**, 6223-83-2; **6**, 7083-63-8; **7**, 19459-33-7; **8**, 19459-34-8; **8** methyl ester, 19459-35-9; **9**, 19459-36-0.

(18) On one occasion when P_2O_5 was used in the desiccator the azide exploded. All subsequent drying was effected in the absence of any desiccant. This azide should be treated as a potentially dangerous compound.

(19) P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).

(20) C. DeMilt and G. vanZandt, *J. Amer. Chem. Soc.*, **58**, 2044 (1936).

(21) P. H. Grantham, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **26**, 1008 (1961).

(22) H.-W. Schwechten, *Ber.*, **65**, 1605 (1932).

(23) M. S. Newman, W. B. Lutz, and D. Lednicer, *J. Amer. Chem. Soc.*, **77**, 3420 (1955).

(24) We thank the General Aniline and Film Corp. for a generous gift of N-methylpyrrolidone.

6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocins from the Reactions of *o*-Coumaric Acids and Salicylaldehydes

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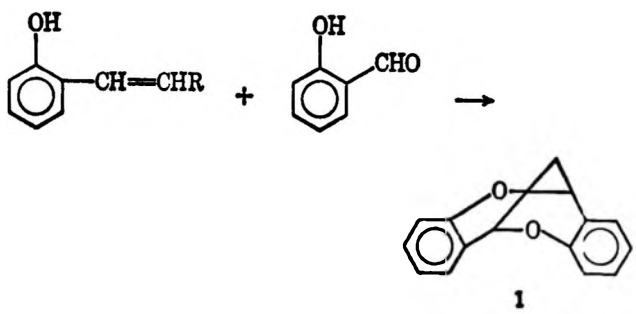
Received March 27, 1968

6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin was prepared from the reaction of *o*-vinylphenol or *o*-coumaric acid and salicylaldehyde in 4.6% yield. 2-Methyl-, 2-bromo-, and 2-nitro-6H,12H-6,12-methanodibenzo[*b,f*]-[1,5]dioxocins were synthesized by the reactions of 2-hydroxy-5-methylcinnamic acid with salicylaldehyde and *o*-courmaric acid with 5-bromo- and 5-nitrosalicylaldehydes, respectively. The reactions of 2-hydroxy-1-naphthaldehyde gave heterocyclics containing a naphthalene ring. 6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin was brominated to the 2,8-dibromo derivative. Both the 2-bromo and 2,8-dibromo derivatives were converted into the nitriles by the reaction with cuprous cyanide. Neither the mono nor dibromo compounds could be converted into Grignard reagents, but were readily metalated with *n*-butyllithium. The organometallics were carbonated to yield carboxylic acids. The heterocyclic ring system of the parent compound was cleaved by hydrogenolysis to 2,2′-trimethylenediphenol. (±)-2-Amino-6H,12H-6,12-methanodibenzo-[*b,f*]-[1,5]dioxocin, prepared by the catalytic hydrogenation of the corresponding nitro compound, was resolved *via* the tartrate salts to yield the optical isomers with specific rotations $[\alpha]^{25}D$ +389.0 and −393.3°. The more abundant (+)-amino compound was reduced *via* diazotization to (+)-6H,12H-6,12-methanodibenzo[*b,f*][1,5]-dioxocin, $[\alpha]^{25}D$ +266.7°.

The reaction of either *o*-vinylphenol or *o*-coumaric acid and salicylaldehyde gave an unexpected neutral product. It was concluded on the basis of elemental and instrumental analyses and conversion of the product into a known compound that the product was the fused



1

R=H or COOH

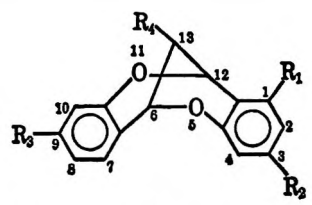
bicyclic heterocyclic structure, 6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**1**). This article is concerned with the extension of the synthesis to substituted products, some chemistry of the parent compound, and the resolution of the 2-amino derivative.

The methanodioxocin ring structure was first recognized in 1,4,6,9-tetrahydro-3,4,8,9-tetramethyl-1,6-diphenyl-4,9-methano[1,5]dioxocino[2,3-*c*:6,7-*c*′]-dipyrazole, the product from the reaction of 2,4-pentanedione and 1-phenyl-3-methyl-2-pyrazolin-5-one.[1] The 6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin structure has recently received considerable attention since Nair, *et al.*,[2] concluded that cyanomaclurin, a compound isolated from the heartwood of *Artocarpus integrifolia* (jackwood),[3] was 1,3,9,13-tetrahydroxy-6H,12H-6,12-methanodibenzo[*b*,f][1,5]dioxocin (**2a**, Chart I). The same investigators synthesized compounds **2b** and **2c** for nmr spectral comparison. Their method consisted of cyclization of appropriate 2,2′-dihydroxychalcones to 2′-hydroxyflavanones, sodium borohydride reduction to flavan-4-ol epimeric mixtures, and then cyclization to the final heterocyclic. Bhatia, Mukerjee, and Seshardi[4] utilized a similar scheme to prepare (±)-trimethylcyanomaclurin (**2d**). This synthesis required a selective oxidation process of the intermediate flavanone to insert a hydroxyl group at the C-13. They also prepared (±)-trimethylcyanomaclurin acetate (**2e**) by direct acetylation of **2d** and by acetylation of the intermediate flavanone before reduction and cyclization.

CHART I

PREVIOUSLY REPORTED

6H,12H-6,12-METHANODIBENZO[*b,f*][1,5]DIOXOCINS



Compd	R_1	R_2	R_3	R_4
2a	OH	OH	OH	OH
2b	OCH_3	H	H	H
2c	OCH_3	OCH_3	H	H
2d	OCH_3	OCH_3	OCH_3	OH
2e	OCH_3	OCH_3	OCH_3	OAc

Structure Proof of Neutral Product from the Reaction of *o*-Vinylphenol and Salicylaldehyde.—A mixture of *o*-vinylphenol, salicylaldehyde, and dilute (5%) hydrobromic acid was heated at the reflux temperature for 12 hr. The neutral product was isolated after alkaline extraction of acidic components and purified (4.6% yield). Elemental analysis and molecular weight determination indicated the molecular formula $C_{15}H_{12}O_2$. The ir spectrum was characteristic for structure **1**. Intense absorption at 753 cm^{-1} with the distinctive pattern in the 1650–2000-cm^{-1} region was compatible with an *ortho*-substituted phenyl ring.

(1) G. Westöö, *Acta Chem. Scand.*, **13**, 679 (1959).

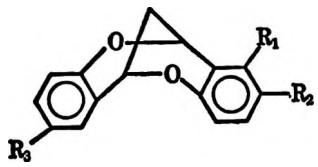
(2) (a) P. M. Nair and K. Venkataraman, *Tetrahedron Lett.*, No. 5, 317 (1963). (b) P. M. Nair, P. C. Parthasarathy, P. V. Radhakrishnan, and K. Venkataraman, *ibid.*, No. 44, 5357 (1966).

(3) A. G. Perkin and F. Cope, *J. Chem. Soc.*, 937 (1895).

(4) G. D. Bhatia, S. K. Mukerjee, and T. R. Seshardi, *Tetrahedron, Suppl.*, 8 (2), 531 (1966).

TABLE I

6H,12H-6,12-METHANODIBENZO[*b*,*f*][1,5]DIOXOCINS FROM *o*-COUMARIC ACID



Compd	R_1	R_2	R_3	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	H	H	H	4.6	159–160.5	$C_{15}H_{12}O_2$				
3	H	Br	H	6.0	168–169	$C_{15}H_{11}BrO_2$[a]	59.41	3.63	59.2	3.47
4	H	NO_2	H	3.0	159–160	$C_{15}H_{11}NO_4$[b]	66.91	4.09	66.8	5.20
5	H	CH_3	H	5.3	128–128.5	$C_{16}H_{14}O_2$	80.67	5.92	80.9	5.93
6	*o*-C_6H_4[c]		H	3.6	128–131	$C_{19}H_{14}O_2$	83.21	5.11	83.4	5.15
7	*o*-C_6H_4[c]		CH_3	3.8	135–140	$C_{20}H_{16}O_2$	83.33	5.56	83.2	5.87

[a] Calcd: Br, 26.40. Found: Br, 26.3. [b] Calcd: N, 5.20. Found: N, 5.23. [c] *o*-Phenylene radical thus representing a naphthalene nucleus.

Several strong sharp bands in the 1000–1250-cm^{-1} region were characteristic for a cyclic ether. Absorptions at 1220 and 2970 cm^{-1} were indicative of phenyl–oxygen and aliphatic carbon–hydrogen bonds, respectively. The 60-Mcps nmr spectrum of **1** was also compatible with the proposed structure. The methylene and benzylic protons appear as triplets at τ 7.75 and 4.72, respectively. This compares favorably with the absorption at τ 7.87 and 4.81 reported for **2b**.[2b] The aromatic ring protons gave a complicated absorption centered at τ 2.95.

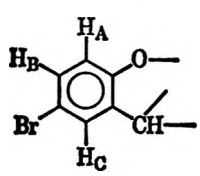
Compound **1** was also prepared from the reaction of *o*-coumaric acid and salicylaldehyde (also a 4.6% yield) under the same reaction conditions. Attempts to isolate **1** with a carboxylic acid group at C-13 were unsuccessful and it is tentatively concluded that the salicylaldehyde is reacting with *o*-vinylphenol formed, *in situ*, by the decarboxylation of *o*-coumaric acid.

Synthesis of Substituted 6H,12H-6,12-Methanodibenzo[*b*,*f*][1,5]dioxocins.—A yield of 4.6% was realized when either *o*-vinylphenol or *o*-coumaric acid was utilized. *o*-Vinylphenols are usually synthesized from *o*-coumaric acids. Therefore, this study was restricted to the reactions of *o*-coumaric acids and salicylaldehydes. The heterocyclics prepared in this study are tabulated in Table I. The reaction conditions were the same as described for the condensation of *o*-vinylphenol and salicylaldehyde.

Compounds **3** and **4** were prepared from the reaction of *o*-coumaric acid with 5-bromo- and 5-nitrosalicylaldehydes, respectively. Compound **5** was synthesized from the reaction of 2-hydroxy-5-methylcinnamic acid and salicylaldehyde. Reactions of 2-hydroxy-1-naphthaldehyde with *o*-coumaric and 2-hydroxy-5-methylcinnamic acids gave the heterocyclics **6** and **7**, thus illustrating the incorporation of a naphthalene nucleus into the molecule.

The yields are low because of polymerization side reactions. However, most of the starting materials are readily available and thus this is a practical way of obtaining this novel structure. Yield comparisons with previously reported methods are not possible because Nair, *et al.*,[2b] did not report yields, and the synthesis by Bhatia, *et al.*,[4] gave an understandably low yield because the preparation of a compound with a hydroxyl group at C-13 was much more difficult. Development work to improve the yields of our method is underway and preliminary results are very encouraging.

Chemistry of 6H,12H-6,12-Methanodibenzo[*b*,*f*][1,5]dioxocins. — 6H,12H-6,12-Methanodibenzo[*b*,*f*][1,5]dioxocin is stable in a basic environment but very unstable in the presence of acids. The benzylic ether linkages are easily cleaved by acids leading to polymeric products. The compound brominates in the presence of ferric oxide or aluminum chloride to produce 2,8-dibromo-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**8**) in 47% yield (Scheme I). The structure of **8** was confirmed by nmr spectral analysis. The aromatic proton spectrum is a single ABC pattern establishing that both rings are substituted in the same manner. H_A, H_B, and H_C (partial structure A) have chemical



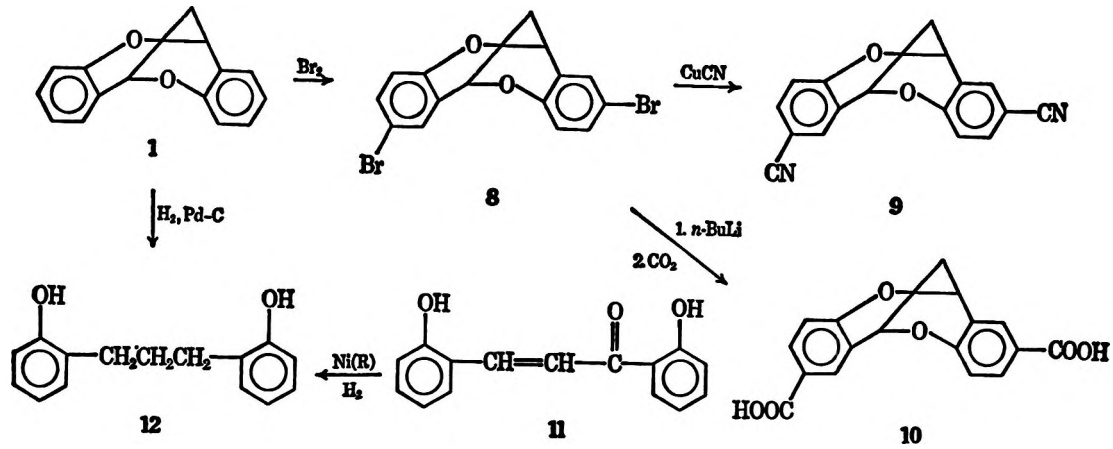
A

shifts of τ 3.37, 2.80, and 2.76, respectively. The coupling constants J_{AB}, J_{AC}, J_{BC} of 8.6 ± 0.1, 0 ± 0.3, and 2.4 ± 0.1 Hz, respectively, indicate that H_A is *ortho* to H_B and *para* to H_C and that H_B is *meta* to H_C. The methylene and methine protons appear as triplets at τ 7.87 and 4.90 indicating that the heterocyclic rings remained intact. This combination of restrictions establishes the structure of the brominated product as 2,8-dibromo-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin. *ortho* substitution in all probability also occurred, but the less abundant *ortho*-substituted products would be lost in the purification of the 2,8-dibromo derivative by crystallization. The brominated heterocyclic was converted into the dicyano compound **9** by reaction with cuprous cyanide in 30% yield.

2,8-Dibromo-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]-dioxocin (**8**) in our hands was completely resistant to Grignard reagent formation. Repeated attempts using a variety of conditions including entrainment techniques and benzene–triethylamine solvent combination[5]

(5) E. C. Ashly, *J. Amer. Chem. Soc.*, **87**, 2506 (1965).

Scheme I



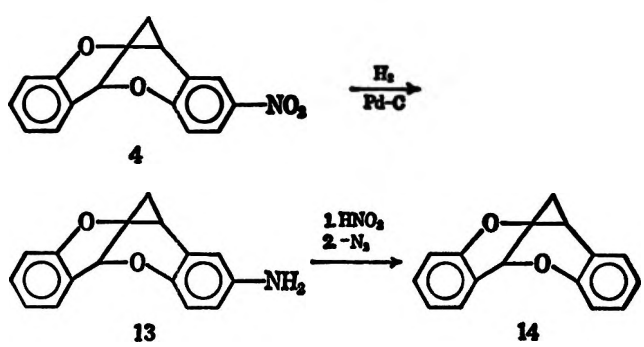
resulted only in almost quantitative recovery of starting material. The chemical was, however, successfully metalated with *n*-butyllithium. This dilithio derivative was carbonated to yield the dicarboxylic acid (**10**) in 63% yield. Similar reactions were conducted with 2-bromo-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**3**), the product of the reaction of *o*-coumaric acid and 5-bromosalicylaldehyde. The compound was converted into the cyano derivative in 30% yield and into the carboxylic acid *via* the organolithium intermediate in only 2% yield. The dibromoheterocyclic was converted into the dicarboxylic acid in 63% yield as noted earlier. The disparity in yields is believed to be due to the difference in solubility of the aryllithium salts in the reaction solvent. The dilithio derivative precipitated from solution and was therefore isolated from possible side reactions so often observed with organolithium compounds.[6] The monolithio derivative was completely soluble and attempts to quickly convert it into the carboxylic acid failed to increase the yield.

Finally, 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin was catalytically hydrogenolyzed to 2,2′-trimethylenediphenol (**12**) in 30% yield. 2,2′-Trimethylenediphenol, a known compound, was also prepared by the reduction of 2,2′-dihydroxychalcone (**11**).[7] The mixture melting point of **12** prepared from **1** and **11** was undepressed and their infrared (ir) spectra were superimposable. More vigorous conditions (75°, 200 lb/in.²) than anticipated were required to open the rings. In fact, the conditions were so vigorous that hydrogenation of the phenol rings to cyclohexanones and cyclohexanols was a serious side reaction resulting in only a 30% yield. Catalytic hydrogenolysis of benzyl ethers often occurs at room temperature in quantitative yields. The difficulty encountered is probably due to the rigidity and nonplanarity of the molecule making it difficult to align properly on the catalyst surface. This hydrogenolysis constituted an important proof of structure of 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin.

Resolution of 2-Amino-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin.—The asymmetry of these heterocyclic molecules was quickly recognized and nonsuperimposability of models of the mirror images was established. The rigidity of the [3.3.1] system prevents the heterocyclic rings from racemizing by turning inside out. The successful resolution of the enantiomers of 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]-dioxocin or a derivative would further confirm the proposed structure for the molecule. Also, it would be of interest to compare the specific rotation of this compound with that of the related natural product, cyanomaclurin, $[\alpha]^{26}D$ +204°.[8]

The chemistry involved in this investigation is outlined in Scheme II. 2-Nitro-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin was hydrogenated to the amine **13** utilizing palladium-on-carbon catalyst at 60° and atmospheric pressure in 87% yield. The hydrogenation was followed by disappearance of the nitro group ir absorption peak at 1350 cm^{-1}. Disappearance

Scheme II



of the cited peak required 4 hr. The high yield indicated that hydrogenolysis of the heterocyclic rings was not a problem.

Resolution utilizing (−)-malate salts was partially successful. Enriched optical isomers of $[\alpha]^{25}D$ +4 and −27° were obtained. Although these results were encouraging, a much better resolution was desired. The complete resolution was achieved using (+)-tartaric acid as the resolving agent. Several recrystallizations of the less soluble tartrate salt and restoration to the original amine yielded the dextrorotatory isomer, $[\alpha]^{25}D$ +389.0°. The tartrate salt in the mother liquor from the first crystallization was converted into the free amine. Recrystallization of the amine to a constant specific rotation yielded the levorotatory isomer, $[\alpha]^{25}D$ −393.3°. The ultraviolet (uv) absorption spectra of (+)- and (−)-2-amino-6H,12H-6,12-

(6) R. G. Jones, *Organic Reactions*, **6**, Chapter 7 (1951).

(7) A. T. Carpenter and R. F. Hunter, *J. Appl. Chem.* (London), **1**, 217 (1951).

(8) H. Appel and R. Robinson, *J. Chem. Soc.*, 752 (1935).

methanodibenzo[*b,f*][1,5]dioxocin were identical and their optical rotatory dispersion curves showed opposite Cotton effects with equal intensities centered at 279 mμ.

After considerable practice of converting (±)-2-amino-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**5**) into **1** by reduction *via* the diazonium salt, the (+)-amino compound was converted into (+)-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**14**), $[\alpha]^{25}D$ +266.7°, in 84% yield. The (−)-amino compound was not similarly treated to yield levorotatory parent compound because so little was isolated in the resolution.

The successful resolution of (±)-2-amino-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin confirms the rigidity of this heterocyclic molecule. The capability of resolution is consistent with the proposed structures for these compounds. The specific rotations of the optical isomers isolated compared favorably with the specific rotation of cyanomaclurin.

Experimental Section[9]

Starting Materials.—*o*-Coumaric acid,[10] *o*-vinylphenol,[10] 2-hydroxy-5-methylcinnamic acid,[11] and 5-bromosalicylaldehyde[12] were prepared by published procedures. Yields and physical properties were in good agreement with literature values. 5-Nitrosalicylaldehyde (Eastman) and 2-hydroxy-1-naphthaldehyde (Aldrich Chemical Co., Inc.) were purchased.

6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin (1) from the Reaction of *o*-Vinylphenol and Salicylaldehyde.—A mixture of 5.2 g (0.043 mol) of *o*-vinylphenol, 7.5 g (0.062 mol) of salicylaldehyde, 50 ml of water, and 5 ml of concentrated (48%) hydrobromic acid was stirred and heated at the reflux temperature for 12 hr. Then 75 ml of 10% sodium hydroxide solution was added and heating was continued for 1 hr. The yellow undissolved solid was collected on a Büchner funnel and recrystallized from aqueous ethanol to yield 0.44 g (4.6%) of fine white needles: mp 160–160.5°; $\lambda_{max}^{isooctane}$ 277 mμ (ε 4310), 286 (3370).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 80.33; H, 5.40; mol wt, 224. Found: C, 80.28; H, 5.56; mol wt, 224 (mass spectrum).

General Procedure for the Preparation of 6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocins from *o*-Coumaric Acids.—The size of the runs ranged from 0.1 to 1 *M* quantities of starting materials. The ratios of reactants, solvents, etc., were kept constant in all the experiments. As a general procedure, a mixture of molar quantities of the *o*-coumaric acid and the salicylaldehyde, 1500 ml of water, and 100 ml of hydrobromic acid (48%) were stirred and heated at the reflux temperature for 12 hr. Sodium hydroxide solution (10%, 2000 ml) was added and heating was resumed at the reflux temperature for 1 hr. Insoluble crude yellow solid product was collected on a Büchner funnel, water washed, and recrystallized from ethanol–water mixtures. In this manner (Table I), the reaction of *o*-coumaric acid with salicylaldehyde, 5-bromosalicylaldehyde, 5-nitrosalicylaldehyde, and 2-hydroxy-1-naphthaldehyde gave compounds **1**, **3**, **4**, and **6**, respectively. The reaction of 2-hydroxy-5-methylcinnamic acid with salicylaldehyde and 2-hydroxy-1-naphthaldehyde gave compounds **5** and **7**, respectively.

2,8-Dibromo-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (8).—A mixture of 5.0 g (0.022 mol) of 6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**1**), 100 ml of carbon tetrachloride, 7.2 g (0.045 mol) of bromine, and 0.1 g of ferric oxide was heated for 6 hr at the reflux temperature. Evaporation of the mixture to dryness left a reddish brown solid which was extracted two times with 75-ml portions of boiling ethanol. The crude product precipitated from the cooled ethanolic extracts. The mother liquors were diluted with water while hot and cooled to give second crops. The combined crude product fractions were recrystallized from ethanol to yield 4.09 g (47%) of product, mp 143–145°. An analytical sample recrystallized twice from ethanol gave white needles, mp 145–146.5°.

Anal. Calcd for $C_{16}H_{10}Br_2O_2$: C, 47.15; H, 2.16; Br, 41.83. Found: C, 47.36; H, 2.53; Br, 41.69.

The compound was also prepared in 49% yield under the same conditions utilizing 0.2 g of aluminum chloride as the catalyst instead of ferric oxide.

2,8-Dicyano-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (9).—A mixture of 1.00 g (0.00262 mol) of 2,8-dibromo-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**8**), 1.0 g (0.011 mol) of cuprous cyanide, and 5 ml of pyridine was heated for 6 hr at 150°. The pyridine was removed by distillation under reduced pressure and the brown residue was heated with 10% hydrochloric acid for 30 min at reflux temperature. The acid-insoluble solid was collected, dissolved in hot acetone, and treated with Norit. Cooling of the acetone solution yielded a white solid, mp 284–289°. Three additional recrystallizations from acetone gave 0.215 g (30%) of white crystalline product, mp 309–312°.

Anal. Calcd for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.65; N, 10.22. Found: C, 74.5; H, 3.63; N, 10.40.

2-Cyano-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin.—This compound was prepared from 2-bromo-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**3**) and cuprous cyanide in pyridine and purified in the same manner as described for the 2,8-dicyano derivative (**9**) yielding white needles also in 30% yield: mp 152–154°; ν_{max}^{Nujol} 2220 cm^{-1} (C≡N).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.41; N, 5.62. Found: C, 76.9; H, 4.31; N, 5.99.

6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin-2,8-dicarboxylic Acid (10).—To a solution of 9.00 g (0.236 mol) of 2,8-dibromo-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**8**) in 100 ml of benzene under a nitrogen atmosphere was added 21 g (0.49 mol, 15% in *n*-hexane) of *n*-butyllithium and 60 ml of dry ether. A white precipitate formed after a short period of heating; copious amounts were present after 30 min at 50–60°. The mixture was poured over crushed Dry Ice. Ether (100 ml) was used to aid the transfer and water was added after carbonation completion. The layers were separated. Acidification of the aqueous layer with concentrated hydrochloric acid precipitated a white solid which was recrystallized from tetrahydrofuran to yield 4.6 g (63%) of white crystalline product: mp >300°; ν_{max}^{Nujol} 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.38; H, 3.85. Found: C, 65.6; H, 4.03.

6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin-2-carboxylic Acid.—This compound was prepared from 2-bromo-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin (**3**) and *n*-butyllithium followed by carbonation in the same manner as previously described for the 2,8-dicarboxylic acid derivative (**10**). The yield of white crystalline product, mp 178–181°, was only 2%.

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.34; H, 4.48. Found: C, 71.4; H, 4.49.

2,2′-Trimethylenediphenol (12).—6H,12H-6,12-Methanodibenzo[*b,f*][1,5]dioxocin (**1**, 2.0 g, 0.089 mol) was hydrogenolyzed in 250 ml of absolute ethanol in the presence of 5 g of palladium (5%) on charcoal in a Parr Series 4500 medium-pressure apparatus. Reaction conditions were 75° for 4 hr at 200 lb/in.² of pressure. The palladium catalyst was collected on a Büchner funnel and the ethanol was removed by distillation under reduced pressure (*ca.* 20 mm). The viscous, colorless, oily residue could not be induced to crystallize. The oil was mixed with 5% sodium hydroxide solution. The alkaline solution was extracted with carbon tetrachloride and then carbonated with Dry Ice. The flocculant white solid which separated was collected and recrystallized from Skellysolvent (bp 60–100°) to yield 0.61 g (30%) of 2,2′-trimethylenediphenol, mp 95.5–96° (lit.[7] mp 97–99°).

Authentic 2,2′-dihydroxychalcone (**12**) (lit. mp 161–163°,[7] 154–155°[13]) was prepared from the reaction of *o*-hydroxyacetophenone and salicylaldehyde,[7] mp 159–162°. This chalcone was hydrogenated to 2,2′-trimethylenediphenol, mp 96.5–97° (lit.[7] mp 97–99°), *via* the method of Carpenter and Hunter.[7] The

(9) Melting points were determined in a "Melt-Pointer" (Scientific Glass Apparatus Co., Inc.) and are corrected. Elemental analyses were done by the staff of Dr. P. Boyd, The Dow Chemical Co. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 237, the ultraviolet spectra on a Cary recording spectrophotometer, Model 15, specific rotations and optical rotatory dispersion curves on a Cary 60 spectropolarimeter, and nmr spectra on a 60-Mcps Varian Associates instrument.

(10) I. H. Updegraff and H. G. Cassidy, *J. Amer. Chem. Soc.*, **71**, 407 (1947).

(11) T. J. Thompson and R. H. Edee, *ibid.*, **47**, 2556 (1925).

(12) A. Auwers and O. Burger, *Ber.*, **37**, 3929 (1904).

(13) E. Shraufestatter and S. Deutch, *Chem. Ber.*, **81**, 489 (1949).

mixture melting point of a mixture of 2,2′-trimethylenediphenol (12) from 11 and 1 was 96.5–97°. The ir spectra of 12 prepared by both methods were superimposable.

(±)-2-Amino-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin (13).—2-Nitro-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin (4,2.60 g, 0.00967 mol) dissolved in 150 ml of benzene was placed in a flask equipped with a hydrogen sparger tube. Palladium-on-carbon catalyst (1.0 g) was added and a stream of hydrogen was sparged through the heated (60°) stirred mixture. Reaction progression was followed by periodically sampling the reaction mixture and observing the diminishment of the nitro group ir absorption at 1350 cm^{-1}. Four hours were required for complete disappearance of the peak and thus reaction completion. The catalyst was collected on a Büchner funnel and the filtrate solvent was removed by evaporation. The yellow residue was dissolved in hot ethanol, treated with Norit, and recrystallized twice from ethanol to yield 1.87 g (81%) of product as white needles: mp 208–210°; ν_{max}^{KBr} 1640, 3400 cm^{-1} (NH_2).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.8; H, 5.47; N, 5.81.

The acetamide was prepared from the reaction of 13 and acetic anhydride and purified by recrystallization from ethanol to yield white needles, mp 173–175°.

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.60; H, 5.34; N, 4.98. Found: C, 72.7; H, 5.40; N, 5.03.

The benzamide was prepared by the reaction of 13 and benzoyl chloride and recrystallized from aqueous ethanol to give white needles, mp 160–162°.

Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.97; H, 4.96; N, 4.08. Found: C, 76.8; H, 5.02; N, 4.04.

The phenylthiourea derivative was synthesized by the reaction of 13 and phenylisothiocyanate and purified by recrystallization from ethanol to yield a white solid, mp 172–175°.

Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.58; H, 4.81. Found: C, 70.2; H, 4.90.

Resolution of (±)-2-Amino-6H-12H-6,12-methanodibenzo[b,f][1,5]dioxocin.—A solution of 2.0 g (0.0084 mol) of (±)-2-amino-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin in 100 ml of ethanol was mixed with 0.90 g (0.00625 mol) of (+)-tartaric acid. The solution was heated to achieve reaction and solution. Ethanol was removed by evaporation until 40 ml of solution remained. This solution was allowed to slowly cool. The salt which precipitated was collected. The filtrate was further reduced by evaporation to ~25 ml. A second crop of crystals were collected. The two crops were combined, recrystallized 10 times from ethanol, and then decomposed with warm 10% sodium hydroxide solution. The free amine was recrystallized twice from ethanol to yield 0.2 g of the dextrorotatory isomer as white needles: mp 238–240°; $[\alpha]^{25}D$ +389.0° (CH_3OH). The mother liquor from the second crop of tartrate salt crystals was made alkaline with 10% sodium hydroxide solution to pH 10. The free amine was collected and recrystallized several times from ethanol to a constant specific rotation to yield 0.05 g of the levorotatory isomer as white needles: mp 242–244°; $[\alpha]^{25}D$ −393.3° (CH_3OH). The uv absorption spectra of the enantiomers were superimposable: $\lambda_{max}^{CH_3OH}$ 301 mμ (ε 2120), 286 (2460), 277 (2420). The (+) and (−) isomers showed positive and negative Cotton effects, respectively, in the ORD curves centered at 279 mμ, $[\alpha]_{291}^{25}$ 7500° (CH_3OH).

(+)-6H,12H-6,12-Methanodibenzo[b,f][1,5]dioxocin from 13.—(+)-2-Amino-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin (0.14 g, 0.000586 mol) was dissolved in 10 ml of 15% hydrochloric acid solution. Sodium nitrite (0.07 g, 0.001 mol) dissolved in 2 ml of water was added dropwise with stirring to the cold (0°) amine salt solution. Starch–iodide paper gave a positive nitrous acid test at the end of the addition. The reaction mixture was kept at 15° for 0.5 hr and then was added in 1-ml portions to a boiling solution of 0.2 g of cupric sulfate pentahydrate dissolved in 50 ml of ethanol. The reaction temperature was maintained between 70 and 80° and gas evolution was allowed to subside considerably between additions. Heating of the reaction mixture was continued for 0.5 hr after addition was complete. The ethanol was removed by distillation. The solid which precipitated in the cooled residue was collected on a filter, washed with water, and recrystallized from acetone to give 0.11 g (84%) of white needles: mp 153–154°; $\lambda_{max}^{CH_3OH}$ 277 mμ (ε 3790), 286 (3090). The uv absorption spectrum compares favorably with the racemate: $\lambda_{max}^{CH_3OH}$ 277 mμ (ε 4040), 286 (3160). The ir spectra of the (+) enantiomer and the racemic mixture were superimposable. Significant points in the ORD spectrum were $[\alpha]_{295}^{25}$ −8900, $[\alpha]_{290}^{25}$ +8900, $[\alpha]_{295}^{25}$ +4000, $[\alpha]_{300}^{25}$ +2800, $[\alpha]_{305}^{25}$ +1800, $[\alpha]_{310}^{25}$ +1100, and $[\alpha]_{315}^{25}$ +800° (CH_3OH).

Reduction of and Coupling Products of (±)-6H,12H-6,12-Methanodibenzo[b,f][1,5]dioxocin-2-diazonium Chloride.—(±)-2-Amino-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin was converted into the corresponding diazonium chloride in the same manner as previously described for the dextrorotatory isomer. A portion was reduced as described for the (+) enantiomer to give (±)-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin, mp 159–160°, which had an ir spectrum superimposable with that of an authentic compound. Another portion of the diazonium chloride was coupled with β-naphthol to form 1-{(6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-2-yl)azo}-2-naphthol which was recrystallized from acetone to yield red needles, mp 260–261°.

Anal. Calcd for $C_{25}H_{18}N_2O_3$: C, 76.14; H, 4.57; N, 7.11. Found: C, 76.5; H, 4.70; N, 6.82.

Reaction of the diazonium salt with 2,6-dichlorophenol gave 2,6-dichloro-4-{(6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-2-yl)azo}phenol which was recrystallized from acetone to yield yellow crystals, mp 208–209°.

Anal. Calcd for $C_{21}H_{14}N_2O_3Cl_2$: C, 61.02; H, 3.39; N, 6.78. Found: C, 61.3; H, 3.40; N, 6.31.

Registry No.—**1,** 7490-81-5; **3,** 19203-30-6; **4,** 19203-31-7; **5,** 19203-32-8; **6,** 19203-33-9; **7,** 19203-34-0; **8,** 19203-35-1; **9,** 19203-36-2; **10,** 19203-37-3; (±) **13,** 19206-21-4; (±) **13** (acetamide), 19206-22-5; (±) **13** (benzamide), 19206-23-6; (±) **13** (phenylthiourea derivative, 19206-24-7; (+) **13,** 19206-25-8; (−) **13,** 19206-26-9; (+) **14,** 19221-85-3; 2-cyano-6H-12H-6,12-methanodibenzo[b,f][1,5]dioxocin, 19221-84-2; 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-2-carboxylic acid, 19203-38-4; 1-{(6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-2-yl)azo}-2-naphthol, 19203-39-5; 2,6-dichloro-4-{(6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-2-yl)azo}phenol, 19203-40-8.

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Novel Intramolecular Cyclizations of Diels–Alder Adducts Derived from Hexachlorocyclopentadiene and Allylic Alcohols

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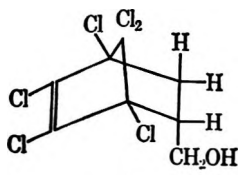
Treatment of 1,4,5,6,7,7-hexachloro-5-norbornene-*endo*-2-methanol (1) with excess alcoholic base results in the formation of a tricyclic ketal, 3a,4,4,5,6-pentachlorohexahydro-6a-methoxy-3,5-methano-2H-cyclopenta[*b*]-furan (2).[2] The ring closure has been shown to take place with sodium or potassium alkoxide, phenoxide, and mercaptide as participating nucleophiles. Bicyclic alcohols 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3-dimethanol, 1,4,5,6-tetrachloro-7,7-dimethoxy-5-norbornene-*endo*-2-methanol, and 1,4,5,6,7,7-hexachloro-*endo*-2-(epoxyethyl)-5-norbornene (**8**) have also been shown to cyclize in a similar manner.

We have observed an unexpected ring closure involving nucleophilic addition to an isolated double bond[3] while studying the chemistry of various unsaturated alcohol–Diels–Alder adducts of hexachlorocyclopentadiene. Refluxing of **1** with a large excess of



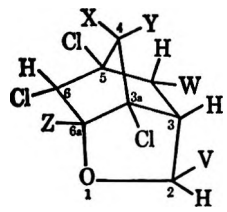
1

sodium methoxide results in the loss of 1 mol equiv of chloride ion and the disappearance of the alcohol group and dichloroethylene unsaturation. The compound resulting is believed to be tricyclic ketal **2**. Cyclization has also been demonstrated with **1** and alcoholic solutions of sodium ethoxide, sodium ethylmercaptide, sodium allyloxide, sodium 4-chlorophenoxide and sodium 2,4-dichlorophenoxide to yield, respectively, **3**, **4**, **5**, **6**, and **7**.

Other bicyclic adducts have been used. The epoxide 1,4,5,6,7,7-hexachloro-*endo*-2-(epoxyethyl)-5-norbornene[4] (**8**) opens up to give an alcohol and when treated with sodium ethoxide yields the ketal **9**. Diol 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3-methanol[5] was cyclized with sodium methoxide to give **10** and with sodium ethoxide to give the corresponding ethoxy ketal.

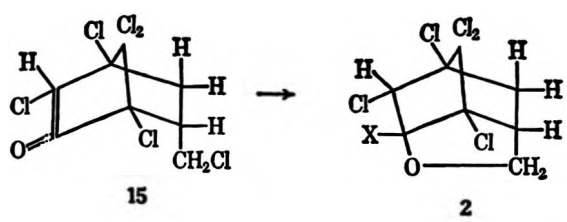
Bicyclic alcohols derived from 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene undergo ring closure also. Ketal **11** results from the reaction of 1,4,5,6-tetrachloro-7,7-dimethoxy-*endo*-5-norbornene-2-methanol[6] (**12**) and sodium ethoxide.

Cyclization of the alcohols occurs most smoothly and in the highest yield when the alkoxides are used in 3–4 molar excess and when they are prepared in the anhydrous form. The cyclization could not be effected with alcoholic potassium cyanide or sodium acetate in acetic acid or with triethylamine in ethanol.



2, V, W = H; Z = OCH_3; X, Y = Cl
3, V, W = H; Z = OCH_2CH_3; X, Y = Cl
4, V, W = H; Z = SCH_2CH_3; X, Y = Cl
5, V, W = H; Z = $OCH_2CH=CH_2$; X, Y = Cl
6, V, W = H; Z = 4-ClC$_6$H$_4$O; X, Y = Cl
7, V, W = H; Z = 2,4-Cl$_2$C$_6$H$_3$O–; X, Y = Cl
9, V = $CH_2OCH_2CH_3$; W = H; Z = OCH_2CH_3; X, Y = Cl
10, V = H; W = CH_2OH; Z = OCH_3; X, Y = Cl
11, V, W = H; Z = OCH_2CH_3; X, Y = OCH_3
13, V, W = H; Z = OH; X, Y = Cl
14, V = H; W = CH_2OH; Z = OH; X, Y = Cl
16, V, W = H; Z = CN; X, Y = Cl
17, V, W = H; Z = COOH; X, Y = Cl

The chemistry of the ketals was explored. For example, hot sulfuric acid converts ketals **2** or **10** into hemiketals **13** and **14**, respectively. An attempt was made to convert hemiketal **13** into the chloro ether with phosphorus pentachloride. However, chloro methyl ketone **15** resulted instead. Ketone **15** upon reaction with 1 mol equiv of methanolic potassium hydroxide at reflux yields ether **2** in excellent yield. Ketone **15** treated with 1 mol equiv of sodium bicarbonate in a tetrahydrofuran–water mixture at reflux yields hemiketal **13**. These transformations shown quite conclusively prove that **13** is a hemiketal.



15 **2**

Ketone **15** reacts quantitatively with potassium cyanide in refluxing ethanol to give cyano ether **16**. The cyano ether as noted earlier cannot be formed from **1** directly. Compound **16** is hydrolyzed with difficulty at elevated temperatures in sulfuric acid to acid **17**.

The structure of **2** is supported by elemental, infrared (ir), and nuclear magnetic resonance (nmr) analysis. The known alcohol **1** shows the characteristic hydroxyl

(1) Address inquiries and requests for reprints to this author.

(2) Nomenclature based on 3,5-methano-2H-cyclopenta[*b*]furan: A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed, American Chemical Society, Washington, D. C., 1960, RR I 2253.

(3) S. Patai and Z. Rappoport "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 8.

(4) E. K. Fields, *J. Amer. Chem. Soc.*, **76**, 2709 (1954).

(5) H. E. Ungrade and E. T. McBee, *Chem. Rev.*, **58**, 249 (1958).

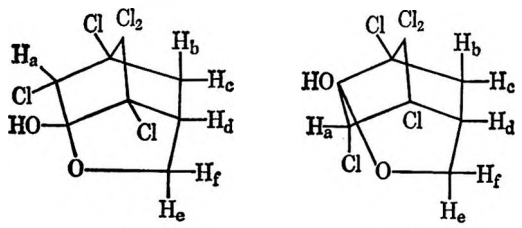
(6) E. T. McBee, W. R. Diveley, and J. C. Burch, *J. Amer. Chem. Soc.*, **77**, 385 (1955).

stretching absorption at 3350 cm^{-1} and the dichloroethylene absorption at 1620 cm^{-1}. Ketal **2** spectrum lacks these absorptions.

Evidence for the fact that **2** is indeed a ketal was cited earlier in that ketone **15** was readily converted back into **2** and hemiketal **13**. There are many related intramolecular cyclizations reported in the literature.[7-9]

One interesting problem with the assignment of structure **2** was whether a five- or six-membered ring was formed. We initially assumed a five-membered ring on the basis of favored geometry. There are other examples in bicyclic systems of preferred five-membered ring closures, *e.g.*, iodo and bromo lactonization.[10] The decomposition of acid peroxides from *endo*-norbornene-2-carboxylic acid gave essentially all five-membered lactone.[11] The nmr spectrum gave us rather conclusive proof that the five-membered ring closure was the correct configuration in the present work.

The nmr spectrum of **13** is shown in Figure 1. The two structures possible are **13** and **13a**. Proton H_a



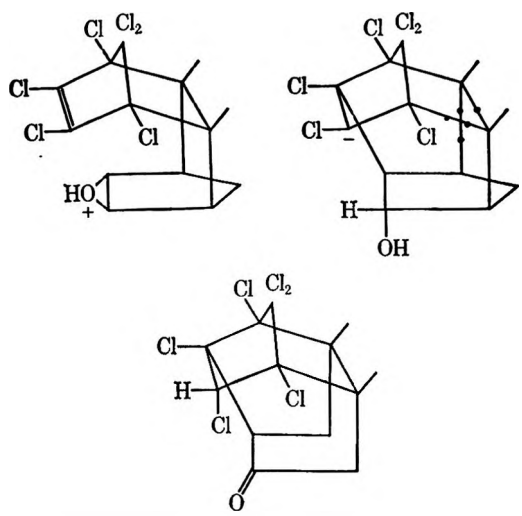
13 **13a**

should show a W[12,13] coupling to H_b if **13** is the correct structure or to H_d if **13a** is correct. The latter proposed coupling between H_d to H_a is not as likely on the basis of inspection of models but cannot be excluded *a priori*. Proton H_a appears as a doublet (J = 1.2 Hz) centered at δ 4.70. Proton H_b is assigned to a skewed quartet centered at δ 2.66. Decoupling of H_a caused this multiplet to collapse to a doublet. This locates the position of the other W-coupled proton. Its identity in the structure must still be designated. Proton H_f was assigned to a quartet centered at δ 4.23 and H_e to a doublet at δ 3.74. Inspection of a molecular model verifies this interpretation in that one is at 90° dihedral angle to H_d and should show little or no coupling to this proton. The other is at about 60° and a 2–4-Hz coupling is expected. Decoupling of H_f causes the doublet assigned to H_e at δ 3.74 to collapse to a singlet. This decoupling of H_f also simplifies the multiplet assigned to H_c at δ 2.88, but does not effect the multiplet assigned to H_b at δ 2.66. We can conclude then that H_b is not coupled to the methylene protons H_e and H_f and is W coupled to H_a. Therefore, we are confident **13** is the correct structure for the ketal. We tacitly assume that all the ketals and derivatives have this same configuration.

Figure 1.—Nmr spectrum of tricyclic hemiketal **13**.

The formation of these cyclic ketals is unique in the chemistry of hexachlorobicyclic Diels–Alder adducts. Generally the dichloroethylene bond in such adducts is very inert to alkoxide reagents. The reaction of the adduct of hexachlorocyclopentadiene, 1,2,3,4,7,7-hexachloro-2,5-norbornadiene with alcohol base was postulated by Mackensie to result in an addition–elimination to the dichloroethylene bond to form 1,3,4,7,7-pentachloro-2-methoxy-2,5-norbornadiene because of the stabilization of the intermediate carbanion through homoconjugation with the 5,6 double bond.[14] The 5,6-dihydro derivative is inert to alcoholic base under the above conditions. Our own studies have demonstrated the inertness of the dichloroethylene bond in similar adducts of hexachloropentadiene with simple olefins and with 2,5-dihydrofuran.

The relative ease of attack of the dichloroethylene group in the bicyclic alcohols of this study is undoubtedly due to the favored geometry for transannular ring closure of the intermediate *endo* anion formed. Other such transannular reactions have been published. An example is epoxide **18** which upon treatment with acidic reagents also undergoes transannular reactions with the dichloroethylene bond to yield a five-membered ring closed ketone.



The driving force for all these reactions is the formation of the favored pentacyclic structure. The cyclizations in the present study represent the first example of an anion being involved in such reactions.

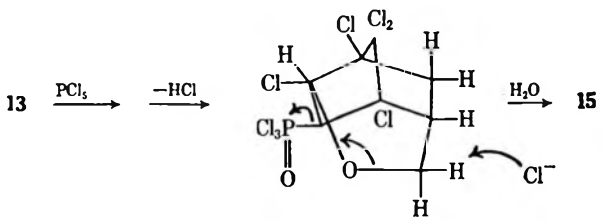
We did observe that higher yields of the cyclic ketals with less byproducts resulted when an excess of base was used and when the alkoxide was prepared with a minimum of water present. This suggests an unfavorable equilibrium between the alkoxide and the bicyclic alcohol.

Once the bicyclic anion is formed, attack on the electron-deficient ethylene bond should be feasible. This addition of the anion introduces a bridgehead at

(7) R. T. Arnold, M. Campos, and K. L. Lindsay, *J. Amer. Chem. Soc.*, **75**, 1044 (1953).
(8) J. R. Holium, D. Jerenby, and P. Mathison, *J. Org. Chem.*, **29**, 769 (1964).
(9) D. J. Pasto and M. P. Serve, *J. Amer. Chem. Soc.*, **87**, 1515 (1965).
(10) G. I. Poos and M. Lehman, *J. Org. Chem.*, **26**, 2575 (1961).
(11) H. Hart and F. J. Chloupek, *J. Amer. Chem. Soc.*, **85**, 1155 (1963).
(12) J. Meinwald and A. Lewis, *ibid.*, **83**, 2769 (1961).
(13) E. W. Garbish, Jr., *Chem. Ind.* (London), 1715 (1964).
(14) K. Mackenzie, *J. Chem. Soc.*, 457, (1962).

the point of oxygen attachment. The strained ring system resulting prevents ejection of a chloride ion since this would introduce a double bond at a bridgehead. It is probable that the anion quickly accepts a proton to form the transient chloro ether. However, this chloro ether was never isolated. It is assumed that under the conditions necessary for ring closure, *i.e.*, excess base, protic solvent, elevated temperature, etc., solvolysis of the bridge chlorine occurs resulting in ketal formation. It must be presumed that there is appreciable resonance assistance to chlorine release by the oxygen, normal with α-chloro ethers, in spite of the apparent strain that would result. Such bridgehead halogens are normally rather inert. In fact, the inertness of the other halogens present in this series of derived compounds under these experimental conditions attests to this.

The reaction of phosphorus pentachloride with hemiketal **13** and subsequent hydrolysis yields ketone **15**. We suggest that attack of the phosphorus pentachloride occurs on the hemiketal first to form a phosphonium complex[15] which weakens the oxygen–carbon bond making it more susceptible to chloride attack. However, for steric reasons chloride attacks the oxymethylene group to yield, on hydrolysis, chloro methyl ketone **15**.



Experimental Section

The melting points were obtained in a capillary tube with the Thomas–Hoover Unimelt apparatus and are corrected. The carbon and hydrogen elemental analysis were carried out by Galbraith Laboratories and the chlorine and nitrogen in the Hooker Chemical Corp. Laboratories. The ir spectra were determined using a Beckman IR-9 or IR-12 spectrophotometer, nmr spectra using either a Varian HA-100 or A-60 spectrophotometer.

3a,4,4,5,6-Pentachlorohexahydro-6a-methoxy-3,5-methano-2H-cyclopenta[*b*]furan (2). Preparation A.—To a stirring solution of sodium methoxide at reflux prepared from 6.9 g (0.3 g-atom) of sodium metal and 200 ml of methyl alcohol was added dropwise a solution of 33.1 g (0.1 mol) of **1**. Addition was made in 1.2 hr and the suspension was refluxed 1 additional hr. The reaction mixture was poured into 1.5 l. of water and the solid that precipitated collected on a filter, dried, and recrystallized from hexane to yield 21.3 g (65%) of product, mp 93.5–94.5°.

Anal. Calcd for $C_9H_9Cl_5O_2$: C, 33.11; H, 2.78; Cl, 54.32. Found: C, 33.24; H, 2.95; Cl, 54.50.

Preparation B.—Over a period of a few minutes, 100 g of **15** was added to 1570 ml of a solution prepared from 25 g of sodium in methyl alcohol at reflux. The resulting dark suspension was refluxed for 12 hr. The excess methyl alcohol was distilled from the product under vacuum, and the residue was acidified and filtered. The filter cake was washed with water and 60 g of solid was recovered and recrystallized from heptane to provide a product having a melting point of 93–94°. The melting point and infrared spectrum indicated the product to be the same as **2** above.

3a,4,4,5,6-Pentachlorohexahydro-6a-ethoxy-3 5-methano-2H-cyclopenta[*b*]furan (3).—A solution of sodium ethoxide was prepared by adding 92 g (4.1 g-atom) of sodium metal to 5 l. of absolute ethanol. To this solution was added, with stirring at reflux, a solution of 331 g (1.0 mol) of **1** in 1 l. of absolute ethanol. Addition was made dropwise over 1 hr and the suspension was stirred at reflux an additional 2 hr. Water (4 l.) was added to the reaction mixture and hydrochloric acid added to neutralize the base. The solid product was collected on a filter, washed several times with water and dried under vacuum at 50° overnight to a constant weight of 332 g (97%). Recrystallization from *n*-heptane and a treatment with Darco yielded 325 g (96%) product, mp 110–111.5°.

Anal. Calcd for $C_{10}H_{11}O_2Cl_5$: C, 35.28; H, 3.26; Cl, 52.07. Found: C, 35.40; H, 3.36; Cl, 52.00.

3a,4,4,5,6-Pentachlorohexahydro-6a-ethylthio-3,5-methano-2H-cyclopenta[*b*]furan (4).—A solution of sodium ethyl mercaptide was prepared from 4.6 g (0.2 g-atom) of metallic sodium, 100 ml of dry ethanol and 12.4 g (0.2 mol) of ethyl mercaptan. To this mercaptide solution heated to 65° was added dropwise with stirring a solution of 16.5 g (0.05 mol) of 1,4,5,6,7,7-hexachloro-5-norbornene-*endo*-2-methanol. The addition was made in 5 min and the reaction mixture was stirred at reflux for 2 hr and then poured into 500 ml of water. The water suspension was made slightly acid with dilute hydrochloric acid and extracted with three 75-ml portions of diethyl ether. The ether solution was washed twice with 50-ml portions of water treated with anhydrous magnesium sulfate and filtered. The dry ether was removed on a Rinco evaporator and the crude brown oil (17.8 g) fractionated.* The major fraction, 8 g (45%), distils at 138–140° (0.1 mm), n^{25}D 1.5721.

Anal. Calcd for $C_{10}H_{11}Cl_5S_6$: C, 33.69; H, 3.11; Cl, 49.74; S, 9.00. Found: C, 33.61; H, 3.05; Cl, 49.9; S, 9.5.

3a,4,4,5,6-Pentachloro-6a-allyloxy-3,5-methano-2H-cyclopenta[*b*]furan (5).—To 250 ml of anhydrous allyl alcohol was added 9.2 g (0.4 g-atom) of metallic sodium. To this solution heated to 100° was added dropwise a solution of 33.1 g (0.1 mol) of **1** over 2 hr. The suspension was stirred at reflux for an additional 4.0 hr, then filtered hot. The alcohol solution was acidified with hydrochloric acid then subjected to a vacuum evaporation. The residue was diluted with excess water and 28.0 g of brown solid was collected on a filter. Recrystallization of the product from heptane treated with Darco gave 22 g (62%) of white crystalline solid, mp 48–49°.

Anal. Calcd for $C_{11}H_{11}Cl_5O_2$: C, 37.48; H, 3.15; Cl, 50.30. Found: C, 37.25; H, 3.09; Cl, 50.40.

3a,4,4,5,6-Pentachlorohexahydro-6a-(4-chlorophenoxy)-3 5-methano-2H-cyclopenta[*b*]furan (6).—A solution of sodium ethoxide was prepared from 9.2 g (0.4 g-atom) sodium metal and 150 ml of anhydrous ethanol. To this solution was added 51.4 g (0.4 mol) of *p*-chlorophenol. A solution of 33.1 g (0.1 m) of **1** in 100 ml of ethanol was added dropwise over 1 hr. The mixture was refluxed 1 hr and passed through a filter. The filtrate was heated to effect solution and adjusted to a pH <1 with 1:1 water–hydrochloric acid. The acid solution was diluted with 500 cc of water and the oil was separated and washed several times with 75-ml portions of water. The oil weighting 28.2 g was taken up in hexane and the solid that formed recrystallized to yield 20 g of white crystals, mp 128.5–129.5°.

Anal. Calcd for $C_{14}H_{10}Cl_6O_2$: C, 39.75; H, 2.38; Cl, 50.30. Found: C, 39.59; H, 2.27; Cl, 50.10.

3a 4,4,5,6-Pentachlorohexahydro-6a-(2,4-dichlorophenoxy)-3,5-methano-2H-cyclopenta[*b*]furan (7).—A solution of sodium alkoxide prepared from 9.2 g (0.4 g-atom) of sodium metal and 200 ml of ethanol was treated with 65.6 g (0.4 mol) of 2,4-dichlorophenol. To this solution at reflux, 32.1 g (0.1 mol) of **1** in 100 ml of ethanol was added dropwise over 0.5 hr. The suspension was stirred at reflux for 3.0 hr. The reaction mixture was evaporated to one-third of its volume and the residue added to a large excess of water. The oil that separated crystallized on standing to yield 32 g of solid which crystallized from hexane to yield 15 g solid, mp 109–129°. The solid was treated with dilute aqueous sodium hydroxide, then recrystallized from heptane to yield 10 g (22%) of a solid, mp 136–138°.

Anal. Calcd for $C_{14}H_9Cl_7O_2$: C, 36.76; H, 1.98; Cl, 54.26. Found: C, 37.00; H, 2.00; Cl, 54.70.

3a,4,4,5,6-Pentachlorohexahydro-6a-ethoxy-2-ethoxymethyl-3,5-methano-2H-cyclopenta[*b*]furan (9).—To a solution of sodium ethoxide prepared by adding 9.2 g (0.40 g-atom) of metallic sodium to 250 ml of absolute ethanol was added 34.4 g (0.10 mol) of **8**. The solution was heated to reflux with stirring for 9 hr, cooled to room temperature, acidified with dilute hydro-

(15) G. A. Wiley, B. M. Rein, R. L. Herskowitz, *Tetrahedron Lett.*, 2509 (1964).

chloric acid and filtered. The filtrate was concentrated and the residue taken up in 100 ml of diethyl ether. The ether solution was washed with 50 ml of water then dried over anhydrous magnesium sulfate. After filtration and removal of the ether by evaporation, the oil residue weighing 35 g was subjected to a vacuum distillation to give 28 g (70.2%) of a pale yellow oil distilling at 150–151° (0.15 mm), $n^{25}D$ 1.5164.

Anal. Calcd for $C_{13}H_{17}O_3Cl_5$: C, 39.18; H, 4.30; Cl, 44.48. Found: C, 39.30; H, 4.30; Cl, 44.45.

3a,4,4,5,6-Pentachlorohexahydro-7-hydroxymethyl-6a-methoxy-3,5-methane-2H-cyclopenta[*b*]furan (10).—A solution of sodium methoxide was prepared from 9.2 g (0.4 g-atom) of sodium metal and 200 ml of methanol. To this solution at reflux with stirring was added over 0.75 hr a solution of 36.1 g (0.1 mol) of 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3-dimethanol in 300 ml of methanol. After addition was complete the suspension was stirred at reflux for 1.0 hr. The mixture was filtered and the filtrate reduced by evaporation to one-fourth its original volume. The residual solution was acidified with hydrochloric acid then diluted with 600 ml of water and chilled. The water was decanted from a semicrystalline solid. The solid was crystallized from toluene then from heptane to yield 14.2 g (40%) of crystalline white solid, mp 157–158.5°.

Anal. Calcd for $C_{10}H_{11}Cl_5O_3$: C, 33.88; H, 3.13; Cl, 50.01. Found: C, 33.78; H, 3.27; Cl, 49.5.

3a,5,6-Trichlorohexahydro-6a-ethoxy-4,4-dimethoxy-3,5-dimethano-2H-cyclopenta[*b*]furan (11).—To 150 ml of anhydrous ethanol was added 10.2 g (0.4 g-atom) of metallic sodium. This solution was warmed with stirring to reflux and a solution of 32.2 g (0.1 mol) of 1,4,5,6-tetrachloro-7,7-dimethoxy-5,5-norbornene-*endo*-2,2-methanol was added in 0.75 hr. The suspension was stirred for 3.0 hr at reflux, filtered, and the solvent removed under vacuum. The residue was treated with excess water, and the suspension acidified with hydrochloric acid. The oil resulting solidified and was crystallized from 150 ml of petroleum ether (immersed in a Dry Ice–acetone cooling bath). The white solid weighing 24.0 g, mp 62–68°, was recrystallized to yield 20.0 g (60%) of product, mp 68.5–69.5°.

Anal. Calcd for $C_{12}H_{17}Cl_3O_4$: C, 43.65; H, 5.17; Cl, 32.07. Found: C, 43.60; H, 5.14; Cl, 32.19.

3a,4,4,5,6-Pentachlorohexahydro-6a-hydroxy-3,5-methano-2H-cyclopenta[*b*]furan (13). Preparation A.—A suspension of 30 g (0.88 mol) of **3** in 50 ml of concentrated sulfuric acid was warmed to 88–100° with stirring and held for 0.75 hr. The hot acid solution was poured into 700 ml of ice and water; the suspension resulting was warmed to 80°, then cooled and filtered. The solid weighing 13.0 g was recrystallized from benzene several times to yield 7.0 g (26%) of white crystals, mp 231–232°.

Anal. Calcd for $C_8H_7Cl_5O_2$: C, 30.76; H, 2.26; Cl, 56.74. Found: C, 30.96; H, 2.20; Cl, 56.90.

The infrared spectrum has an OH band at 2.91 μ but shows no C=O or C=C stretching.

Preparation B.—To a mixture of 84 g of sodium bicarbonate, 500 g by weight of water and 3925 ml of ethyl alcohol were added 330 g of **15**. The mixture was refluxed for 10 hr and then evaporated on a steam cone. Excess water was added to the product, and an oil formed. The oil was treated with hexane. About 25 g of product that was insoluble in hexane was subjected to infrared analysis and found to have a spectrum identical with that of **13** above.

3a,4,4,5,6-Pentachlorohexahydro-6a-hydroxy-7-hydroxymethyl-3,5-methano-2H-cyclopenta[*b*]furan (14).—A suspension of 120 ml of concentrated sulfuric acid and 24 g (0.65 mol) of **10** was stirred with heating to 90–92° and held at this temperature for 8 min. The solution resulting was poured into ice and the solid resulting collected on a filter. After a thorough washing with water, the solid weighing 15 g was recrystallized three times from a methanol–water solution to yield 10.8 g (67.5%) of solid, mp 236–238° with decomposition.

Anal. Calcd for $C_9H_9Cl_5O_3$: C, 31.56; H, 2.65; Cl, 51.77. Found: C, 31.61; H, 2.61; Cl, 52.00.

The infrared spectrum shows OH absorption at 3540 cm^{-1}.

Preparation of 2-Keto-1,3,4,7,7-pentachloro-6-chloromethylnorbornene (15).—A mixture of 18.74 g (0.06 mol) of **13** and 14.6 g (0.061 mol) of phosphorus pentachloride was carefully warmed with shaking. At 50–55° an exothermic reaction took place with vigorous evolution of hydrogen chloride. The pale yellow solution resulting was stirred at reflux (118–120°) for 2.0 hr, then poured into crushed ice. The white solid obtained was washed several times with water and crystallized from hexane to yield 11.0 g (55%), mp 69.5–71.5°.

Anal. Calcd for $C_8H_6Cl_6O$: C, 29.04; H, 1.83; Cl, 64.30. Found: C, 29.23; H, 1.97; Cl, 63.80.

The infrared spectrum shows C=O absorption at 1790 cm^{-1} (CCl_4) and no OH stretching.

3a,4,4,5,6-Pentachlorohexahydro-6a-cyano-3,5-methano-2H-cyclopenta[*b*]furan (16).—A solution containing 13.2 g (0.04 mol) of **15** in 100 ml of ethanol and 30 ml of water was treated with 5.2 g (0.079 mol) of potassium cyanide. The solution was stirred at reflux for 2.0 hr. The resulting dark suspension was acidified with dilute sulfuric acid and then evaporated to near dryness. The residue was poured into 150 ml of water and the brown solid collected on a filter. The solid was dissolved in hexane, dried over magnesium sulfate (anhydrous), and filtered. The excess hexane was removed, and 6.0 g of crystals separated upon cooling the solution, having mp 226–231°. Recrystallization raised the melting point to 235–236°.

Anal. Calcd for $C_9H_6ONCl_5$: C, 33.63; H, 1.88; N, 4.36; Cl, 55.16. Found: C, 33.70; H, 2.02; N, 4.28; Cl, 33.61.

3a,4,4,5,6-Pentachlorohexahydro-3,5-methano-2H-cyclopenta-[*b*]furan-6a-carboxylic Acid (17).—**16** (8 g) was added to 40 ml of 81% sulfuric acid and 100 ml of glacial acetic acid. The solution was stirred at reflux (127°) for 14 hr, cooled and poured into 500 ml of ice water. The resulting solid was collected on a filter, washed thoroughly with water and dried to yield 6 g of white solid, mp 279–281° dec.

Anal. Calcd for $C_9H_7Cl_5O_3$: C, 31.76; H, 2.07; Cl, 52.08; neut equiv, 340.4. Found: C, 31.56; H, 2.07; Cl, 51.8; neut equiv, 341.

Registry No.—Hexachlorocyclopentadiene, 77-47-4; **2**, 17144-77-3; **3**, 17145-53-8; **4**, 17145-58-3; **5**, 17387-24-5; **6**, 19362-33-5; **7**, 17145-56-1; **9**, 19362-35-7; **10**, 17145-51-6; **11**, 17145-54-9; **13**, 17144-71-7; **14**, 17145-62-9; **15**, 17144-74-0; **16**, 17144-75-1; **17**, 17144-76-2.

Acknowledgment.—The authors are deeply greatful to Dr. Victor Mark and Dr. Edward Weil for the many helpful discussions on all aspects of the problem. We also wish to express our gratitude to A Davis and R. L. McCullough of the Hooker Analytical Laboratories for the elemental infrared and nmr spectral data.

Strained Ring Systems. VIII.[1a] An Alternate Synthesis of 2-Oxy Derivatives of Bicyclo[2.2.0]hexane and the Rearrangement of *endo*-Bicyclo[2.2.0]hex-2-yl Acetate[1b]

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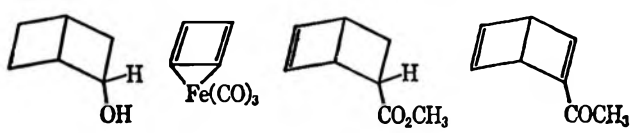
Received February 16, 1968

The synthesis of methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate (**6**) by diimide reduction of methyl bicyclo[2.2.0]hexa-2,5-diene-2-carboxylate (**5**) is reported. Conversion of **6** *via* the methylsulfinyl carbanion and reduction of the resulting adduct leads to a 38:62 mixture of *endo*- (**7**) and *exo*-bicyclo[2.2.0]hex-2-yl methyl ketone (**8**) which on Baeyer–Villiger oxidation yields a mixture of *exo*-bicyclo[2.2.0]hex-2-yl acetate (**9**, 91%), *cis*-bicyclo[3.1.0]hex-2-yl acetate (**10**, 9%), and 3-cyclohexenyl acetate (**11**, <1%). Conversion of **6** into its acid chloride and reaction with dimethylcadmium also gives a mixture of **7** and **8** but in a ratio of 65:35. Baeyer–Villiger oxidation produces a mixture of **9** (49%), *endo*-bicyclo[2.2.0]hex-2-yl acetate (**12**, 27%), **10** (18%), and **11** (6%). On standing in a nonpolar solvent **12** is observed to rearrange to **10** and **11**, thereby establishing them as artifacts of the Baeyer–Villiger reaction. The mechanism of this rearrangement is discussed.

The literature contains relatively few reports of simple functional derivatives of the bicyclo[2.2.0]hexane system.[2] Our reported synthesis of *endo*-bicyclo[2.2.0]hexan-2-ol[2b] (**1**) did not appear attractive for the preparation of the amounts of this alcohol required for solvolytic and other studies. In considering possible alternate routes to **1**, we hoped to synthesize some new monosubstituted derivatives of bicyclo[2.2.0]hexane (as well as **1**) which might be interesting to study in their own right. The present work describes the achievement of certain of these goals. However, *endo* alcohol **1** has been obtained as a mixture with its *exo* epimer which, in our hands, cannot be separated.

The procedure takes advantage of Pettit's elegant conversion of Nenitzescu's *cis*-3,4-dichlorocyclobutene[3] into cyclobutadieneiron tricarbonyl[4–6] (**2**) and its decomposition in the presence of acetylenes to yield substituted bicyclo[2.2.0]hexa-2,5-dienes.[7] Our initial approach to the synthesis of **1** was to attempt to trap the generated cyclobutadiene (from ceric ion oxidation of **2**) with an olefinic substrate. The olefins which we investigated were vinyl acetate, 2-butenone, and methyl acrylate. Each olefin was subjected to the reaction conditions and 2-butenone was found to be very reactive to the ceric ion being immediately converted into polymeric material. Vinyl acetate, although the most stable of these three olefinic compounds to the ceric ion, failed to trap the cyclobutadiene.

Methyl acrylate was intermediate in its stability to the ceric ion. A mixture of products was formed which on column chromatography yielded a substance in 3% yield whose nuclear magnetic resonance (nmr) spectrum was consistent with the expected structure, methyl *endo*-bicyclo[2.2.0]hex-5-ene-2-carboxylate (**3**).[8] Catalytic reduction of **3** gave a 50% yield of at least three products, but no conclusive structural data was obtained.



1 **2** **3** **4**

2-Butynone was found to react with **2** in the presence of the ceric ion to give a mixture of **4** and acetophenone. Attempted gas phase chromatography (gc) of this mixture resulted in quantitative conversion of **4** into acetophenone. Three successive attempts at diimide reduction of this mixture gave a product which by gc analysis showed at least 13 components present.

Rather than fighting this portion of the synthetic sequence further, we turned to the use of methyl propiolate which has already been shown to be a trap for liberated cyclobutadiene.[7] In our hands a 49% yield of a mixture of methyl bicyclo[2.2.0]hexa-2,5-diene-2-carboxylate (**5**) (71% of the mixture) and methyl benzoate (29% of mixture) was obtained. Attempted gc analysis or catalytic reduction with Adams catalyst gave quantitive conversion into methyl benzoate. Diimide reduction[9] of this mixture containing **5** gave a product in 52% yield (based on available **5**) which is assigned the structure of methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate (**6**) from analysis of its nmr spectrum, its subsequent conversions, and analogy with diimide reductions in other bicyclic olefins.[10] The yield is based on the amount of **5** present in the mixture from the nmr integration. The mass spectrum of the ethyl ester of **6** showed the parent ion at *m/e* 154 with the base peak at *m/e* 81 corresponding to loss of the carboethoxy group. Ester **6** was found to be epimerized by methanolic sulfuric acid, but not when treated with methanolic sodium methoxide.

(1) (a) For paper VII in this series, see R. N. McDonald and D. G. Frickey, *J. Amer. Chem. Soc.*, **90**, 5315 (1968). (b) A portion of this research was communicated in *Tetrahedron Lett.*, 1449 (1968). (c) Taken from the M.S. thesis of G. E. Davis.

(2) Although there are a number of reports of substituted bicyclo[2.2.0]-hexanes highly alkylated or involved in higher polycyclic molecules, we have been concerned with mono- and disubstituted derivatives of the [2.2.0] ring system. These are (a) *exo*-2-ol, its acetate, and tosylate [R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967)]; (b) *endo*-2-ol and 2-one [*ibid.*, 1888 (1967)]; (c) 1- and *exo*-2-chloride [R. Srinivasan and F. I. Sonntag, *Tetrahedron Lett.*, 603 (1967)]; (d) 1,4-dichloride [W. Luettke and V. Schabacker, *Ann.*, **698**, 86 (1966)]; (e) 4-chloro-1-bromide (K. V. Scherer, Abstracts of the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, P180); (f) 4-chloro-1-carboxylic acid, its methyl ester, 4-chloro-1-methanol, and 1-methanol and its *p*-nitrobenzoate [W. G. Dauben, J. L. Chitwood, and K. V. Scherer, *J. Amer. Chem. Soc.*, **90**, 1014 (1968)]; (g) *cis*-2,3-dicarboxylic acid and its anhydride.[2a]

(3) M. Avram, I. Dinulescu, M. Elian, M. Farcasiu, E. Marica, G. Mateescu, and C. D. Nenitzescu, *Ber.*, **97**, 372 (1964).

(4) G. F. Emerson, L. Watts, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 131 (1965).

(5) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967).

(6) M. Rosenblum and C. Gatsonis, *ibid.*, **89**, 5074 (1967).

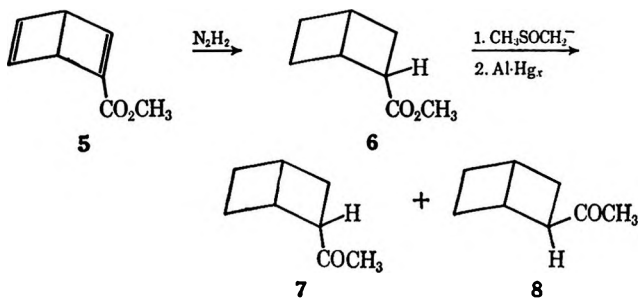
(7) L. Watts, J. D. Fitzpatrick, and R. Pettit, *ibid.*, **87**, 3253 (1965).

(8) The analogy with the exclusive formation of dimethyl *cis,endo*-bicyclo-[2.2.0]hex-5-ene-2,3-dicarboxylate from similar treatment of **2** in the presence of dimethyl maleate [L. Watts, J. D. Fitzpatrick, and R. Pettit, *ibid.*, **88**, 623 (1966)] supports the assignment of the *endo* configuration of the carbomethoxy group in **3**.

(9) E. E. van Tamelen and S. P. Pappas [*ibid.*, **85**, 3297 (1963)] have reported that diimide reduces bicyclo[2.2.0]hexa-2,5-diene to bicyclo[2.2.0]hexane.

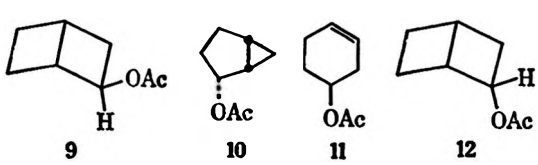
(10) P. G. Gassman and J. M. Hornback, *ibid.*, **89**, 2487 (1967); E. E. van Tamelen and R. J. Timmons, *ibid.*, **84**, 1067 (1962); C. E. Miller, *J. Chem. Educ.*, **42**, 254 (1965).

Reaction of methylsulfinyl carbanion[11] with **6** was considered to be a convenient route to *endo*-bicyclo[2.2.0]hex-2-yl methyl ketone (**7**). When this reaction was carried out on crude **6** (containing some methyl benzoate), a mixture of two adducts was formed. The white solid adduct was shown to be ω-(methylsufinyl)-acetophenone by comparison with that reported.[11] The second adduct, a yellow oil, was then reduced with aluminum amalgam to ketonic products. The nmr spectrum of this product indicated it to be a mixture of **7** and the *exo* ketone **8** since two distinct methyl singlets



are present. From the results of subsequent conversions of this mixture, an alternate synthesis of a mixture of **7** and **8**, and the results of its further reactions, we assign the τ 8.20 absorption to the *exo* epimer **8** and that of the *endo* epimer **7** at 8.13. Using these assignments the mixture produced by this route contains **7** and **8** in a ratio of 38:62.[12]

Baeyer–Villiger oxidation of this mixture of ketones **7** and **8** with *m*-chloroperbenzoic acid resulted in a mixture of acetates which exhibited two peaks on gc analysis. The major gc peak was identified as *exo*-bicyclo[2.2.0]hex-2-yl acetate (**9**, 91%), and the minor peak as a mixture of *cis*-bicyclo[3.1.0]hex-2-yl acetate (**10**, 9%) and 3-cyclohexenyl acetate (**11**, <1%).



The percentage composition of this mixture is derived from a combination of nmr spectral and gc integrations.

Since none of the desired *endo*-bicyclo[2.2.0]hex-2-yl acetate (**12**) was produced, the more classical method of converting an acid into its methyl ketone was investigated. Saponification of ester **6** and conversion into its acid chloride were found to proceed without isomerization.[13] Treatment of the acid chloride with dimethylcadmium produced a mixture of ketones **7** and **8**, but with **7** in predominance, in a ratio of 65:35. After standing for 40 days stored in Dry Ice the ratio had changed to 51:49. It was first assumed that magnesium halide present in the dimethylcadmium reagent had caused the isomerization of **7** to **8**, but the use of magnesium halide free dimethylcadmium[14] gave a similar result.[15] *m*-Chloroperbenzoic acid oxidation of the 51:49 mixture of **7** and **8** led to a mixture of acetates again showing only two major peaks on gc analysis. The first of these gc peaks was collected and identified by infrared (ir) and nmr spectroscopy as a mixture of acetates **9** (49%) and **12** (27%) while similar identification of the second peak showed it to consist of acetates **10** (18%) and **11** (6%).[16] Monoperphthalic acid oxidation of a portion of the 65:35 mixture of ketones **7** and **8** also give a mixture of **9** (40%), **10** (32%), **11** (9%), and **12** (19%), however, in somewhat different proportions.

Lithium aluminum hydride reduction of the product from the Baeyer–Villiger oxidation utilizing *m*-chloroperbenzoic acid gave a mixture of alcohols in 82% yield which showed four peaks on gc analysis. The first peak (72.2% of the mixture by weight) was collected and identified as a mixture of **1** and its *exo* epimer, *exo*-bicyclo[2.2.0]hexan-2-ol, by comparison of the ir and nmr spectra and gc retention times with those of authentic samples, in a ratio of 36:64, respectively.[17] All attempts to separate these isomers failed. The second gc peak (12.5% of the mixture) was collected and similarly identified as *cis*-bicyclo[3.1.0]hexan-2-ol. The third (5.2%) and fourth (10.1%) peaks were collected but no positive identification was made.

Acetates **10** and **11** were prepared by Simmons–Smith reaction with 2-cyclopentenol[18] followed by acetylation and were found to be identical with the products in the second gc fraction. To establish that none of the acetate of *trans*-bicyclo[3.1.0]hexan-2-ol was a product, it was synthesized by oxidation of the *cis* alcohol, Meerwein–Ponndorf reduction of the ketone to an 88:12 mixture of *trans*- and *cis*-bicyclo[3.1.0]-hexan-2-ols,[19] and acetylation. The acetate, *trans*-bicyclo[3.1.0]hex-2-yl acetate, was found to be different from any of the rearrangement products. Acetates **10**, **11**, and *trans*-bicyclo[3.1.0]hex-2-yl acetate were found to be stable to the Baeyer–Villiger reaction conditions. *exo* acetate **9** had been previously shown to be stable to acetolysis at 90° [2a] and its stability was assumed in the present case as well.

The question of how acetates **10** and **11** were being produced in the Baeyer–Villiger oxidations was answered by observing the change in the nmr spectrum of a sample of the first gc fraction containing acetates **9** and **12** in a ratio of 46:54. After storage in carbon tetrachloride solution at −26° for 21 days, the composition had changed to 46% **9**, 22% **12**, 25% **10**, and 7% **11** by nmr integration. After being stored for an additional 25 days in methylene chloride, the product composition had changed further to 46% **9**, 14% **12**, 31% **10**, and 9% **11**.

(11) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(12) In the conversion of **6** into the mixture of **7** and **8**, it is believed that the isomerization occurs in the aluminum amalgam reduction since the nmr spectrum of the **6**–methylsulfinyl carbanion adduct suggests the presence of only one isomer.

(13) The acid was reconverted into **6** with diazomethane and the acid chloride was hydrolyzed to the acid.

(14) J. Cason, *ibid.*, **68**, 2078 (1946).

(15) See K. B. Wiberg and B. A. Hess, *J. Org. Chem.*, **31**, 2250 (1966), for a discussion of related isomerizations.

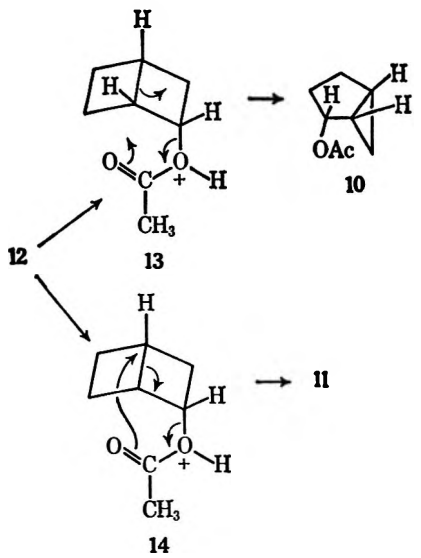
(16) The reasons for the quite different results in the Baeyer–Villiger oxidations with *m*-chloroperbenzoic acid are unknown, but it should be pointed out that the concentrations of peroxy acid and visual appearances of the two reactions were different.

(17) This ratio of *exo* and *endo* alcohols was obtained by integration of the nmr spectrum of the original acetate mixture.

(18) E. J. Corey and R. L. Dawson, *J. Amer. Chem. Soc.*, **85**, 1782 (1963), using a zinc-copper couple prepared according to R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).

(19) We employed a relatively short reaction time in order to produce this mixture rich in the *trans* alcohol; see M. Hanack and H. Allmendinger, *Ber.*, **97**, 1669 (1964), for the use of longer reaction times giving a *cis*/*trans* ratio of 38:62.

From the facts that the rearrangement produces only *cis* acetate **10** and **11**[20] and the low polarity of the media,[21] we suggest that the rearrangement of **12** to **10** proceeds by an acid-catalyzed, concerted mechanism, *i.e.*, structure **13**. Since acetates **9** and **10** do not rearrange to give **11**, this acetate must also arise directly from **12** in either a concerted process or one which incorporates a tight ion pair. A concerted mechanism in going from **12** to **11** may be questionable owing to the rather extensive steric crowding in the *endo* face of the molecule by migration of the acetoxy group to C4 (structure **14**). Rearrangement from the [2.2.0] to the [3.1.0] system would be favored by about 18 kcal/mol based on simple strain energy considerations.[22]



Experimental Section[23]

cis-3,4-Dichlorocyclobutene.—The procedure used starting with cyclooctatetraene[24] has been described.[3] From an average run with 83.2 g of cyclooctatetraene there was obtained 5.9 g (5.4%) of *trans,trans*-1,4-dichlorobutadiene, bp 60° (60 mm) [lit.[3] bp 60° (68 mm)], and 30.0 g (31%) of *cis*-3,4-dichlorocyclobutene, bp 74° (58 mm), $n^{25.5}$D 1.4983 [lit.[3] bp 74° (60 mm), n^{25}D 1.49832]. The ir and nmr spectra were in agreement with these structures.

Diiron Enneacarbonyl.—This compound was prepared by a modification of the method of Speyer and Wolf.[25] Iron pentacarbonyl (200 g, 1.02 mol) in 410 ml of glacial acetic acid was maintained under a nitrogen atmosphere while being irradiated with a GE-AH4 uv lamp (with the Pyrex envelope removed) in a quartz, water-cooled well. At the end of 37 hr, the solid product was filtered from the reaction mixture, washed repeatedly with anhydrous ether, and air dried (100.9 g). The mother liquor (without ether) was irradiated for another 70.6 hr and the golden crystals were worked up as before (42.7 g). The total yield was 143.6 g (81%) with a total reaction time of 107.6 hr. Dry diiron enneacarbonyl is stable toward oxygen and moisture, but burns spontaneously in the air if moistened with iron pentacarbonyl.

Cyclobutadieneiron Tricarbonyl (2).—To a solution of 28.0 g (0.23 mol) of *cis*-3,4-dichlorocyclobutene in 980 ml of pentane heated under reflux (bath temperature 47–48°) and a nitrogen atmosphere was added 171.0 g (0.470 mol) of diiron enneacarbonyl in portions over a 20-hr period. After heating for an additional 3 hr, the reaction mixture was cooled to room temperature and the deep green liquid was filtered under a nitrogen atmosphere from the solid residue. The solvent and iron pentacarbonyl were removed from the complex by trap-to-trap distillation at reduced pressure. The product distilled as a yellow-green liquid (21.05 g, 48%) at 27° (0.05 mm) [lit. 40%, bp 68–70° (3 mm),[4] and 51%, bp 45–47° (3 mm)[5]] and solidified to a yellow-green solid when cooled below room temperature. This complex slowly decomposes in the presence of air or moisture to give a reddish brown solid insoluble in water and most organic solvents.

Methyl *endo*-Bicyclo[2.2.0]hex-5-ene-2-carboxylate (3).—Ceric ammonium nitrate (10.0 g, 18.2 mmol) in 22 ml of water was added over a 15-min period to a solution of cyclobutadieneiron tricarbonyl (1.0 g, 5.2 mmol) and methyl acrylate (4.49 g, 52 mmol) in 40 ml of 95% ethyl alcohol. The reaction mixture was maintained at 0 to −2°. Bubbles were given off during the addition of the ceric ion solution. The reaction mixture was extracted with six 20-ml portions of ether, the combined ether extracts were washed with several portions of water, and the resulting solution was dried over magnesium sulfate. The concentrated reaction mixture was chromatographed on silica gel. The fraction which eluted with 1:1 ether, methylene chloride was trap-to-trap distilled [27° (0.05 mm)] to yield a clear, colorless liquid (0.02 g, 3%). The nmr spectrum [$CDCl_3$, internal tetramethylsilane (TMS)] exhibited absorptions at τ 3.58 (multiplet, 2) and 6.0–8.17 (continuous absorption, 8) with a singlet at 6.25.

Bicyclo[2.2.0]hexa-2,5-dien-2-yl Methyl Ketone (4).—Ceric ammonium nitrate (10.0 g, 18.2 mmol) in 22 ml of distilled water was added to a mixture of cyclobutadieneiron tricarbonyl (1.0 g, 5.2 mmol) and 2-butynone (1.77 g, 26.0 mmol) in 40 ml of 95% ethanol. The reaction was maintained at −1 to −3° during an addition time of 70 min. After the addition the solution was stirred for another 30 min and 0.2 g of ferrous ammonium sulfate was added. This mixture was stirred an additional 10 min and extracted with five 40-ml portions of ether, and the ether was washed with five 40-ml portions of water. The resulting ether extract was dried, concentrated at reduced pressure, and trap-to-trap distilled [27° (0.05 mm)] to yield 0.17 g (27%) of a light yellow liquid. Gc analysis of this product on a 6 ft × 0.25 in. Carbowax 20M column (20% on Chromosorb W) at a temperature of 175° showed one major peak which when collected proved to be acetophenone.

From the nmr spectrum (CCl_4, internal TMS) of the product it is estimated to be composed of 4 and acetophenone in a ratio of 3:1. The nmr absorptions attributed to 4 appear at τ 2.98 (multiplet, 1), 3.44 (multiplet, 1), 3.54 (multiplet, 1), 6.08 (multiplet, 1), 6.21 (multiplet, 1), and 7.89 (singlet, 3).

Methyl Bicyclo[2.2.0]hexa-2,5-diene-2-carboxylate (5).—Ceric ammonium nitrate (50.0 g, 91 mmol) in 110 ml of distilled water was added to a mixture of cyclobutadieneiron tricarbonyl (5.4 g, 28 mmol) and methyl propiolate (21.9 g, 0.26 mol) in 200 ml of 95% ethanol. The reaction was maintained at −1 to −3° during an addition time of 1.5 hr. After the addition, the solution was stirred for another 15 min and 0.2 g of ferrous ammonium sulfate was added. This mixture was stirred an additional 10 min and extracted with five 40-ml portions of ether, and the combined ether extracts were washed with five 40-ml portions of water. After drying and concentration under reduced pressure, the residual material was trap-to-trap distilled [26° (0.01 mm)] to yield 3.0 g of a light yellow liquid. Gc analysis of this product on a Carbowax 20M column (20% on Chromosorb W) showed two major components to be present; the first was identified as methyl propiolate and the second as methyl benzoate (45% of product mixture). From the inte-

(20) P. K. Freeman, M. F. Grostic, and F. A. Raymond [*J. Org. Chem.*, **30**, 771 (1965)] have reported that the *p*-toluenesulfonic acid catalyzed addition of methanol to bicyclo[3.1.0]hex-2-ene yields a mixture of *trans*- (53%) and *cis*-2-methoxybicyclo[3.1.0]hexanes (32%) and 4-methoxycyclohexene (15%).

(21) R. S. Bly, R. K. Bly, A. O. Bedenbaugh, and O. R. Vail [*J. Amer. Chem. Soc.*, **89**, 880 (1967)] observed a rearrangement of β-(*syn*-7-norbornenyl)-methyl brosylate in unbuffered carbon tetrachloride, but not in the buffered solvent.

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 193.

(23) All boiling points are uncorrected. Infrared absorption spectra were determined on a Perkin-Elmer Model 137 double-beam recording spectrophotometer and nmr spectra were determined on a Varian A-60 recording spectrometer. The mass spectrum was obtained with a Bendix time-of-flight mass spectrometer. The gas chromatographic analyses were performed using a F & M Model 500 high temperature programmed gas chromatograph. Analyses were performed by Gailbraith Laboratories, Inc., Knoxville, Tenn.

(24) We wish to thank BASF-AG for a generous sample of cyclooctatetraene.

(25) E. Speyer and H. Wolf, *Ber.*, **60**, 1424 (1927).

grated nmr spectrum of the mixture, 71% of the methyl benzoate from the gc analysis originally was 5 and 29% was methyl benzoate. From these values, the mixture of 5 and methyl benzoate was obtained in 49% yield.

Methyl *endo*-Bicyclo[2.2.0]hexane-2-carboxylate (6).—Glacial acetic acid (12.65 ml, 13.26 g, 0.222 mol) in 30 ml of methanol was added under nitrogen to a mixture of potassium azodicarboxylate [prepared from 9.32 g (0.111 mol) of azodicarbonamide] and the previous mixture containing methyl bicyclo[2.2.0]hexa-2,5-diene-2-carboxylate (2.90 g, 21.4 mmol)[26] in 200 ml of methanol and 50 ml of water. The addition was complete after 3.5 hr. The resulting mixture was stirred for an additional 4 hr and added to 500 ml of ether. The ether solution was washed with eight 100-ml portions of water, dried, concentrated under reduced pressure, and trap-to-trap distilled [27° (0.05 mm)] to yield 2.54 g. The integrated nmr spectrum indicated that this product mixture was composed of 52% **6**, 28% methyl benzoate, and 20% methyl propiolate; the amount of **6** present was 1.56 g (52%). The combined products from four such runs were distilled through a 30-cm spinning-band column [81° (60 mm)] to yield 4.5 g of **6** (>95% pure by nmr analysis). The over-all yield from **2** was 20%.

The ir spectrum of **6** (gc collected) exhibited absorptions at 5.77 (C=O) and 8.30 μ (C—O). The nmr spectrum (CCl_4, internal TMS) showed a singlet absorption at τ 6.4 with almost continuous absorption from 6.24 to 8.32 in a ratio of 3:8.3.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.67; H, 8.82.

In a single run using ethanol instead of methanol as solvent, the corresponding ethyl esters were isolated.

Attempted Base Equilibration of Methyl *endo*-Bicyclo[2.2.0]-hexane-2-carboxylate.—Methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate (50 mg), sodium metal (5 mg), and 0.3 ml of anhydrous methanol were stirred together for 48 hr at room temperature. At the end of this period the reaction mixture was added to 5 ml of water, extracted with four 10-ml portions of ether, dried over magnesium sulfate, concentrated at reduced pressure, and trap-to-trap distilled [27° (0.05 mm)] to yield 10 mg of a clear, colorless liquid. An nmr spectrum identified this as the starting *endo* ester. The aqueous portion from the reaction work-up was acidified with dilute hydrochloric acid, extracted with ether, dried, and esterified with diazomethane. An nmr spectrum of the resulting ester (30 mg) proved to be identical with that of the starting *endo* isomer.

Acid Equilibration of Methyl *endo*-Bicyclo[2.2.0]hexane-2-carboxylate.—Methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate (30 mg), 6 ml of anhydrous methanol, and 4 drops of concentrated sulfuric acid were stirred together for 13 days at room temperature. At the end of this period the reaction mixture was diluted with 20 ml of ether, washed with three 10-ml portions of water, dried, concentrated at reduced pressure, and trap-to-trap distilled [27° (0.05 mm)]. The clear, colorless distillate was analyzed by gc and found to have the same retention time as the starting *endo* ester **5**. A mixture of the distillation product and the starting ester gave a single peak. The ir and nmr spectra for this product and **5** showed distinct differences, although similarities were evident. The extent of equilibration is uncertain but is assumed to be high from considerations of the spectra.

Bicyclo[2.2.0]hex-2-yl Methylsulfinylmethyl Ketone.—To a stirred solution of the methylsulfinyl carbanion [prepared from 0.556 g (10 mmol) of 44% sodium hydride suspension and 1.3 ml of dimethyl sulfoxide] in 1.3 ml of tetrahydrofuran[11] cooled in an ice bath under nitrogen was added 0.65 g (4.7 mmol) of ester **6** (containing some methyl benzoate) over a 10-min period. Stirring at room temperature was continued for 1 hr followed by the addition of 7.8 ml of water and the mixture was acidified to pH 3 with dilute hydrochloric acid. This was extracted with three 40-ml portions of chloroform and the combined extracts were washed with three 20-ml portions of water, dried, and concentrated at reduced pressure to yield 0.86 g (>95% yield) of a yellow oil. Trituration of this oil with cold isopropyl ether and ethyl ether produced 0.28 g of a white solid and 0.58 g of yellow oil. The solid was identified by its nmr spectrum as ω-(methylsulfinyl)acetophenone derived from methyl benzoate. The ir spectrum of the yellow oil exhibited absorptions at 5.90 (C=O) and 9.60 (S=O) μ while the nmr spectrum ($CDCl_3$, internal TMS) showed absorptions at τ 6.2 (singlet, 2), 7.29 (singlet, 3), and continuous absorption at 6.08–8.32 (9 H).

Aluminum Amalgam.—Strips (~10 cm × 1.0 cm) of aluminum foil (0.83 g, 31 mg-atoms) were rinsed with absolute alcohol and anhydrous ether, immersed in a saturated, aqueous mercuric chloride solution for 45 sec, rinsed with absolute alcohol followed by anhydrous ether, and used immediately in the following reaction.[27]

Reduction of Bicyclo[2.2.0]hex-2-yl Methylsulfinylmethyl Ketone.—The strips of aluminum amalgam prepared above were cut into small pieces and added to a solution of 0.58 g (3.0 mmol) of the sulfinylmethyl ketone in 36 ml of 90% aqueous tetrahydrofuran. The reaction mixture was stirred under reflux for 2 hr, cooled, filtered from the solid residue, and concentrated by distillation of the solvent through a 30-cm Vigreux column. The concentrated product mixture was added to 250 ml of ether, dried over magnesium sulfate, concentrated, and trap-to-trap distilled to yield 0.20 g (85%) of a clear, colorless liquid, bp ~27° (0.05 mm). Gc analysis on a Carbowax 20M column showed only one major peak which was collected. The ir spectrum of this peak showed a single, sharp carbonyl absorption at 5.88 μ and the nmr spectrum (CCl_4, internal TMS) exhibited continuous absorption at τ 6.41–8.32 with methyl singlets at 8.02 and 8.13. From the integration and factors presented in the discussion section, this gc peak is assigned the composition of *endo*- (**7**) and *exo*-bicyclo[2.2.0]hex-2-yl methyl ketones (**8**) in the ratio of 38:62.

Baeyer–Villiger Oxidation of the 38:62 Mixture of Ketones 7 and 8.—The mixture of ketones **7** and **8** (0.19 g, 1.5 mmol) prepared as described above and 0.37 g (2.1 mmol) of 80% *m*-chloroperbenzoic acid in 2.8 ml of methylene chloride was allowed to stir at room temperature for 3 days. The reaction mixture was diluted with 10 ml of methylene chloride, washed with two 5-ml portions of 10% sodium hydroxide, two 2-ml portions of water, two 5-ml portions of 10% sodium bisulfite, and 3 ml of water. The organic layer was dried, concentrated, and trap-to-trap distilled through a short-path column [27° (0.05 mm)] to give 0.19 g (89%) of a clear, colorless liquid. Gc analysis on a Carbowax 20M column showed two peaks, the first of which was collected and proven to be *exo*-bicyclo[2.2.0]-hex-2-yl acetate by comparison of its nmr spectrum with that of authentic material.[28a] This comprised 91% of the product mixture.

The second gc peak was collected and identified as a mixture of *cis*-bicyclo[3.1.0]hex-2-yl acetate (9% of product mixture) and 3-cyclohexenyl acetate (<1% of product mixture) by nmr spectral comparisons with the spectra of authentic samples. No indication of the presence of *endo*-bicyclo[2.2.0]hex-2-yl acetate could be found.

***endo*-Bicyclo[2.2.0]hexane-2-carboxylic Acid.**—Methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate (4.5 g, 32 mmol) and potassium hydroxide (3.62 g, 65 mmol) were combined in 21 ml of dry methanol and heated under reflux for 2.3 hr. The reaction mixture was added to 60 ml of water (0°), washed with three 50-ml portions of ether, acidified with concentrated hydrochloric acid, and extracted with six 50-ml portions of ether. This extract was dried, concentrated at reduced pressure, and trap-to-trap distilled [60° (0.005 mm)] to yield 4.0 g (98%) of a clear, colorless liquid. The ir spectrum was in agreement with the assigned structure and the nmr spectrum exhibited absorptions at τ 1.33 (singlet, 1) with continuous absorption at 6.25–8.41 (10.6 H).

Treatment of a portion of the acid with ethereal diazomethane gave the corresponding methyl ester, the ir spectrum of which was identical with that of starting *endo* ester **6**.

***endo*-Bicyclo[2.2.0]hexane-2-carbonyl Chloride.**—*endo*-Bicyclo[2.2.0]hexane-2-carboxylic acid (4.0 g, 32 mmol), thionyl chloride (7.6 g, 64 mmol), and 1 drop of dimethylformamide were combined under a nitrogen atmosphere, stirred at room temperature for 1 hr, and heated under reflux for 4 hr. The excess thionyl chloride was removed under reduced pressure and the product was trap-to-trap distilled at 27° (0.05 mm) to yield 4.2 g (90%) of the desired acid chloride as a clear, colorless liquid.

(26) This amount of **5** is based on the above integrated percentages in its preparation since the crude mixture was employed in this reduction.

(27) Little success was observed using a 2% mercuric chloride solution and shorter times for the amalgamation process described in ref 11.

A portion of the acid chloride was hydrolyzed to an acid whose ir spectrum was identical with that of the starting *endo* acid.

***exo*- (8) and *endo*-Bicyclo[2.2.0]hex-2-yl Methyl Ketone (7).**—The above acid chloride (4.20 g, 29 mmol) in 15 ml of benzene was added slowly with cooling to a solution of distilled [25° (0.1 mm)] dimethylcadmium[14] (prepared from 16.3 g of methyl bromide, 3.1 g of magnesium, and 12.7 g of cadmium chloride) in 20 ml of benzene. At the end of the addition the mixture was stirred an additional 2 hr. at room temperature under a nitrogen atmosphere. A saturated solution of ammonium chloride was slowly added, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed twice with water, dried, and concentrated under reduced pressure. Trap-to-trap distillation at 27° (0.05 mm) gave 1.85 g (51%) of a clear, colorless liquid. Gc analysis showed one major component whose ir and nmr spectra were similar to those of the mixture of ketones **7** and **8** previously obtained. However, in this case *endo* ketone **7** was predominant in a ratio of 65:35 (from comparison of the methyl singlet peak heights in the nmr spectrum). After 40 days at Dry Ice temperature, this ratio of **7** and **8** had changed to 51:49.

Baeyer–Villiger Oxidations of the Mixture of Methyl Ketones 7 and 8. A. Using *m*-Chloroperbenzoic Acid.—The 51:49 mixture of ketones **7** and **8** (1.80 g, 14.5 mmol) and 10.33 g (48.4 mmol) of 80% pure *m*-chloroperbenzoic acid in 65 ml of methylene chloride was allowed to react as previously described to yield, after work-up, 1.81 g (89%) of a clear, colorless liquid. The integrated nmr spectrum of this product showed it to be a mixture of acetates **9** (49%), **10** (18%), **11** (6%), and **12** (27%).

In a smaller run using 47 mg (0.4 mmol) of a 71:29 mixture of **7** and **8**, a 90% yield of acetates was obtained composed of 35% **9**, 17% **10**, 6% **11**, and 42% **12**. The rearrangements of this product mixture in carbon tetrachloride and methylene chloride are presented in the discussion section.

B. Using Monoperphthalic Acid.—The 65:35 mixture of ketones **7** and **8** (86 mg, 0.69 mmol) and 0.29 g (1.59 mmol) of monoperphthalic acid in 4.5 ml of ether was stirred at room temperature for 2 hr. The reaction mixture was diluted with 10 ml of ether, washed with two 3-ml portions of 10% sodium hydroxide solution followed by two 2-ml portions of water, two 3-ml portions of 10% sodium bisulfite solution, and finally 3 ml of water. The organic layer was dried and concentrated, and the residue was trap-to-trap distilled [27° (0.05 mm)] to give 80 mg (83%) of a clear, colorless acetate mixture. Integrated nmr spectral analysis showed this produce to contain 40% **9**, 32% **10**, 9% **11**, and 19% **12**.

Lithium Aluminum Hydride Reduction of the Mixture of Acetates Obtained from Baeyer–Villiger Oxidation Procedure A.—The mixture of acetates obtained in procedure A above (1.81 g, 12.9 mmol) dissolved in 40 ml of anhydrous ether was added over a 15-min period to a suspension of 1.0 g (26.4 mmol) of lithium aluminum hydride in 50 ml of anhydrous ether. The mixture was heated under reflux for 6 hr, cooled in an ice bath, and carefully hydrolyzed with water. The layers were separated. The aqueous layer was extracted with two 50-ml portions of ether, then acidified with concentrated hydrochloric acid, and further extracted with three 75-ml portions of ether. The latter ether extracts were combined, dried, concentrated, and trap-to-trap distilled [24° (0.02 mm)] to yield 1.04 g (82%) of a clear, colorless liquid. Gc analysis of this product on a 12 ft × 0.25 in. β,β'-oxydipropionitrile column (10% on Chromosorb W) at a temperature of 100° showed four peaks and each was collected.

The first peak (581 mg, 72.2%) was identified as a mixture of **1** (36%) and its *exo* epimer (64%) by comparison of the ir and nmr spectra and gc retention times with those of authentic samples. The 36:64 ratio was assigned from integration of the nmr spectrum of the acetate mixture prior to reduction. It was found that this mixture of *exo*- and *endo*-[2.2.0] alcohols could not be separated by gc (a wide variety of columns and conditions were investigated), alumina column chromatography, or thin layer chromatography on silica gel.

The second peak (101 mg, 12.5%) was identified as *cis*-bicyclo[3.1.0]hexan-2-ol by comparison of its ir and nmr spectra and gc retention time with those of an authentic sample. The third (5.2%) fourth (10.1%) peaks were collected and spectrally shown to be alcohols, but no positive identification was made.

***cis*-Bicyclo[3.1.0]hexan-2-ol.**—The method of Corey and Dawson[18] was followed to prepare this compound from 15.8 g (0.188 mol) of 2-cyclopentenol, 84.8 g (0.316 mol) of methylene iodide, and 30.7 g (0.474 mol) of zinc–copper couple.[18] The product was distilled through a 30-cm Vigreux column to give 11.66 g (63% yield), bp 58–48° (7–4 mm), $n^{28.5}$D 1.4782[28] [lit.[18] 60% yield, bp 60–61° (10 mm)]. Gc analysis on a β,β'-oxydipropionitrile column showed the product to be formed in >87% yield contaminated with 3-cyclohexenol. The integrated nmr spectrum of the mixture indicated only 6% 3-cyclohexenol to be present and is believed to be correct owing to the overlap of the gc peaks.

***cis*-Bicyclo[3.1.0]hex-2-yl Acetate (10).**—This acetate was prepared by the reported procedure.[20] The product obtained in 94% yield was analyzed on a newly prepared Carbowax 20M gc column (20% on Chromosorb W) and found to give partial separation of acetates **10** (94%) and **11** (6%) under analytical conditions. The integrated nmr spectrum agreed with this analysis and supports the nmr spectral analysis of the starting alcohol mixture.

Bicyclo[3.1.0]hexan-2-one.—A solution of 13.5 g (0.133 mol) of chromic anhydride in 20 ml of distilled water was added, with cooling, over a period of 20 min to 5.0 g (51 mmol) of the mixture containing *cis*-bicyclo[3.1.0]hexan-2-ol (prepared above) in 20 ml of ether. The resulting mixture was stirred at room temperature for 4 hr and worked up by separating the layers and extracting the aqueous layer with two 20-ml portions of ether. The ether fractions were washed with three 15-ml portions of saturated sodium bicarbonate solution and two 20-ml portions of saturated sodium chloride solution, dried, concentrated at reduced pressure, and trap-to-trap distilled [27° (0.05 mm)]. The light yellow liquid (2.44 g, 50% yield) was analyzed by gc on a Carbowax 20M column and showed a single major peak. The ir and nmr spectra were in excellent agreement with the assigned structure. A 2,4-dinitrophenylhydrazone of this ketone was prepared and recrystallized from aqueous ethanol, mp 188.5–189.5°.

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38. Found: C, 52.35; H, 4.48.

***trans*-Bicyclo[3.1.0]hexan-2-ol.**—Bicyclo[3.1.0]hexan-2-one (2.4 g, 25.0 mmol), prepared as described above, was reduced with 14.8 g (72.5 mmol) of freshly sublimed aluminum isopropoxide in 74 ml of dry isopropyl alcohol by stirring under reflux for 18 hr. The reaction mixture was cooled to room temperature, 100 ml of water added, the mixture was neutralized with concentrated hydrochloric acid and extracted with five 30-ml portions of pentane. The pentane solution was washed with 40 ml of saturated sodium chloride solution, dried, concentrated, and trap-to-trap distilled [50° (0.005 mm)]. The light yellow liquid product (1.3 g, 53% yield) was analyzed by gc on a β,β'-oxydipropionitrile column and three peaks were observed in a 33:48:19 ratio. The first peak was identified as starting ketone, and the second and third peaks were identified as *trans*- and *cis*-bicyclo[3.1.0]hexan-2-ols, respectively. The ir and nmr spectra of the collected second gc peak agreed with those previously reported.[20]

***trans*-Bicyclo[3.1.0]hex-2-yl Acetate.**—This compound was prepared by the method previously reported[20] in 65% yield from crude *trans* alcohol. The nmr spectrum showed the presence of a trace of 3-cyclohexenyl acetate and 12% *cis*-bicyclo[3.1.0]hex-2-yl acetate.

Registry No.—**3**, 19203-09-9; **4**, 19203-58-8; **6**, 19203-10-2; **7**, 19203-11-3; **8**, 19203-12-4; **12**, 19203-13-5; 2,4-dinitrophenylhydrazone of bicyclo-[3.1.0]hexan-2-one, 19203-59-9; bicyclo[2.2.0]hex-2-yl methylsulfinylmethyl ketone, 19245-02-4.

Acknowledgment.—The authors wish to express their gratitude to the National Science Foundation (GP-4888, GP-7818) for support of this research and for a departmental grant for the purchase of the Varian A-60 nmr spectrometer.

(28) W. G. Dauben and G. H. Berezin [*J. Amer. Chem. Soc.*, **85**, 468 (1963)] have reported the refractive index to be n^{25}D 1.4742.

Synthesis of Tetraallylmethane

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Tetraallylmethane has been synthesized by the following route: triallylcarbinol → triallylmethyl chloride → triallylmethylmagnesium chloride → tetraallylmethane *via* reaction with allyl bromide. Its stability is such that it can be kept for many months without polymerizing. An isomer of the tetraallylmethane is formed in the last step of the synthesis and is believed to be 4-allyl-4-vinyl-1,7-octadiene. It is presumed to be formed by the rearrangement of one homoallylic carbanion to an isomeric one through a cyclopropylmethyl carbanion intermediate.

We have prepared and characterized tetraallylmethane, an interesting olefin due to the tetrahedral symmetry about the quaternary central carbon atom. Although two syntheses were reported in a patent,[1] the yields were not stated and no evidence was included to support the assigned structure. The first synthesis involved the reaction of pentaerythritol tetrabromide with vinylmagnesium chloride in tetrahydrofuran solvent at 50°; the second involved the reaction of carbon tetrabromide with allylmagnesium bromide under Grignard conditions. We repeated the latter, but the only material obtained having approximately the right boiling range contained 25% bromine plus oxygen (*i.e.*, the analysis for carbon and hydrogen totalled 75%), and quantitative hydrogenation showed only two double bonds per molecular weight of $C_{13}H_{20}$. Our successful synthesis started with the known triallylcarbinol, which was converted successively into the triallylmethyl chloride and into the corresponding Grignard reagent, both of which are new compounds. The latter reacted with allyl bromide to yield a mixture of tetraallylmethane and an isomeric compound in a ratio of ~2:1.

Conversion of the triallylcarbinol into the chloride was noteworthy in that the reaction occurred relatively slowly (2 hr were required) with the usual concentrated hydrochloric acid–zinc chloride mixture at 0°, and that the triallylmethyl chloride was soluble in the concentrated hydrochloric acid. A striking array of dark red to deep purple colors was produced during this reaction. The colorless triallylmethyl chloride was isolated in 66% yield from the concentrated acid mixture by extraction with benzene followed by distillation. Attempts to prepare the chloride from the alcohol using concentrated hydrochloric acid alone were unsuccessful both at 0° (incomplete reaction). 25°, and steam bath temperature (where polymeric material was formed). The alcohol reacted incompletely with cold, concentrated hydrobromic acid, and only polymeric material was obtained by warming the alcohol with thionyl chloride.

Triallylmethyl chloride was converted into the Grignard reagent in 85% yield, using tetrahydrofuran as the solvent. The filtered Grignard solution was allowed to react at room temperature overnight with a threefold excess of allyl bromide; 5 hr was sufficient for the reaction to go to approximately 90% completion. The mechanism may be either S_N2 or S_N2' with respect to the attack of the nucleophilic Grignard reagent on the allyl bromide; the same product results in either case. A tridecatetraene fraction was obtained in 34% yield based on triallylmethyl chloride. It consisted of two major components: two-thirds was tetraallylmethane and one-third was an isomer. Distillation through a spinning band column gave only incomplete separation. However, the two isomers could be separated by vpc using an 8-m diisodecyl phthalate column.

The tetraallylmethane fraction, obtained in 15% yield based on the starting triallylcarbinol, was characterized by elemental analysis, quantitative hydrogenation, and ir and nmr spectra. Tetraallylmethane appears to be quite stable insofar as samples could be kept for 1 year without noticable change. In contrast, the isomeric material polymerized under the same conditions. Most of the common oxidizing agents were used in attempts to convert the tetraallylmethane into methanetetraacetic acid, but only traces could be obtained.

Nmr Spectra.—Triallylcarbinol, triallylmethyl chloride, and tetraallylmethane all have nmr spectra typical of an allyl group. The outstanding features are a sharp doublet at about δ 2.2 (J = 7 Hz) due to the methylene group, and a sharp peak at δ 5.2 due to each of the terminal vinyl hydrogens coupling with the nonterminal vinyl hydrogen (J = 10 and 17 Hz) and two of these split peaks being superimposed. The other peaks due to the terminal vinyl hydrogens caused a poorly resolved quartet at δ 4.9. The splitting constant for the terminal vinyl hydrogens was 2 Hz. The nonterminal vinyl hydrogen showed up as a broad multiplet centered at δ 5.9.[2]

Structure of the Isomer.—The identical features of the spectra of allyl alcohol, triallylcarbinol, triallylmethyl chloride, and the final isolated tetraallylmethane (Figure 1) clearly show that no isomerized product is present in the triallylcarbinol or the triallylmethyl chloride, even though the formation of the latter presumably procceds through a triallylmethyl carbonium ion. It is in the final reaction step involving a homoallylic carbanion that the nmr spectrum of the product gives the first evidence (broad multiplet at δ 1.4) that an isomeric material is present.

All of the analytical and spectral data for the isomeric compound are consistent with structure **4**. This could arise from the homoallylic carbanion (**1**) rearranging through a cyclopropylmethyl carbanion (**2**) to an isomeric homoallylic carbanion (**3**) which in turn would give **4**, 4-allyl-4-vinyl-1,7-octadiene.[3]

(1) A. J. Mital and J. F. Jones, U. S. Patent 2,996,488 (1961).

(2) The nmr spectra were initially obtained by Dr. William McFarlane and we are deeply indebted to him for his interpretation. A detailed analysis of the spectra is in the M. S. thesis of R. J. Bianchi, University of Maryland, 1964.

(3) We are indebted to Dr. Paul Mazzocchi for this explanation of the formation of **4**. A review of many interesting examples of this rearrangement is in D. J. Cram's "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 215–217.

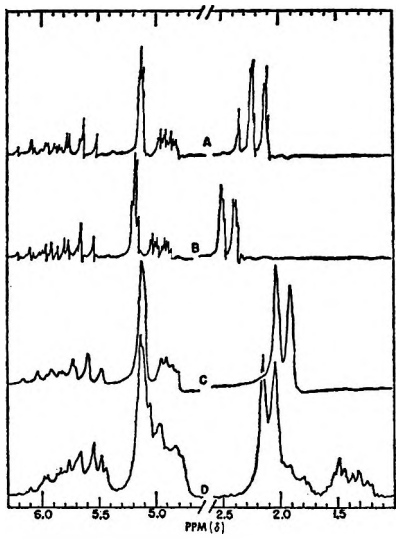
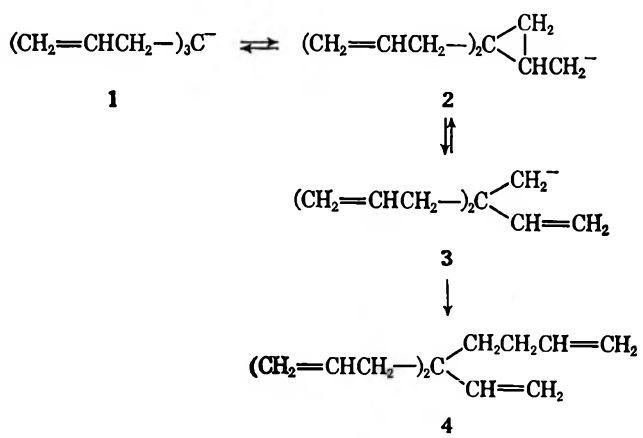


Figure 1.—Partial 60-Mc nmr spectra of (a) triallylcarbinol, (b) triallylmethyl chloride, (c) tetraallylmethane, and (d) isomer of tetraallylmethane; neat (tetramethylsilane, internal standard).



Examination of Fisher–Hirshcfelder models shows that there is no free rotation between the methylene groups in the butenyl chain of IV. These four hydrogens would accordingly appear in the nmr spectrum as an AA'BB' multiplet superimposed in part on the allylic doublet at δ 2.0, and this is what is observed.

Experimental Section

All melting and boiling points are corrected. The ir spectra were recorded on a Beckman IR-5 except for those of tetraallylmethane and the isomer which were recorded on a Beckman IR-8; the liquids were measured as films between sodium chloride plates. The nmr spectra were recorded on a Varian A-60, using tetramethylsilane as the internal standard. An F & M Model 300 vapor phase chromatograph was used for the vpc analyses. Other analyses are by Dr. Franz J. Kasler.

Triallylmethyl Chloride.—Triallylcarbinol was prepared from allylmagnesium bromide and ethyl carbonate.[4] It was converted into the chloride by stirring 46 g (0.3 mol) at ice-bath temperature with 169 g (0.7 mol of acid) of Lucas reagent prepared by mixing equimolar amounts of anhydrous zinc chloride and concentrated hydrochloric acid. After 20 min, the ice bath was removed and the mixture was stirred for another 2 hr. When 100 ml of benzene was added and the mixture was stirred for 5 min, two layers separated. After the acid layer was reextracted with benzene, the combined benzene extracts were dried overnight with anhydrous magnesium sulfate and filtered. Small portions of magnesium sulfate and anhydrous sodium bicarbonate were then added until there was no detectable odor of hydrogen chloride. On distillation through a short fractionating column, there was obtained 30 g (59%) of triallylmethyl chloride: bp 69–70° (9 mm); n^{25}D 1.4725; ir 3025, 2900, 1850, 1640, 1430, 1310, 1290, 1270, 1240, 1145, 1030, 1000, 970, 920, 855, 830, and 660 cm^{-1}; nmr (neat) δ 5.9 (m, 3, =CH–), 5.2 (sharp singlet, 3, one-half H_2C=, see Discussion), 5.0 (m, 3, J = 2 and 17 Hz, one-half H_2C=), 2.50 (d, 6, J = 7 Hz, –CH_2–).

Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.38; H, 8.85; Cl, 20.77. Found: C, 70.75; H, 8.87; Cl, 20.40.

Triallylmethylmagnesium Chloride.—A 500-ml three-necked flask was charged with 18 g of magnesium turnings, and a crystal of iodine was added and sublimed onto the magnesium with a small flame. After the flask had cooled, 15 ml of tetrahydrofuran was added, the mixture was heated to 50°, and 1 ml of triallylmethyl chloride together with a few drops of methyl iodide were added. The reaction started shortly thereafter and an ice bath was temporarily required to control the temperature. Finally, a heating mantle was used to maintain the temperature at the refluxing point. An additional 40 g (total of 0.24 mol) of triallylmethyl chloride dissolved in 165 ml of tetrahydrofuran was added dropwise over a period of 6 hr while the reaction was maintained at reflux temperature. Refluxing was continued for an additional 1.5 hr, and the mixture was then allowed to stand overnight. An acidimetric titration, using Gilman's method,[5] indicated an 85% yield of the Grignard reagent. The latter was placed in a narrow-mouth funnel containing a medium-porosity sintered glass plate, and was filtered under nitrogen pressure into a dropping funnel for use in the next reaction.

Tetraallylmethane.—The triallylmethylmagnesium chloride reagent (0.2 mol) was added over a 4-hr period under an atmosphere of nitrogen to 81 g (0.67 mol) of allyl bromide dissolved in 60 ml of tetrahydrofuran while the reaction mixture was cooled to 15°. The reaction was followed by testing qualitatively for the presence of Grignard reagent with Michler's ketone. (The usual iodometric procedure could not be used because of the addition of iodine to the double bonds, and the acidimetric titration failed because of rapid hydrolysis of the excess allyl bromide.) The reaction was also followed by decomposing a sample with acid and analyzing the hydrocarbon mixture by vpc using a diisodecyl phthalate column. Four hours after the last addition of the Grignard reagent, the size of the major peak indicated that the reaction was complete. After standing overnight, the reaction mixture was decomposed with dilute hydrochloric acid and the hydrocarbon mixture was extracted with ether and washed with water. Distillation gave 19.7 g of crude tetraallylmethane, bp 102–103° (25 mm). Following a steam distillation, the material was distilled using a 60-cm spinning band column and the fractions obtained are listed in Table I.

The mixtures were analyzed by vpc using a 2-m diisodecyl phthalate column. The total of 10.4 g of tetraallylmethane in the various fractions corresponds to a 30% yield based on the Grignard reagent or a 15% yield based on the starting triallylcarbinol. Data on the 90% tetraallylmethane–10% isomer fractions are as follows: n^{25}D 1.4726; ir and nmr same as pure tetraallylmethane separated by vpc (see below). A quantitative hydrogenation of 79 mg of the sample resulted in the absorption of 42 ml of hydrogen at 23° (762 mm), equivalent to 3.92 double bonds per mole of $C_{13}H_{20}$.

Anal. Calcd for $C_{13}H_{20}$: C, 88.58; H, 11.42. Found: C, 88.79; H, 11.20.

Data on the 50% tetraallylmethane–50% isomer fraction are as follows: n^{25}D 1.4712; for spectra, see data below on pure isomer fraction separated by vpc. A quantitative hydrogenation of 81 mg of the sample resulted in the absorption of 46 ml of hydrogen at 23° (760 mm), equivalent to 4.08 double bonds per mole of $C_{13}H_{20}$.

TABLE I

FRACTIONATION OF CRUDE TETRAALLYLMETHANE

Fraction	Amount, g	Bp (mm), °C	Ratio, tetraallylmethane/isomer
1	1.4	82 (14)	1:1
2	3.3	84.5–85.5 (13)	1:1
3	1.4	86.5–88 (12)	4:1
4	5.7	88–88.5 (12.5)	8:1
Residue	2.2		9:1

(4) M. P. Dreyfuss, *J. Org. Chem.*, **28**, 3269 (1963).

(5) H. Gilman, E. A. Zoellner, and E. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).

Anal. Calcd for $C_{13}H_{20}$: C, 88.58; H, 11.42. Found: C, 88.85; H, 11.70.

The two isomers were separated by vpc using an 8-m 10% diisodecyl phthalate on 60–80 mesh silanized diatomaceous earth column (Diatoport S). Data on tetraallylmethane are as follows: ir 3068, 3000, 2980, 2840, 1638, 1440, 1410, 989, 905, and 850 cm^{-1}; nmr (neat) δ 5.8 (m, 4, =CH–), 5.13 (sharp singlet, 4, one-half H_2C=, see Discussion), 4.87 (q, 4, J = 2 and 17 Hz, one half H_2C=), and 1.98 (d, 8, J = 7 Hz, $-CH_2-$). Data on the isomeric compound (believed to be 4-allyl-4-vinyl-1,7-octadiene) are as follows: ir 3068, 3000, 2980, 2920, 2845, 1638, 1450–1430, 1410, 989, and 905 cm^{-1}. The nmr spectrum was similar to that of tetraallylmethane except for the following: the singlet at δ 5.13 and the quartet at 4.87 merged to give an eight-proton multiplet from 5.2 to 4.8; the sharp doublet at 1.98 now accounted for only six protons including a one proton shoulder from 2.0 to 1.7; and there was a two-proton multiplet from 1.7 to 1.2.

Registry No.—Tetraallylmethane, 19255-02-8; triallylmethyl chloride, 19255-03-9; **4**, 19255-04-0.

Negatively Substituted Acetylenes. II.[1] Cycloaddition Reactions with Styrenes

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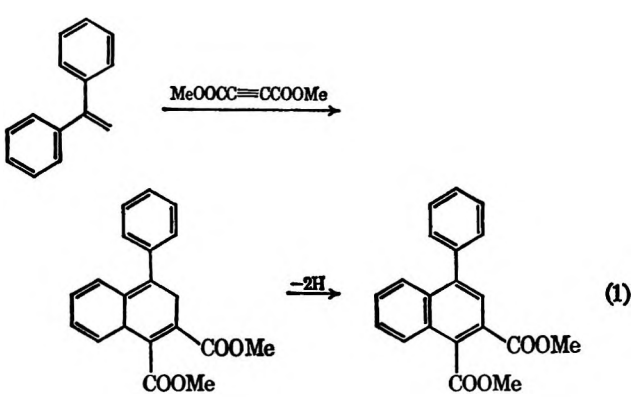
Received September 26, 1968

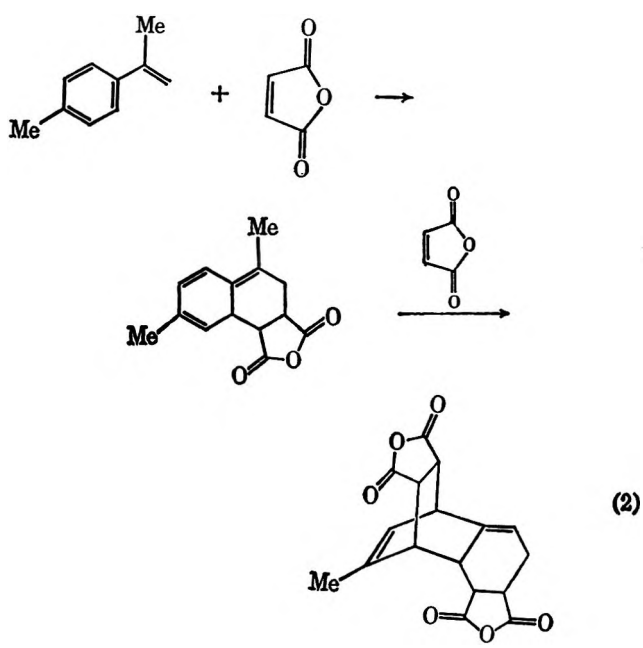
Activated acetylenes, such as dicyanoacetylene, acetylenedicarboxylic ester, and benzyne, react with styrenes to give 1:2 adducts of type **2** by a sequence of Diels–Alder addition and ene reaction. Unlike in previously reported additions of this nature, the styrene, and not the acetylene, acts as the enophile in the second step. From the reactions of dicyanoacetylene and benzyne with styrene, mixtures of *threo* and *erythro* adducts have been isolated, resulting from exoid and endoid attack by the styrene in the ene reaction. The fact that no β-phenylethyldihydronaphthalenes (*e.g.*, **22**) could be detected among the products indicates that in the transition state of the second-step ene reaction, hydrogen transfer has proceeded to a larger extent than carbon–carbon bond formation. The scope of these reactions is discussed.

The vinyl group and one of the aromatic double bonds of styrene form a diene system that is potentially capable of undergoing the Diels–Alder reaction. Although this possibility was foreseen at an early stage, examples of such additions are not so numerous as might be expected because of the tendency of styrenes to polymerize and copolymerize under the reaction conditions required. As a rule, only very reactive dienophiles will give nonpolymeric products in acceptable yields. The initial 1:1 adducts usually cannot be



(1)

isolated; they either aromatize to give derivatives of dihydro- or tetrahydronaphthalene as exemplified in eq 1,[2,3] or add a second molecule of the dienophile. This second addition can either be another Diels–Alder reaction (*e.g.*, eq 2[4,5]), an ene reaction[6] as shown in



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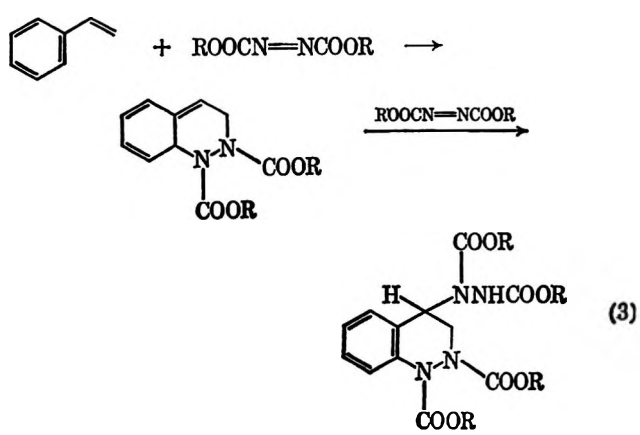


(3)

(1) E. Ciganek and C. G. Krespan, *J. Org. Chem.*, **33**, 541 (1968) is considered to be paper I in this series.

(2) K. Alder, F. Pascher, and H. Vagt, *Ber.*, **75**, 1501 (1942).

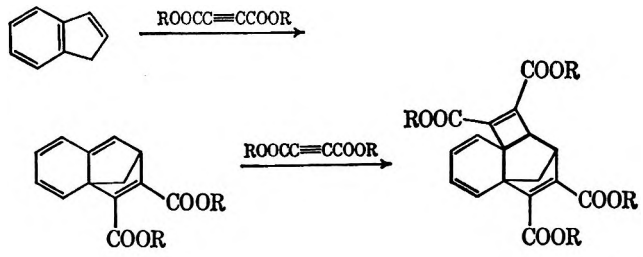
(3) For reviews of the Diels–Alder addition, see A. S. Onishchenko, "Diene Synthesis," English translation, D. Davey, New York, N. Y., 1964; J. Sauer, *Angew. Chem.*, **78**, 233 (1966).

(4) This type of addition was first observed by T. Wagner-Jauregg, *Ber.*, **63**, 3213 (1930); *Ann. Chem.*, **491**, 1 (1931). The example of eq 2 is from ref 5.

(5) J. Hukki, *Acta. Chem. Scand.*, **5**, 31 (1951).

(6) For a brief review of the ene reaction see W. R. Roth, *Chimia (Aarau)*, **20**, 229 (1966).

eq 3,[7] or a 2 + 2 cycloaddition (*e.g.*, eq 4[2,8]). Only in special cases, such as the reaction of 2-vinylnaphthalene with tetracyanoethylene, can a simple 1:1 Diels–Alder adduct be obtained.[9]



(4)

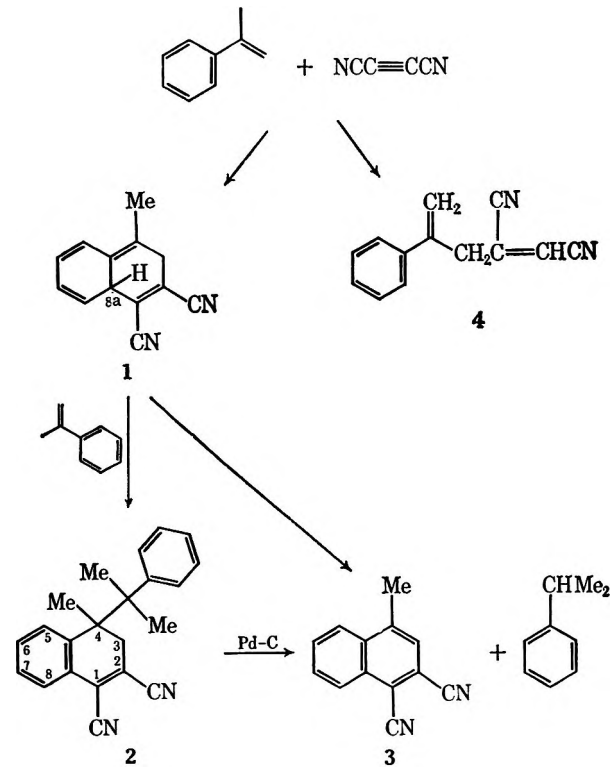
The extremely high reactivity of dicyanoacetylene in the Diels–Alder reaction[10] led us to investigate its reaction with styrenes. It was hoped that the addition would occur at sufficiently low temperatures so that secondary reactions could be avoided, the initial 1:1 adduct could be isolated, and its properties could be studied.

Results

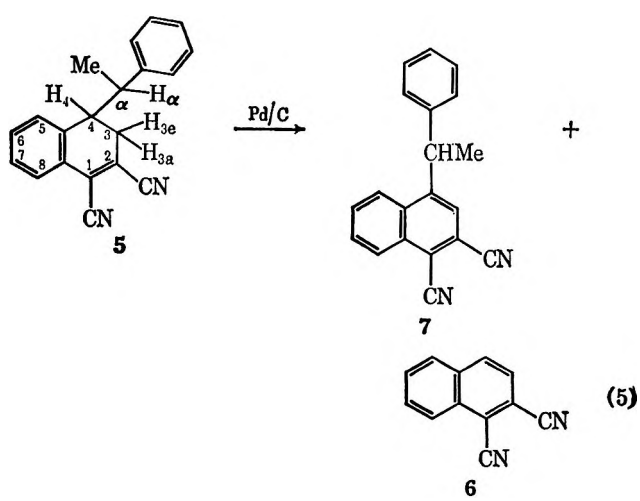
The reaction of dicyanoacetylene with excess α-methylstyrene proceeded quite rapidly at room temperature (pseudo-first-order half-life *ca.* 5 hr), but, as in previous cases, the 1:1 adduct was not obtained. The main product, formed in 63% yield, was an adduct of two molecules of α-methylstyrene to one of dicyanoacetylene to which structure **2** was assigned. Its nmr spectrum showed nine aromatic protons at τ 2.5–3.2, the two protons on C-3 as an AB quartet (J = 18 cps) at 7.0 and 7.6, and a singlet at 8.8 (methyl on C-4). The two geminal α-methyl groups gave rise to a barely split signal at τ 8.5, which at 220 Mc was resolved into two singlets of equal intensity separated by 3.5 cps. The two α-methyl groups are magnetically nonequivalent as a consequence of their proximity to an asymmetric center (C-4).[11] Further structure proof was obtained by the catalytic or photochemical aromatization of **2** to give 1,2-dicyano-4-methylnaphthalene (**3**) and isopropylbenzene. In addition to the diadduct **2**, the reaction of dicyanoacetylene with α-methylstyrene gave, in 4% yield, a compound believed to be 1,2-dicyano-4-phenyl-1,4-pentadiene (**4**) on the basis of its nmr spectrum (see Experimental Section) as well as 1,2-dicyano-4-methylnaphthalene (**3**, 1% yield) (Scheme I). Attempts to trap the intermediate 1:1 adduct (**1**) with excess isobutene or acetone were unsuccessful.

The reaction of dicyanoacetylene with excess styrene

SCHEME I



also proceeded at room temperature, but at a somewhat diminished rate (pseudo-first-order half-life *ca.* 40 hr). The products, isolated in 70% yield, proved to be a mixture of the *threo* and *erythro* isomers of 1,2-dicyano-3,4-dihydro-4-(α-methylbenzyl)naphthalene (**5**). The structure proof again rests on the nmr spectra and the fact that both isomers could be aromatized to give a mixture of 1,2-dicyanonaphthalene (**6**) and 1,2-dicyano-4-(α-methylbenzyl)naphthalene (**7**) (eq 5).



(5)

The two isomers were formed in a ratio of 70:30. The nmr spectrum of the major isomer showed the aromatic protons as well-separated multiplets at τ 2.4–2.9 (6 H) and 3.0–3.3 (3 H), the protons on C-3 and C-4 and the α proton as an unresolved multiplet at 6.9–7.2 (4 H), and the methyl group as a doublet (J = 7 cps) centered at 8.68. The spectrum of the minor isomer displayed the nine aromatic protons as a single group of signals at τ 2.4–3.0, the protons on C-3 and C-4 and the α proton

(7) O. Diels and K. Alder, *Ann. Chem.*, **450**, 237 (1926); K. Alder and H. Niklas, *Ann. Chem.*, **585**, 97 (1954); C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, **127**, 378 (1925).

(8) K. W. Muir, G. A. Sim, P. Stracham, and C. F. Huebner, *Chem. Ind.* (London), 1581 (1964); C. F. Huebner, P. L. Strachan, E. M. Donogue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32**, 1126 (1967); K. W. Muir and G. A. Sim, *J. Chem. Soc., B*, 667 (1968).

(9) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Amer. Chem. Soc.*, **80**, 2783 (1958).

(10) C. D. Weis, *J. Org. Chem.*, **28**, 74 (1963); R. C. Cookson and J. Dance, *Tetrahedron Lett.*, 879 (1962); R. C. Cookson, J. Dance, and M. Godfrey, *Tetrahedron*, **24**, 1529 (1968); E. Ciganek, *Tetrahedron Lett.*, 3321 (1967).

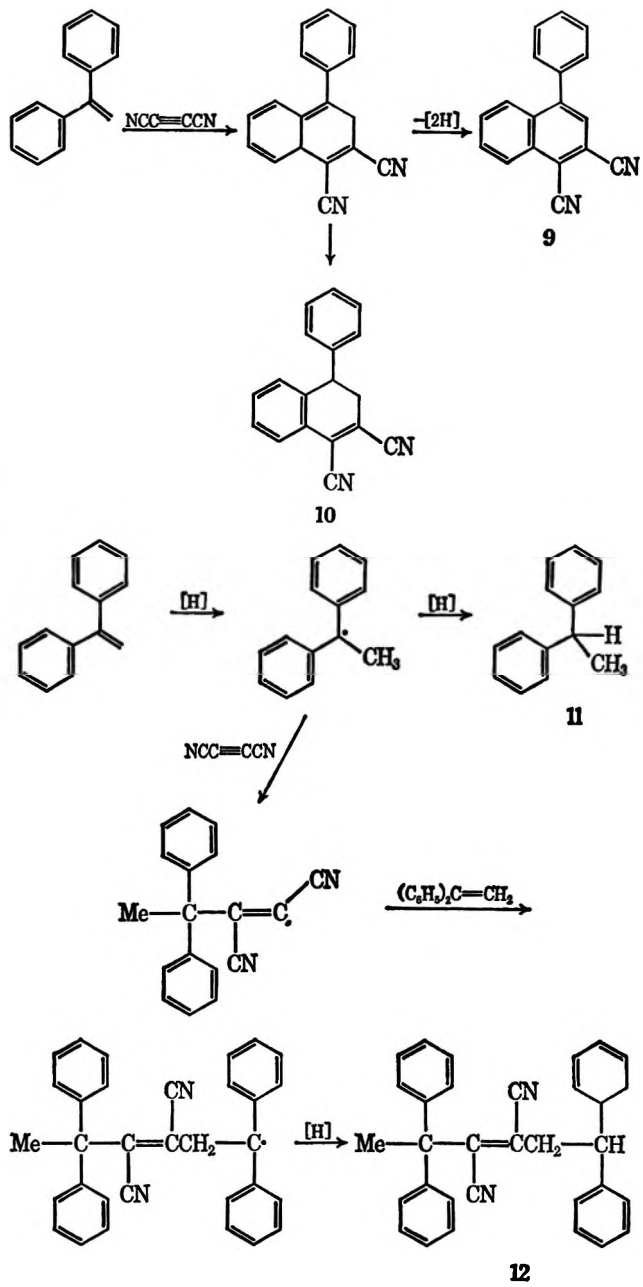
(11) M. van Gorkom and G. E. Hall, *Quart. Rev.* (London), **22**, 14 (1968).

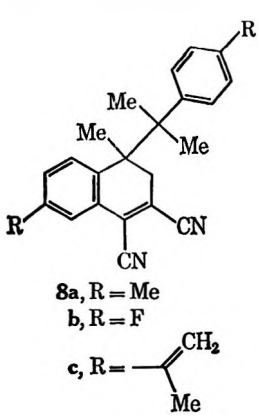
at 7.0–7.5, and the methyl group as a doublet (J = 7 cps) centered at 8.85. Unlike the major isomer, the τ 7.0–7.5 region of the minor isomer was well resolved at 220 Mc and the signals due to H-3 and H-α became amenable to first-order analysis. In both isomers, H-4 is believed to be equatorial, and the α-methylbenzyl group axial, since models show serious interactions between H-3, H-5 and the phenyl- and α-methyl groups in the reverse situation precluding free rotation around C-4–C-α. With this assumption, the following assignments were made in the 220-Mc nmr spectrum of the minor isomer: H-3 (equatorial), doublet, ($J_{3e,3a}$ = 18 cps) split into doublets ($J_{3e,4e}$ = 1.5 cps); H-3 (axial), doublet ($J_{3e,3a}$ = 18 cps) split into doublets ($J_{3a,4e}$ = 6.5 cps); H-α, doublet ($J_{4e,\alpha}$ = 9 cps) split into quartets ($J_{\alpha,Me}$ = 7 cps). H-4e was an unresolved multiplet. The coupling constants provide further evidence for H-4 being equatorial; if it were axial, it would be *trans* and almost coplanar to one of the protons on C-3, and a coupling constant larger than 6.5 cps would result. The dihedral angle between H-3a and H-4e from models is about 50° (and decreases as the 1,3-cyclohexadiene portion of the molecule becomes flatter); on the basis of the Karplus equation, $J_{3a,4e}$ should be *ca.* 4 cps (or larger in a flatter molecule); similarly, $J_{3e,4e}$ should be 2 cps (or smaller) for a dihedral angle of 65° (or more in a flatter molecule).

Knowledge of the coupling constant between H-4e and H-α forms the basis of the stereochemical assignments to the two isomers. $J_{4e,\alpha}$ in the minor isomer is 9 cps, indicating that in the most populated rotamer the substituents on C-4 and C-α are either eclipsed (H-4e and H-α *cis* and coplanar) or staggered (H-4e and H-α *trans* and coplanar). Models show that the latter situation is much more likely and that, in this case, the phenyl group on C-α points away from the molecule in the *erythro* isomer. In the *threo* isomer the C-α phenyl group resides over the C-5 to C-6 portion of the molecule, which should result in an upfield shift of some of the aromatic protons as a result of the diamagnetic shielding. Whereas all aromatic protons are in the normal region (τ < 3) in the minor isomer, three are shifted upfield in the major isomer. On the basis of this argument, the major isomer would thus have the *threo*, and the minor the *erythro* configuration.

A number of α-methylstyrenes substituted in the *para* position gave analogous 2:1 adducts with dicyanoacetylene. Thus, α,*p*-dimethylstyrene, *p*-fluoro-α-methylstyrene, and *p*-diisopropenylbenzene gave adducts **8a**, **8b**, and **8c**, respectively. Dicyanoacetylene reacted readily also with 1,1-diphenylethylene, but the main product, isolated in 52% yield, was 1,2-dicyano-4-phenylnaphthalene (**9**) (Scheme II). The reaction

SCHEME II





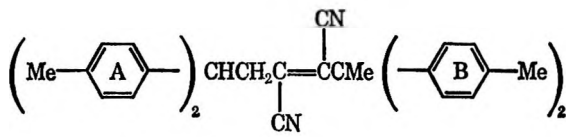
thus followed the same path as that reported for dimethyl acetylenedicarboxylate (eq 1).[2] The recovered 1,1-diphenylethylene contained 1,1-diphenylethane (**11**) identified by nmr spectroscopy and by comparison of its retention time on gas chromatography with that of an authentic sample. There were also isolated, in 0.3 and 7% yield, two compounds assigned structures **10** and **12**, respectively. The nmr spectrum of **10**[12,13] showed an unsymmetrical doublet (separation

(12) A very similar spectrum has been reported[13] for the related 9-phenyl-9,10-dihydrophenanthrene (**19**).

(13) W. L. Dilling, *Tetrahedron Lett.*, 939 (1966).

8.5 cps) at τ 7.0 (2 H) and an unsymmetrical triplet (separation 8.5 cps) at 5.7 (1 H). The aromatic absorption (τ 2.1–3.1) corresponded to 11.5, rather than 9.0 protons, indicating that the sample may have been contaminated by a small amount of 1,2-dicyano-4-phenylnaphthalene (**9**). Dehydrogenation of compound **10** gave 1,2-dicyano-4-phenylnaphthalene (**9**).

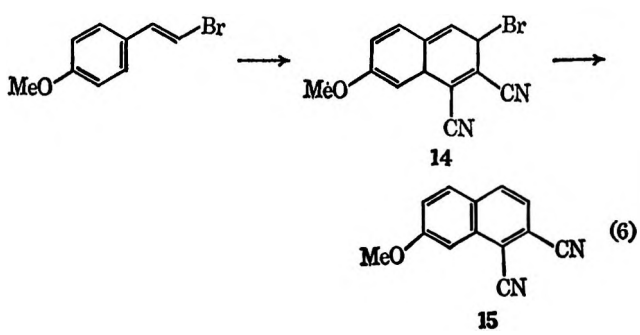
The nmr spectrum of compound **12** displayed 20 aromatic protons at τ 2.5–3.3, a triplet (J = 8.5 cps) at 5.5 (1 H), a doublet (J = 8.5 cps) at 6.5 (2 H), and a singlet at 8.0 (3 H). The analogous product **13** was prepared from dicyanoacetylene and 1,1-di-*p*-tolylethylene; although the amount isolated was too small to be characterized by micro analysis, its nmr spectrum (at 100 Mc) strongly indicated structure **13**.



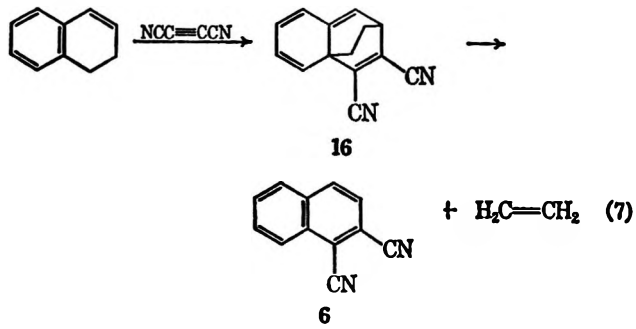
13

The spectrum showed the aromatic protons in ring A as a weakly split single band at τ 2.8, the aromatic protons in ring B as an AB quartet (J = 8.5 cps) at 2.9 and 3.2, a triplet (J = 8 cps) at 5.6 (1 H), a doublet (J = 8 cps) at 6.5 (2 H), two singlets (6 H each) at 7.6 (separation 3 cps at 100 Mc and 1.6 cps at 60 Mc), and a singlet at 8.0 (3 H). The observation of only two signals due to methyl groups attached to aromatic rings indicates the presence of two pairs of equivalent phenyl rings in **13** and, consequently, also in **12**. A possible mechanism for the formation of compound **12** is shown in Scheme II.

Reaction of dicyanoacetylene with *p*-methoxystyrene caused polymerization of the latter; with *p*-methoxy-β-bromostyrene, 1,2-dicyano-7-methoxynaphthalene (**15**) was formed in 42% yield, presumably by 1,4-dehydrobromination of the initial adduct **14** (eq 6).

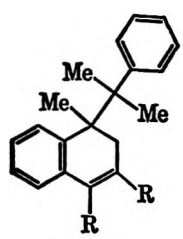


Indene and dicyanoacetylene reacted readily below room temperature; the only product isolated (in 10% yield) had the composition of an adduct of two molecules of dicyanoacetylene and one of indene. The structure was not determined, but it is probably analogous to that of the product[8] from the reaction of dimethyl acetylenedicarboxylate with indene (eq 4). Reaction of dicyanoacetylene with 1,2-dihydronaphthalene required heating to 120°. The product, isolated in 36% yield, was identified as 1,2-dicyanonaphthalene (**6**) (eq 7); it was probably formed by retrodiene fission of the initial adduct **16**. The analogous reaction course was reported for the interaction of

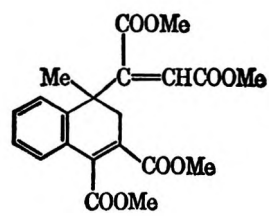


1,2-dihydronaphthalene with dimethyl acetylenedicarboxylate.[14] No reaction occurred between dicyanoacetylene and methyl cinnamate, coumarin, or acetophenone at elevated temperatures. Reaction between dicyanoacetylene and vinylmesitylene required heating to 100°, but no pure adducts could be isolated.

The formation of 2:1 adducts of type **2** was also observed with other activated acetylenes, but elevated temperatures were required. Thus, reaction of hexafluoro-2-butyne with excess α-methylstyrene at 100° gave the adduct **17a** in 58% yield. Dimethylacetylenedicarboxylate reacted with excess α-methylstyrene at 100° to give the 1:2 adduct **17b** (23% yield) as well as a second product (10% yield) believed to be the 2:1 adduct **18** on the basis of its nmr spectrum (see Experimental Section). Alder and co-workers[2] reported the formation of dimethyl 4-methylnaphthalene-1,2-dicarboxylate (in unspecified yield) in the reaction of equimolar amounts of α-methylstyrene and dimethyl acetylenedicarboxylate at 120°. From the reaction of styrene with dimethyl acetylenedicarboxylate, they obtained a 1:2 adduct of unspecified structure; this may have been an adduct of type **18**.



17a, R = CF_3
b, R = COOMe



18

The reaction of benzyne with styrene[13] and with α-methylstyrene[15] has been reported. With styrene (fivefold excess), 9-phenyl-9,10-dihydrophenanthrene (**19**) was isolated in 87% yield; this product corresponds to an adduct of two molecules of benzyne to one of styrene and the reaction thus is analogous to that of azodicarboxylic ester with styrene (eq 3).[7,16,17] The reaction between α-methylstyrene and benzyne[15] gives mainly the product of an ene reaction involving the isopropenyl group of α-methylstyrene; a small

(14) F. Pascher, Ph.D. Thesis, University of Cologne, 1944.

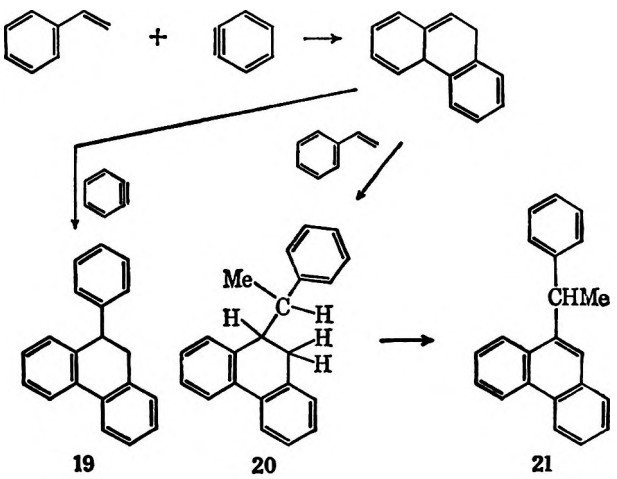
(15) E. Wolthuis and W. Cady, *Angew. Chem.*, **79**, 575 (1967).

(16) Dilling[13] suggests a three-step ionic mechanism for the addition of the second molecule of benzyne to the initial Diels–Alder adduct. A more likely mechanism would be a concerted, one-step ene reaction, since benzyne is known[15,17] to undergo this type of addition very readily.

(17) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Verlag Chemie Gmbh, Weinheim, 1967, pp 197–199.

amount of 9-methylphenanthrene, the aromatization product of an initial Diels–Alder adduct, was also isolated. We repeated the reaction of benzyne with styrene using a large (fiftyfold) excess of the latter. In this case, the 1:2 adducts **20** (*threo* and *erythro* isomers) were obtained instead of the 2:1 adduct isolated[13] when a small excess of styrene was used. The ratio of the two isomers was about 1:1. The structures follow from the nmr spectra and the fact that catalytic aromatization of **20** gave 9-(α-methylbenzyl)-phenanthrene (**21**) (Scheme III), an authentic sample of which was prepared by standard methods.

SCHEME III

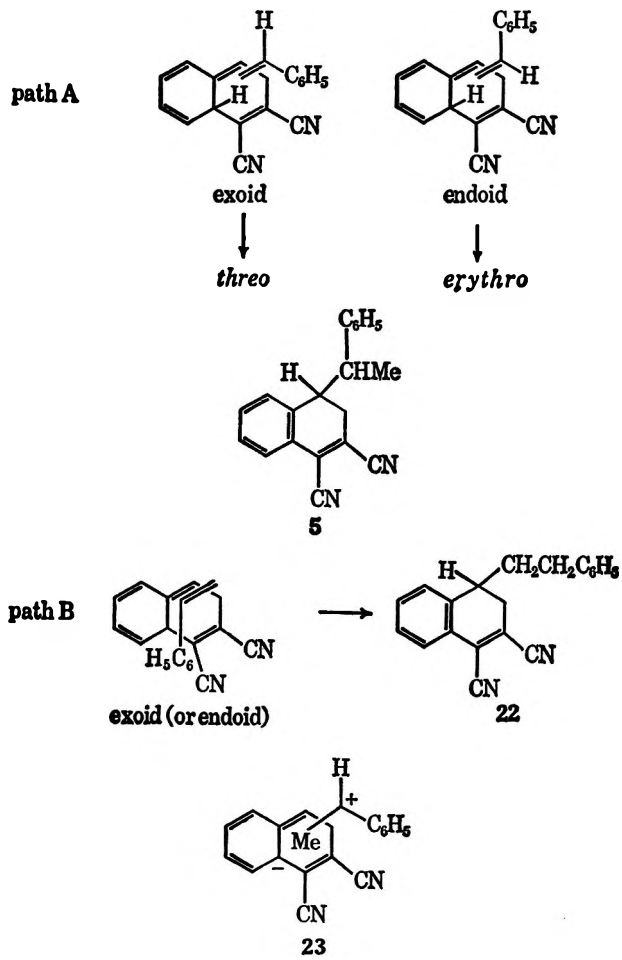


Discussion

The formation of 2:1 adducts such as compound **2** (Scheme I) from styrenes and activated acetylenes is most easily explained as proceeding by a sequence of a Diels–Alder addition and an ene reaction. The unusual features of these reactions are that both proceed under such mild conditions and that the styrene, rather than the acetylene, acts as the enophile in the second step. The driving force for the ene reaction is provided by the rearomatization of ring A. Even so, the low activation energy of this reaction is surprising in view of the stringent entropy requirements and the fact that in the case illustrated in Scheme I, carbon–carbon bond formation produces a crowded hexasubstituted ethane derivative. It is noteworthy in this connection that 1,2-dicyano-1,4-cyclohexadiene, which is analogous to **1** except for the lack of ring A, does not react with α-methylstyrene at 150°.

The two centers of the allylic system involved in the ene reaction, namely the π orbitals of the exocyclic double bond, and the C-8a–H bond in **1** (Scheme I), are almost coplanar and thus well oriented for a concerted reaction. In principle, the enophile can approach the allylic system in four different ways as illustrated in Scheme IV. There may be *exo*- or *endo*-like transition states, and the allylic hydrogen may be transferred either to the methylene carbon of styrene, or to the one carrying the phenyl group. The latter course is not followed to any significant extent since the product of such a reaction, 1,2-dicyano-2,3-dihydro-4(β-phenylethyl)naphthalene (**22**), could not be detected. Models indicate that there is little

SCHEME IV



difference in nonbonded interactions between the transition states of paths A and B. It is thus likely that the ene reaction, at least in this case, is not completely synchronous. In the transition state, carbon–hydrogen bond formation has proceeded to a larger extent than carbon–carbon bond formation, resulting in a partial carbonium, carbanion, or radical character of the carbon carrying the phenyl group. A two-step process, involving complete transfer of the hydrogen followed by carbon–carbon bond formation, is considered unlikely since the allylic anion, cation, or radical (*e.g.*, **23**) should be prone to side reactions such as aromatization or hydrogen abstraction, unless recombination of the two fragments is favored by occurring in a cage. Furthermore, the observed transfer of optical activity in two examples of an ene reaction[18,19] precludes intermediates of type **23** in these reactions.[20a]

As far as orientation of the styrene in path A is concerned, it appears that exoid attack is slightly favored in the case of the dicyanoacetylene adduct, if one accepts the rather tentative stereochemical assignments of the isomers of **5**. There is no stereochemical preference in the formation of adducts **20** from benzyne and styrene. In the case of the ene reaction of maleic anhydride with *cis*- and *trans*-2-butenes,[19] slight

(18) R. K. Hill and M. Rabinowitz, *J. Amer. Chem. Soc.*, **86**, 965 (1964).
(19) J. A. Berson, R. G. Wall, and H. D. Perlmutter, *ibid.*, **88**, 187 (1966).
(20) (a) See footnote 7 in ref 19; (b) see footnote 10 in ref 19.

preference for endoid attack was observed. Orbital symmetry considerations predict that endoid attack should be favored in the ene reaction, but that the preference should be smaller than in the Diels–Alder reaction.[20b]

Experimental Section

Reaction of Dicyanoacetylene with Styrene.—A mixture of 3.75 g of dicyanoacetylene[1] and 60 ml of styrene (Eastman White Label, undistilled) was allowed to stand at room temperature for 190 hr. Gas chromatographic analysis (silicone grease column, 95°) showed the half-life of dicyanoacetylene to be *ca.* 40 hr. Most of the excess styrene was removed at 40° bath temperature (0.5 mm), the residue was passed through 100 g of Florisil, and the material eluted with 1.75 l. of methylene chloride was kept at 100° under 0.1-μ pressure for 1 hr to give 9.81 g (70% yield) of a viscous oil. Its nmr spectrum showed the ratio of the two isomeric 2:1 adducts (see below) to be *ca.* 70:30. The mixture could be short-path distilled at 115° bath temperature (0.1-μ pressure) without change in composition. The two isomers could be separated by chromatography on Florisil and elution successively with hexane–benzene (1:1), benzene, and methylene chloride–tetrahydrofuran (THF) (99:1). The minor isomer was eluted first. However, isolation of larger amounts by this method was tedious. The crude mixture (5.86 g) was dissolved in 30 ml of hot ethanol; the mixture was cooled, filtered, and seeded with a crystal of the major isomer obtained by chromatography. There was obtained 1.82 g of the major isomer in the form of colorless crystals; a second crop of 0.81 g was obtained by crystallization of the concentrated mother liquor from 15 ml of ethanol. Removal of the solvent from the mother liquors of the second crystallization gave 3.04 g of an oil, which was dissolved in 9 ml of ethanol. Seeding with a crystal of the minor isomer gave 1.10 g of that product in the form of colorless crystals. Analytical samples of the two isomers of 1,2-dicyano-3,4-dihydro-4-(α-methylbenzyl)naphthalene were prepared by recrystallizations from ethanol.

The major isomer had mp 100–101°; λ_{max}^{MeCN} 311 mμ (ϵ 9800) and 243 (11,800); ν_{max}^{KBr} 3080, 3040, 2980, 2920, 2235 (sh), 2220, 1610, and 1575 cm^{-1}, among others.

Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.58; H, 5.81; N, 9.68.

The minor isomer had mp 121–122°; λ_{max}^{MeCN} 308 mμ (ϵ 10,900) and 242 (12,200); ν_{max}^{KBr} 3080, 3030, 2980, 2220 (sh), 2210, 1605 and 1565 cm^{-1}, among others.

Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85; mol wt, 284. Found: C, 84.52; H, 5.79; N, 9.76; mol wt, 299 (cryoscopically in benzene).

The nmr spectra of the two isomers are presented in the Discussion.

Aromatization of 1,2-Dicyano-3,4-dihydro-4-(α-methylbenzyl)naphthalene.—The crude mixture of the two adducts (1.060 g) was stirred and heated under reflux in 25 ml of xylene with 400 mg of palladium on charcoal (10%) for 2 hr. Removal of the solvent from the filtered solution gave 1.059 g of a dark semisolid. Chromatography over Florisil gave first 576 mg of a product (eluted with benzene followed by methylene chloride) consisting mostly of 1,2-dicyano-4-(α-methylbenzyl)naphthalene; methylene chloride–THF (7:3) eluted 226 mg of a mixture of the above product and 1,2-dicyanonaphthalene. An analytical sample of 1,2-dicyano-4-(α-methylbenzyl)naphthalene, prepared by crystallization from isopropyl alcohol, had mp 145–146°; uv λ_{max}^{MeCN} 348 mμ (ϵ 5600), 330 (4700), 315 (7800), 305 (sh, 6600), 242 (63,000), and 219 (32,000); ir ν_{max}^{KBr} 3080, 3030, 2980, 2230, 1585, 760, 750, 710, and 675 cm^{-1}, among others; nmr (in $CDCl_3$) multiplets at 1.7–1.9 (2 H) and 2.2–2.4 (3 H), a fairly sharp singlet at 2.8 (5 H), a quartet (J = 7 cps) centered at 5.0 (1 H), and a doublet (J = 7 cps) centered at 8.2 (3 H).

Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 85.02; H, 4.84; N, 10.29.

The 1,2-dicyanonaphthalene had mp 194–195° after crystallization from isopropyl alcohol (lit.[21] mp 190°); uv λ_{max}^{MeCN} 345 mμ (ϵ 3700), 330 (3300), 311 (5300), 300 (sh, 4900), 247 (68,000), and 214 (36,000); nmr only aromatic protons.

(21) P. T. Cleve, *Ber.*, **25**, 2475 (1892).

Anal. Calcd for $C_{12}H_6N_2$: C, 80.89; H, 3.40; N, 15.72. Found: C, 81.43; H, 3.42; N, 15.86.

Reaction of Dicyanoacetylene with α-Methylstyrene.—A mixture of 3.098 g of dicyanoacetylene[1] and 55 ml of freshly distilled α-methylstyrene was allowed to stand at room temperature for 24 hr. The half-life of dicyanoacetylene, determined gas chromatographically, was *ca.* 5 hr. Removal of excess α-methylstyrene at 40° (0.3 mm) gave 11.39 g of a dark solid which was purified by chromatography on 100 g of Florisil. Elution with 1 l. of methylene chloride gave 9.27 g of the crude adduct. Crystallizations from benzene and acetonitrile gave a total of 8.04 g (63%) of 1,2-dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)naphthalene (**2**). An analytical sample (acetonitrile) had mp 193–194°; uv λ_{max}^{MeCN} 313 mμ (ϵ 8100), 245 (12,700), and 240 (sh, 11,100); ir ν_{max}^{KBr} 3050, 3010, 2970, 2870, 2220, 1620, 1600, 770, 755, and 700 cm^{-1}, among others; for nmr, see Discussion.

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; mol wt, 312. Found: C, 84.90; H, 6.45; N, 8.63; mol wt, 320 (ebullioscopically in benzene).

The nmr spectrum of the combined mother liquors showed the presence of 1,2-dicyano-4-phenyl-1,4-pentadiene (**4**, *ca.* 5% yield) and 1,2-dicyano-4-methylnaphthalene (**3**, *ca.* 1% yield) in addition to 1,2-dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)-naphthalene. Chromatography over Florisil and elution with benzene first gave fractions enriched in **2**, followed by fractions enriched in **4**. The nmr spectrum of 1,2-dicyano-4-phenyl-1,4-pentadiene (**4**) showed a triplet (J = 1.5 cps) at τ 4.1 (1 H), a singlet at 4.3 (1 H), a broadened singlet (width at half-height 2 cps) at 4.7 (1 H), and a narrow multiplet at 6.4 (2 H) in addition to aromatic absorption. No further purification and characterization were attempted. Elution with methylene chloride–THF (95:5) and crystallization from isopropyl alcohol gave 1,2-dicyano-4-methylnaphthalene (**3**), identified by comparison of its ir spectrum with that of the sample obtained by aromatization of 1,2-dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)-naphthalene (see below).

Aromatization of 1,2-Dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)naphthalene.—A mixture of 400 mg of 1,2-dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)naphthalene, 200 mg of palladium on charcoal (10%), and 10 ml of toluene was stirred under reflux for 4 hr. Removal of the solvent from the filtered solution and crystallization of the residue from acetonitrile gave 1,2-dicyano-4-methylnaphthalene: mp 206.5–207.5°; uv λ_{max}^{MeCN} 348 mμ (ϵ 5000), 332 (4100), 318 (6900), 307 (6000), 246 (69,000), and 219 (29,000); ir ν_{max}^{KBr} 3080 3050, 2990, 2960, 2230, 1595, 890, 765, 695, and 675 cm^{-1}, among others; nmr (in $CDCl_3$) multiplets at τ 1.7–2.1 (2 H) and 2.1–2.4 (2 H) and singlets at 2.6 (1 H) and 7.2 (3 H).

Anal. Calcd for $C_{13}H_8N_2$: C, 81.23; H, 4.20; N, 14.58; mol wt, 192.21. Found: C, 81.12; H, 4.32; N, 14.70; mol wt, 222 (ebullioscopically in benzene).

Reaction of Dicyanoacetylene with 4,α-Dimethylstyrene.—A mixture of 1.55 g of dicyanoacetylene[1] and 40 ml of 4,α-dimethylstyrene (Shell Chemical Co.) was allowed to stand at room temperature for 15 hr. Removal of excess styrene under 0.1-mm vacuum at 40° and crystallization of the residue from 30 ml of acetonitrile gave 3.75 g of 1,2-dicyano-3,4-dihydro-4-(4′,α,α-trimethylbenzyl)-4,7-dimethylnaphthalene (**8a**), mp 191.5–193°, unchanged on recrystallization from acetonitrile. A second crop of 0.45 g of product was obtained from the mother liquors. The combined yield was 4.20 g (61%); uv λ_{max}^{MeCN} 345 mμ (sh) (ϵ 3800), 307 (8000), and 250 (15,000); ir ν_{max}^{KBr} 2220, 1615, 1565, 840, and 820 cm^{-1}, among others; nmr (in $CDCl_3$) multiplet at τ 2.6–2.8 (3 H), AB quartet at 2.9 and 3.2 (J = 8 cps, 4 H), AB quartet at 7.0 and 7.6 (J = 18 cps, 2 H), and singlets at 7.5 (3 H), 7.6 (3 H), 8.5 (6 H), and 8.7 (3 H).

Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.21. Found: C, 84.51; H, 7.17; N, 8.25.

Reaction of Dicyanoacetylene with *p*-Diisopropenylbenzene.—To a refluxing solution of 18.20 g of *p*-diisopropenylbenzene (Shell Development Co.) in 100 ml of benzene was added, under nitrogen, during 35 min, a solution of 1.79 g of dicyanoacetylene in 20 ml of benzene. The mixture was heated under reflux for 2.5 hr and then allowed to stand at room temperature for 4 days. The solvent was removed and most of the unreacted diisopropenyl benzene was sublimed at 110° (0.1 mm). The residue, on chromatography over 180 g of Florisil and elution with methylene chloride, gave a slowly solidifying solid which on crystallization from isopropyl alcohol gave 2.08 g (23% yield) of 1,2-dicyano-3,4-

dihydro-4-methyl-4-(α,α-dimethyl-4-isopropenylbenzyl)-7-isopropenylnaphthalene (**8c**): mp 163–165°; uv λ_{max}^{MeCN} 360 mμ(sh, ε 200), 310 (8300), 260 (35,000), and 206 (35,000); nmr (in $CDCl_3$) multiplets at τ 2.3–2.8 (5 H), 3.0–3.3 (2 H), and 4.5–5.0 (4 H), AB quartet (J = 18 cps) at 7.0 and 7.6 (2 H), singlet, split further, at 7.8 (6 H), and singlets at 8.5 (6 H) and 8.7 (3 H).

Anal. Calcd for $C_{28}H_{28}N_2$: C, 85.68; H, 7.19; N, 7.14. Found: C, 85.65; H, 7.23; N, 7.25.

Reaction of Dicyanoacetylene with *p*-Fluoro-α-methylstyrene.—A mixture of 23 g of *p*-fluoro-α-methylstyrene (Aldrich Chemical Co, Inc.) and 1.302 g of dicyanoacetylene was allowed to stand at room temperature for 5 days. Most of the excess styrene was removed at 30° (0.1 μ). The residue was heated with 20 ml of ethanol. The mixture was cooled and the tan crystals were collected by filtration and washed with cold ethanol to give 4.430 g (74%) of 1,2-dicyano-3,4-dihydro-4-methyl-4-(α,α-dimethyl-4-fluorobenzyl)-7-fluoronaphthalene. An analytical sample (ethyl acetate) had mp 230–231°; uv λ_{max}^{MeCN} 335 mμ (ε 3800), 295 (7700), and 244 (13,500); ir ν_{max}^{KBr} 3080, 2990, 2900, 2225 and 1610 cm^{-1}, among others.

Anal. Calcd for $C_{22}H_{18}F_2N_2$: C, 75.85; H, 5.21; F, 10.91; N, 8.04. Found: C, 75.79; H, 4.91; F, 10.92; N, 8.49.

Reaction of Dicyanoacetylene with 1,1-Diphenylethylene.—A mixture of 4.91 g of dicyanoacetylene and 100 ml of 1,1-diphenylethylene, contained in a large molecular still, was allowed to stand at room temperature for 137 hr. Excess diphenylethylene was distilled at 95° bath temperature (0.1 μ). The nmr spectrum of the recovered 1,1-diphenylethylene indicated the presence of 1,1-diphenylethane (quartet at τ 6.6 and doublet at 9.0). This was confirmed by gas chromatography [1-m 20% *m*-bis(phenoxy)-phenoxybenzene column] which showed a peak (5% of the total area) having the same retention time as that of authentic 1,1-diphenylethane. This peak was not present in the 1,1-diphenylethylene used.

The residue from the distillation was heated with 30 ml of acetonitrile and the crystals obtained on cooling were collected by filtration to give 8.65 g (52% yield) of 1,2-dicyano-4-phenylnaphthalene: mp 196–197°; uv λ_{max}^{MeCN} 353 mμ (ε 8400), 322 (9100), 250 (63,000), and 215 (31,000); nmr only aromatic protons at τ 1.5–3.1.

Anal. Calcd for $C_{18}H_{10}N_2$: C, 85.02; H, 3.97; N, 11.02; mol wt, 254. Found: C, 84.82; H, 3.96; N, 11.14; mol wt, 259.

The mother liquor was concentrated and the residue (7.19 g of a brown oil) was chromatographed over 200 g of Florisil. Elution with benzene–hexane (1:1) gave additional 1,1-diphenylethylene; with methylene chloride there was first eluted 2.30 g of a slowly solidifying oil which on crystallization from ethanol gave 1.95 g (7% yield) of 1,2-dicyano-1-(2,2-diphenylethyl)-2-methyldiphenylmethylethylene (**12**): mp 130–131°; uv (in MeCN) only end absorption with a long trail (ϵ_{300} 600, ϵ_{250} 7500, and ϵ_{220} 25,000); ir ν_{max}^{KBr} 3070, 3030, 2990, 2910, 2220, and 1600 cm^{-1}, among others; for nmr, see Discussion.

Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.63; H, 5.98; N, 6.39. Found: C, 87.55; H, 5.79; N, 6.77.

Further elution with methylene chloride gave a mixture of 1,2-dicyano-4-phenylnaphthalene (**9**) and 1,2-dicyano-3,4-dihydro-4-phenylnaphthalene (**10**). Crystallization from isopropyl alcohol first gave pure **9**; concentration of the mother liquors and two crystallizations of the residue from isopropyl alcohol gave *ca.* 50 mg (0.3% yield) of 1,2-dicyano-3,4-dihydro-4-phenylnaphthalene (**10**): mp 127–128°; ir ν_{max}^{KBr} 3080 (s), 3030 (s), 2930 (w), 2850 (s), 2200 (m), 1600 (m), and 1560 cm^{-1} (m), among others; uv $\lambda_{max}^{cyclohexane}$ 347 mμ (shoulder, ε 1500), 305 (12,300), 249 (14,600), 242 (18,800), and 235 (sh, 13,700);[22] for nmr, see Discussion.

Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.73; N, 10.93. Found: C, 84.13; H, 4.74; N, 10.84.

A solution of 15 mg of 1,2-dicyano-3,4-dihydro-4-phenylnaphthalene in 15 ml of xylene was heated under reflux with 124 mg of 10% palladium on charcoal for 1 hr. Concentration of the filtered solution left 12 mg of a solid, the ir spectrum of which was that of 1,2-dicyano-4-phenylnaphthalene (**9**). Recrystallization from ethanol gave a sample, mp and mmp 196–197°.

Reaction of Hexafluoro-2-butyne with α-Methylstyrene.—A mixture of 124 g of freshly distilled α-methylstyrene and 10 g of hexafluoro-2-butyne, contained in a 400-ml stainless steel cylinder, was heated to 100° for 12 hr. Removal of the excess α-methylstyrene and short-path distillation of the residue [120–140° bath temperature (0.2 μ)] gave 14.23 g (58%) of 1,2-bis(trifluoromethyl)-3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)-naphthalene (**17a**) as an oil which crystallized slowly on scratching. An analytical sample (acetonitrile) had mp 84.5–85.5°; uv λ_{max}^{MeCN} 276 mμ (ε 6700) and 223 (sh, 17,300); ^1H nmr (in $CDCl_3$) multiplet at τ 2.6–3.0 (9 H), AB quartet at 7.05 and 7.82 (J = 20 cps, all components are split further, 2 H), and singlets at 8.68 (6 H) and 8.73 (3 H); ^{19}F nmr (in $CDCl_3$, shifts in cycles per second from external Freon 11) two quartets of equal intensities (J = 13.5 cps) at +3206 and +3475, both of which are split further.

Anal. Calcd for $C_{22}H_{20}F_6$: C, 66.33; H, 5.07; F, 28.61. Found: C, 66.40; H, 5.00; F, 28.56.

Reaction of Dimethyl Acetylenedicarboxylate with α-Methylstyrene.—A mixture of 1.018 g of dimethyl acetylenedicarboxylate and 25 ml of α-methylstyrene was allowed to stand at room temperature for 23 hr. Removal of excess ester and styrene from a 10-ml aliquot gave only 46 mg of an oil. The remaining mixture was transferred to a Carius tube, which was sealed under vacuum and heated to 100° for 4 hr. The unreacted starting materials were removed at 40° (0.5 μ), leaving 986 mg of a colorless semisolid. Chromatography on Florisil (30 g), elution with methylene chloride, and crystallization from ethanol gave 387 mg (23%) of dimethyl 3,4-dihydro-4-methyl-4-(α,α-dimethylbenzyl)-naphthalene-1,2-dicarboxylate (**17b**). An analytical sample (acetonitrile) had mp 135–137°; uv λ_{max}^{MeCN} 299 mμ (ε 10,400) and 232 (16,600); ir ν_{max}^{KBr} 1740, 1715, and 1635 cm^{-1}, among others; nmr ($CDCl_3$) multiplet at τ 2.6–3.1 (9 H), singlets at 6.1 (3 H) and 6.2 (3 H), AB quartet at 6.8 and 7.7 (J = 18 cps, 2 H), and singlet at 8.7 (9 H).

Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 75.89; H, 6.92.

Further elution with methylene chloride–THF (9:1) gave 140 mg (10% crude yield) of an oil, which, according to its nmr spectrum in $CDCl_3$, appeared to be mostly dimethyl 3,4-dihydro-4-(1,2-dicarbomethoxyvinyl)-4-methylnaphthalene-1,2-dicarboxylate: singlet at τ 8.3 (3 H), AB quartet (J = 17 cps) at 6.8 and 7.5 (2 H), four singlets of equal intensities at 6.1–6.4 (3 H each), singlet at 4.7 (1 H), and aromatic protons at 2.5–2.8.

Reaction of Dicyanoacetylene with 1,2-Dihydronaphthalene.—A mixture of 10 ml of 1,2-dihydronaphthalene and 447 mg of dicyanoacetylene was heated in a sealed Carius tube to 120° for 10 hr. Removal of the excess dihydronaphthalene gave 931 mg of a dark residue which on chromatography over Florisil gave 382 mg (36% yield) of 1,2-dicyanonaphthalene, eluted with methylene chloride and identified by comparison of its ir spectrum with that of the minor aromatization product of the styrene–dicyanoacetylene adducts (see above).

Reaction of Dicyanoacetylene with Indene.—To a solution of 10 ml of freshly distilled indene in 50 ml of toluene was added, at −50°, under nitrogen, a solution of 1.05 g of dicyanoacetylene in 10 ml of toluene. The mixture was stirred at −70° for 3 hr and at room temperature for 60 hr. The solvent and excess indene were removed under vacuum, leaving 1.614 g of a dark oil. Chromatography on Florisil first gave 300 mg of indene. Elution with methylene chloride gave 400 mg of a mixture of an oil and crystals. Trituration with methylene chloride gave 185 mg (10% yield) of the crystalline adduct. A sample crystallized from acetonitrile melted with decomposition at 250°: uv λ_{max}^{MeCN} 242 mμ (ε 14,700) and 235 (14,300).

Anal. Calcd for $C_{17}H_8N_4$: C, 76.10; H, 3.01; N, 20.89. Found: C, 76.41; H, 3.04; N, 20.97.

Reaction of Dicyanoacetylene with *p*-Methoxy-β-bromostyrene.—A mixture of 900 mg of *p*-methoxy-β-bromostyrene,[23] 738 mg of dicyanoacetylene, and 7 ml of benzene was heated in a Carius tube to 160° for 6 hr. Removal of the solvent left 1.357 g of a tan solid, which on chromatography on Florisil first gave 334 mg of a yellow semisolid, eluted with benzene. Elution with methylene chloride and crystallization from acetonitrile gave 371 mg (42% yield) of 1,2-dicyano-7-methoxynaphthalene in the form of pink fluffy needles: mp 187–188°; uv λ_{max}^{MeCN} 373 mμ (ε 4600), 306 (3500), 295 (4400), 286 (sh, 3600), 257 (54,000), and 222 (39,000); ir ν_{max}^{KBr} 2235 and 1630 cm^{-1}, among

(22) Part of these absorptions may be due to a small amount of 1,2-dicyano-4-phenylnaphthalene (**9**) present in this sample; see Discussion.

(23) W. Manchot, *Ann.*, **387**, 257 (1912).

others; nmr (in hexadeuteriodimethyl sulfoxide) multiplet at τ 1.6–2.9 (5 H) and singlet at 6.1 (3 H).

Anal. Calcd for $C_{13}H_8N_2O$: C, 74.98; H, 3.88; N, 13.46. Found: C, 74.81; H, 4.06; N, 13.45.

Reaction of Benzyne with Styrene.—To a refluxing mixture of 250 g (2.32 mol) of styrene and 200 ml of methylene chloride were added, simultaneously from two addition funnels, solutions of 6.60 g (48.2 mmol) of anthranilic acid in 30 ml of THF and of 6.15 g (57.2 mmol) of isopentyl nitrite in 35 ml of methylene chloride. The addition took 4 hr. After heating under reflux for an additional 2 hr, the solvents and excess styrene were removed and the residue was short path distilled, giving 4.11 g of viscous oil boiling at 150–170° bath temperature (0.3 μ). The nmr spectrum showed the ratio of *threo*- and *erythro*-9,10-dihydro-9-(α-methylbenzyl)phenanthrenes to be 1:1 as judged from the ratio of the two methyl doublets. Chromatography of 1.10 g of this material over 55 g of silicic acid (elution with hexane) gave a total of 951 mg (26% yield) of the two isomers. The nmr spectrum of the isomer being eluted first showed multiplets at τ 2.1–3.2 (13 H) and 6.8–7.9 (4 H) and a doublet (J = 6.3 cps) at 9.0 (3 H). The spectrum of the other isomer showed multiplets at τ 2.1–3.7 (13 H) and 6.8–7.5 (4 H) and a doublet (J = 6.4 cps) at 8.8 (3 H). Complete separation of the two isomers could not be achieved. The fractions were combined and short path distilled at 150° bath temperature (0.5 μ) to give an analytical sample of a *ca.* 1:1 mixture of the two isomers: uv $\lambda_{max}^{cyclohexane}$ 299 mμ (ϵ 3900), 266 (15,000), and 210 (48,000).

Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.08; mol wt, 284. Found: C, 93.10; H, 7.08; mol wt, 284 (mass spectroscopically).

Dehydrogenation of 9,10-Dihydro-9-(α-methylbenzyl)phenanthrene.—A mixture of *threo* and *erythro* isomers (ratio 1:1, 400 mg), 10% palladium on charcoal (350 mg), and toluene (3 ml), contained in a sealed Carius tube, was heated to 220° for 6 hr. Removal of the solvent from the filtered solution gave 353 mg of a colorless oil consisting mostly of 9-(α-methylbenzyl)-phenanthrene as judged from its nmr spectrum. Chromatography over silicic acid gave first a small amount of unknown hydrocarbons (eluted with hexane), followed by 198 mg (50% yield) of 9-(α-methylbenzyl)phenanthrene (eluted with benzene). A sample crystallized from cyclohexane had mp 118.5–119.5°, undepressed by admixture of an authentic sample of 9-(α-methylbenzyl)phenanthrene (see below). The ir spectra of the two samples were also identical.

9-(α-Styryl)phenanthrene.—To a stirred solution of 20.0 g (91 mmol) of 9-acetylphenanthrene (Columbia Organic Chemicals Co., Inc.) in 400 ml of anhydrous ether was added, over a period of 30 min, 35 ml of a 3 M solution of phenylmagnesium bromide (105 mmol) in THF. The mixture was then heated under reflux for 1 hr, cooled, and treated with 100 ml of 5% hydrochloric acid. The layers were separated, the aqueous phase was extracted twice with 100-ml portions of ether, and the combined ether extracts were washed with water, 5% sodium bicarbonate solution, and concentrated sodium chloride solution, and dried. Removal of the solvent gave 27.0 g of a viscous oil. It was dissolved in 100 ml of glacial acetic acid and 8.0 g of *p*-toluenesulfonic acid hydrate was added with stirring. A pale yellow crystalline precipitate formed after *ca.* 20 min; it was collected by filtration after 12 hr, washed with glacial acetic acid, and dried. The yield of crude 9-(α-styryl)phenanthrene, mp 133–135°, was 4.22 g (17%). An analytical sample (glacial acetic acid) had mp 136–137°; nmr (in $CDCl_3$) multiplets at τ 1.3–1.6 (2 H) and 2.1–3.0 (12 H) and doublets (J = 1.5 cps) at 4.1 and 4.6 (1 H each); uv $\lambda_{max}^{cyclohexane}$ 348 mμ (ϵ 270), 340 (300), 332 (360), 324 (370), 298 (12,600), 286 (10,600), 272 (sh, 15,500), and 255 (65,000).

Anal. Calcd for $C_{22}H_{16}$: C, 94.25; H, 5.75. Found: C, 94.11; H, 5.92.

9-(α-Methylbenzyl)phenanthrene.—Catalytic hydrogenation of 571 mg of 9-(α-styryl)phenanthrene in 10 ml of ethyl acetate with 450 mg of 10% palladium on charcoal at room temperature resulted in the uptake of 1 mol equiv of hydrogen. The filtered solution was concentrated to dryness and the residue was sublimed at 150° bath temperature (0.1 μ) to give 454 mg (80% yield) of 9-(α-methylbenzyl)phenanthrene: mp 118.5–119.5°, unchanged on crystallization from cyclohexane; nmr (in $CDCl_3$) multiplets at τ 1.3–1.7 (2 H) and 1.9–3.0 (12 H), quartet (J = 7 cps) at 5.2 (1 H), and doublet (J = 7 cps) at 8.3 (3 H); uv $\lambda_{max}^{cyclohexane}$ 347 mμ (ϵ 230), 339 (240), 331 (280), 324 (240), 317 (230), 297 (12,000), 285 (10,700), 277 (14,100), 270 (20,800), 254 (63,000), and 248 (sh, 49,000).

Anal. Calcd for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.88; H, 6.50.

Registry No.—**2**, 19291-71-5; **3**, 19291-72-6; **4**, 19291-73-7; **5** (*threo*), 19291-74-8; **5** (*erythro*), 19291-75-9; **6**, 19291-76-0; **7**, 19291-77-1; **8a**, 19291-78-2; **8b**, 19291-79-3; **8c**, 19291-80-6; **9**, 19291-81-7; **10**, 19291-82-8; **12**, 19291-83-9; **17a**, 19291-84-0; **17b**, 19291-85-1; **18**, 19291-86-2; **20** (*threo*) 19291-87-3; **20** (*erythro*), 19291-88-4; **21**, 19291-89-5; 1,2-dicyano-7-methoxynaphthalene, 19291-90-8; 9-(α-styryl)phenanthrene, 19291-91-9.

The Reaction of Triisobutylaluminum with Butadiene[1]

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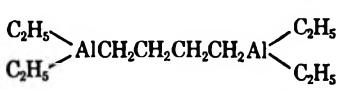
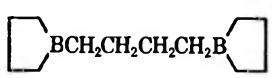
The reaction of triisobutylaluminum with butadiene in an open vessel yielded a polymer which on hydrolysis gave butane and three 1,2,3-trimethylcyclopentane isomers. Treatment of the polymer with ethylene in the presence of nickel acetylacetonate afforded a mixture of 2-methyl-1,3-dimethylenecyclopentane and 1-methyl-2,3-dimethylenecyclopentane.

Considerable work has been devoted in the last decade, especially by Ziegler and his group,[2-4] to the study of the preparation and reactions of trialkylaluminum compounds. However, very little information is available about dialuminoalkanes derived from diolefins and triisobutylaluminum (TIBA).

Ziegler found that 1,5-hexadiene and TIBA did not give any of the desired 1,6-dialuminohexane polymer; the products isolated were (aluminomethyl)cyclopentane and methylenecyclopentane.[5] Gellert and Kempkes tried to prepare triallylaluminum and 1,3-dialuminopropane from allene. In addition to complicated ring closures involving three molecules of allene, some 1,3-dialuminopropane was obtained.[6] Ziegler reported that the reaction of butadiene with aluminum alkyls has not yet been studied in detail in his laboratories.[7] Compound **1** was prepared from diethylaluminum hydride and butadiene.[8] The di-



1



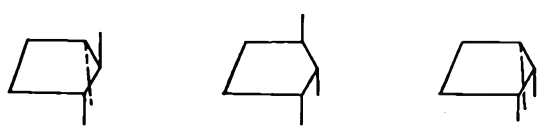
2

aluminobutane polymer of the proposed composition $[Al_2(C_4H_8)_3]_x$ has been obtained from **2** and triethylaluminum.[9] Zakharkin, Savina, and Antipin[10] have found that diethylaluminum hydride reacts with butadiene to give, after hydrolysis, butane, butenes, and unknown C_8H_{16} hydrocarbons. A recent patent[11] claims as an intermediate an organoaluminum reaction product containing a substantial amount of tributenylaluminum obtained from diisobutylaluminum hydride and an excess of butadiene; however, no detailed information is given concerning the structure of the reaction product. Hata and Miyake[12] have investigated the reaction of diisobutylaluminum hydride with α,ω-dienes ranging from pentadiene to undecadiene; their studies with 1,5-hexadiene confirmed earlier work by Ziegler,[5] while the reaction with the other dienes yielded mainly the expected dialuminoalkanes.[13]

We attempted to prepare dialuminobutane by bubbling butadiene through TIBA at 100–120°. The desired alkylation can be described by eq 1 (al = $\frac{1}{3}$Al).

$$CH_2{=}CHCH{=}CH_2 + 2alCH_2CH(CH_3)_2 \longrightarrow alCH_2CH_2CH_2CH_2al + 2CH_2{=}C(CH_3)_2 \quad (1)$$

The amount of isobutylene displaced together with unchanged butadiene was collected in a cold trap, and the composition was determined by mass spectroscopy. At the end of the reaction the polymeric product was a very viscous liquid at the reaction temperature and a colorless solid glass at room temperature. Hydrolysis of the product gave about 29% butane and 27% saturated hydrocarbons that boiled between 110 and 120°. By far the largest component of this cut was 1,*trans*-2,*cis*-3-trimethylcyclopentane (**3**); some of the 1,*cis*-2,*trans*-**3** isomer (**4**) and the 1,*cis*-2,*cis*-3 isomer (**5**) was also present.



3 **4** **5**

The isomers were separated by gas chromatography. Isomers **3** and **5** were identified by comparing their infrared and mass spectra as well as their gas chromatographic retention times with those of National Bureau of Standards samples. The structure of the predominant 1,*trans*-2,*cis*-3 isomer (**3**) was further confirmed by comparing its nuclear magnetic resonance spectrum with that of an authentic sample. Although a National Bureau of Standards sample of **4** was not available, there is little doubt that this isomer was actually obtained; besides, hydrogenation of 2-methyl-1,3-dimethylenecyclopentane (**6**) and 3-methyl-1,2-dimethylenecyclopentane (**7**) gave the same three isomeric trimethylcyclopentanes, one of which was identical with the 1,*cis*-2,*trans*-3 isomer (**4**) in question.

In addition there was found a very small amount of a fourth compound, which according to mass spec-

(1) Presented in part at the 145th Meeting of the American Chemical Society, New York, N. Y., Sept 1963, Abstracts p 74Q; see also E. Marcus, U. S. Patent 3,356,704 (Dec 5, 1967).

(2) K. Ziegler, *Angew. Chem.*, **72**, 829 (1960).

(3) K. Ziegler, *et al.*, *Ann.*, **629**, 1 (1960).

(4) American Chemical Society Monograph No. 147, Reinhold Publishing Corp., New York, N. Y., 1960. pp 194–269.

(5) K. Ziegler, *Angew. Chem.*, **68**, 721 (1956).

(6) A. Kempkes, "Über Neue Reaktionen des Allens and über Allylaluminiumverbindungen", Ph.D. Thesis, Technische Hochschule Aachen, 1959.

(7) See ref 4, p 235.

(8) K. Ziegler and H. G. Gellert, U. S. Patent 2,826,598 (March 11, 1952).

(9) E. Stahnecker and H. Friederich, German Patent 1,108,217 (June 6, 1959).

(10) L. I. Zakharkin, L. A. Savina, and L. M. Antipin, *Bull. Acad. Sci. USSR*, 931 (1962).

(11) H. L. Johnson and G. G. Eberhardt, U. S. Patent 3,035,077 (May 15, 1962).

(12) G. Hata and A. Miyake, *J. Org. Chem.*, **28**, 3237 (1963).

(13) Similar work by the authors of the present paper had been carried out independently prior to 1962, but was never published. α,ω-Dienes, ranging from pentadiene to octadiene, were treated with TIBA at about 100° in a molar ratio of 3:2. Our data agreed essentially with those reported in ref 12; however, in the case of 1,6-heptadiene we obtained a larger amount of methylcyclohexane, after hydrolysis of the reaction product. The C_7 fraction contained 38% methylcyclohexane, while under the conditions employed by Hatta and Miyake only 1–8% of this hydrocarbon was formed.

TABLE I

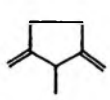
NMR DATA OF METHYLDIMETHYLENECYCLOPENTANE

Hydrogen type	Position, ppm[a]	Relative integrated intensities: Found	Calcd for pure 1,3-dimethylene isomer	Calcd for 80:20 isomer mixture[b]	Special pattern
Methyl hydrogens	1.12	2.8	3.0	3.0	Doublet
Singly allylic hydrogens	2.33	3.8	4.0	3.8	Single resonance with fine structure
Doubly allylic hydrogens	2.86	1.0	1.0	0.8	Broad, unresolved resonance
Vinylidene hydrogens	4.79	4.0	4.0	4.0	Single resonance with fine structure
Other methylene hydrogens	1.62	0.4	0.0	0.4	Broad unresolved resonance

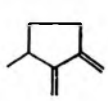
[a] Chemical shift from tetramethylsilane. [b] 80% 2-methyl-1,3-dimethylenecyclopentane and 20% 3-methyl-1,2-dimethylenecyclopentane.

troscopy was a C_8H_{14} hydrocarbon. In the infrared spectrum, absorptions were noted at 5.95 (weak) and at 12.45 μ (strong) which are characteristic of trisubstituted ethylenes. This compound has not been further identified.

When the TIBA–butadiene reaction product was treated with ethylene in a bomb at 75° for 7 hr in the presence of nickel acetylacetonate as catalyst and benzene as solvent, the C_8 fraction contained, after hydrolysis, as major products **3**, two dimethylmethylenecyclopentanes and methyldimethylenecyclopentane. However, when the same reaction was carried out for 21 hr and the reaction product worked up without hydrolysis, the butadiene dimer, methyldimethylenecyclopentane, was isolated as the only hydrocarbon in the C_8 range. Vapor phase chromatography indicated the presence of only one major component which the mass spectrum characterized as a C_8H_{12} hydrocarbon. The infrared spectrum showed a strong absorption at 6.06 and 11.35 μ which is characteristic of nonconjugated vinylidene groups; it also showed a weak absorption at 7.3 μ indicative of a methyl group. The infrared absorptions at 6.06 and 11.35 μ were much stronger than those of two dimethylmethylenecyclopentanes isolated in another experiment; the absorption at 7.3 μ was much weaker that that of the dimethylmethyleneeyclopentanes. The nuclear magnetic resonance spectrum showed peaks in the approximate 3:4:1:4 intensity ratio for methyl, singly allylic, doubly allylic, and vinylidene hydrogens, respectively (see Table I). These data are in good agreement with the proposed structure **6** for this hydrocarbon.



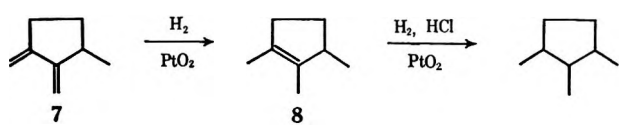
6



7

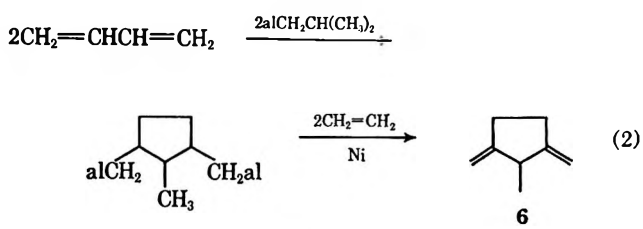
However, the ultraviolet spectrum did show an absorption at 2480 Å (ϵ_{max} 1900), exactly where the known conjugated diene **7**, 3-methyl-1,2-dimethylenecyclopentane, has a molar extinction coefficient of 8500.[14] Careful investigation of the infrared spectrum showed also a shoulder at 6.14 μ, the frequency at which the conjugated dimethylene compound absorbs Hydrogenation of the butadiene dimer over platinum oxide produced not only the three expected trimethylcyclopentanes, but also a small amount of a fourth compound of mass 110 having a weak C=C absorption at 5.95 μ with no evidence of a hydrogen attached to the double bond. Blomquist reported that 3-methyl-1,2-dimethylenecyclopentane (**7**) absorbed only 1 mol of hydrogen, when it was hydrogenated over platinum oxide. However, addition of a few drops of hydrochloric acid to the half-hydrogenated product allowed the uptake of the second mole of hydrogen.[14] Most probably the intermediate 1,2,3-trimethylcyclopentane (**8**) resists hydrogenation under ordinary conditions (Scheme I).

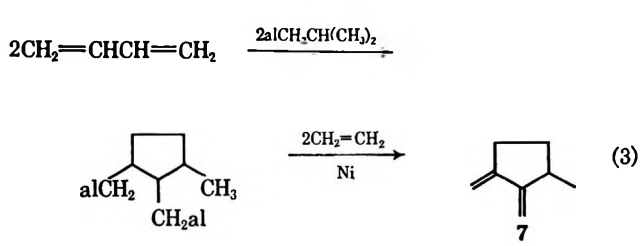
SCHEME I



7 **8**

Hydrogenation of our butadiene dimer produced 52% **5**, 25% **4**, 8% **3**, and 15% of the fourth compound (**8**). Continued hydrogenation after the addition of a few drops of hydrochloric acid eliminated the fourth compound and produced 66% **5**, 26% **4**, and 8% **3**. On the basis of the ultraviolet absorption spectrum and the hydrogenation data it appears that the butadiene dimer is approximately an 80:20 mixture of the 1,3-dimethylene and the 2,3-dimethylene isomers (**6** and **7**), respectively. The over-all reaction leading to methyldimethylenecyclopentane can be described by reactions 2 and 3.



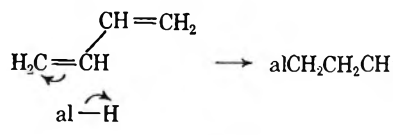


It is of interest to note that hydrogenation over platinum oxide results predominantly in the formation

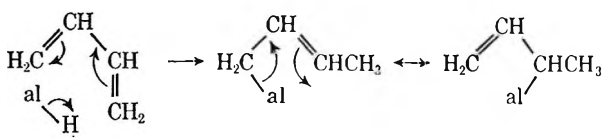
(14) A. T. Blomquist, J. Wolinsky, Y. C. Meinwald, and D. T. Longone, *J. Amer. Chem. Soc.*, **78**, 6057 (1956).

of the 1,*cis*-2,*cis*-3 isomer (**5**), *i.e.*, the thermodynamically least stable isomer. This result is in agreement with data found by investigators[15,16] who studied the hydrogenation of dimethylcyclohexenes and methylenemethylcyclohexanes. On the other hand, hydrolysis of the bis(aluminomethyl)methylcyclopentane polymer gives rise to a predominant amount of the 1,*trans*-2,*cis*-3 isomer (**3**), the thermodynamically most stable isomer. The stereochemical distribution of isomers gives us a clue about the possible mechanism.

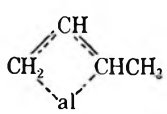
It is reasonable to assume that addition of alH to butadiene occurs both in 1,2 and 1,4 fashion (eq 4 and 5, respectively). The 1,4 adduct can then by allylic rearrangement be in equilibrium with the reverse 1,2 adduct.



(4)



(5)

or possibly 

alH = >AlH in R_2AlH

The situation here is probably similar to that of the well-known butenyl Grignard reagent.[17] It is of interest to note that allylmagnesium halides are markedly more reactive in addition reactions than alkylmagnesium halides.[18] It is thought that β,γ unsaturation exerts a weakening influence upon the carbon–metal bond.

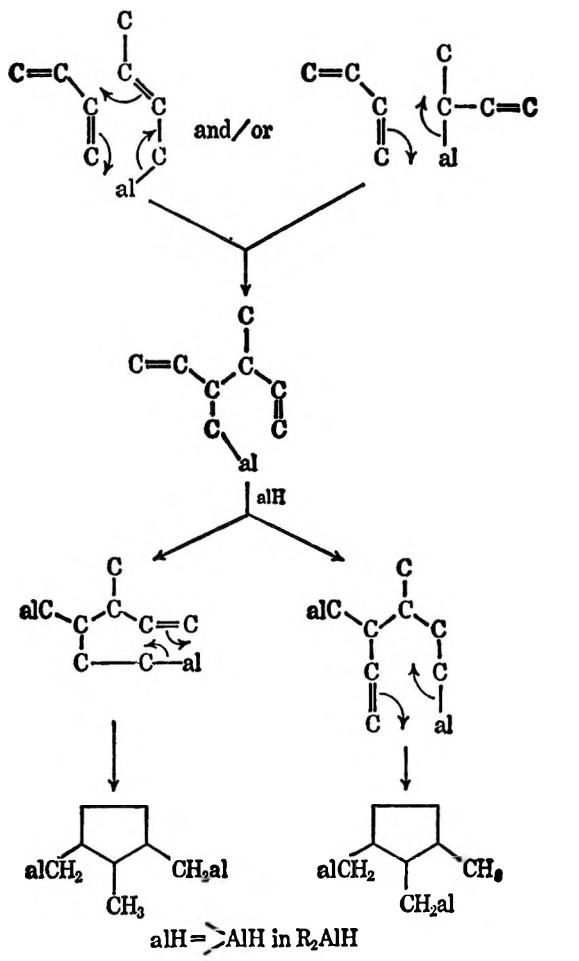
The reactive butenylaluminum intermediate can add to another molecule of butadiene and cyclize to give a variety of C_8H_{16} hydrocarbons after hydrolysis. Possible products are 1,2,3-trimethylcyclopentane, 1-ethyl-1-methyl- and 1-ethyl-3-methylcyclopentane, ethylcyclohexane, and 1,2- as well as 1,4-dimethylcyclohexane. 1,2,3-Trimethylcyclopentanes were the only C_8H_{16} hydrocarbons we were able to detect. If any of the other hydrocarbons mentioned are in the reaction product, they must be present in very small amounts. The formation of the trimethylcyclopentanes can be rationalized as in Scheme II.

The predominance of the 1,*trans*-2,*cis*-3 isomer (**3**) is in agreement with Scheme III. During the addition of a second molecule of butadiene such conformations which are of lowest energy will be preferentially assumed; after cyclization the new CH_2al group prefers to be *trans* with respect to the CH_3 group on the neighboring carbon atom.

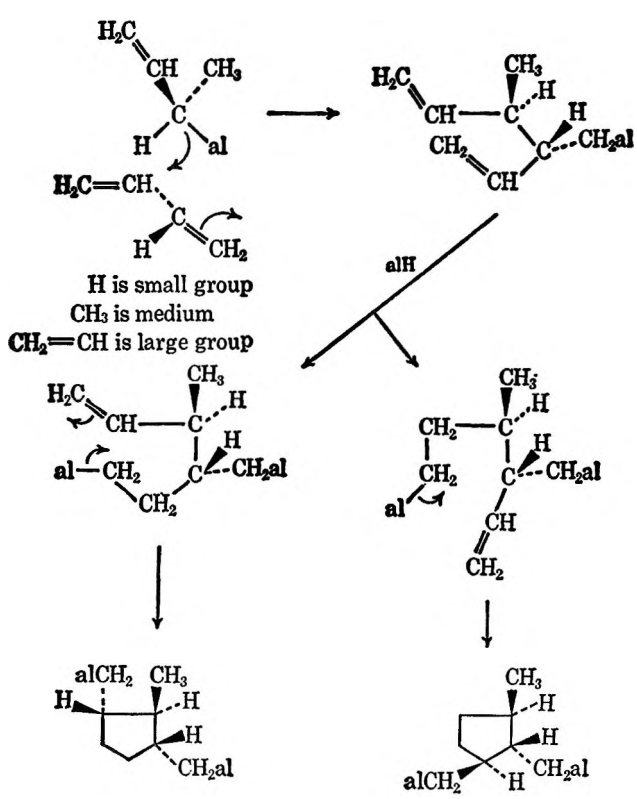
When TIBA and butadiene were heated in a closed vessel, the result was much more complex. In this case the isobutylene, which could not escape, reacted with the butenylaluminum or dialuminobutane to give after hydrolysis significant amounts of 2,2-dimethylhexane

(15) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082 (1960).
(16) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **82**, 6090 (1960).
(17) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1954, pp 1154–1158.
(18) H. Gilman and J. Eisch, *J. Amer. Chem. Soc.*, **79**, 2150 (1957).

SCHEME II

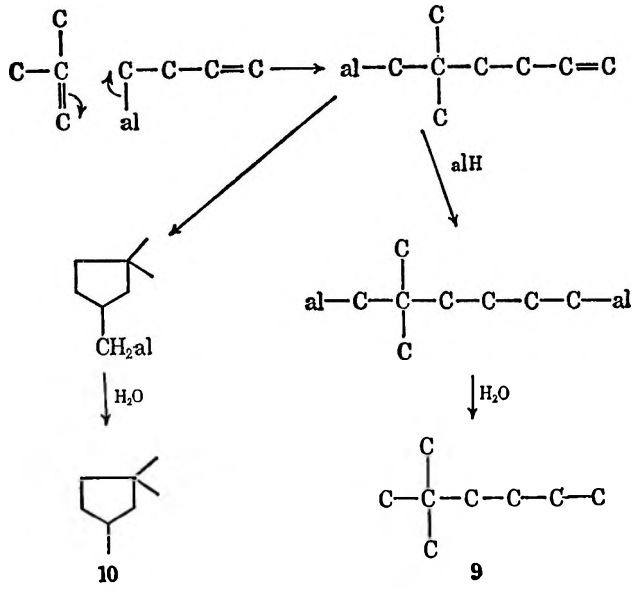


SCHEME III



(9) and some 1,1,3-trimethylcyclopentane (10) (Scheme IV).

SCHEME IV



Both compounds were again isolated by gas chromatography. 9 was identified by comparing its mass and infrared spectra as well as its gas chromatographic retention time with corresponding properties of a National Bureau of Standards sample. 10 could not be obtained pure even by gas chromatography. However, a comparison of the mass and infrared spectra with an authentic sample showed that compound 10 possessed all of the significant features of 1,1,3-trimethylcyclopentane; besides, the gas chromatographic retention times were identical.

The liberated isobutylene was also able to interact with the bis(aluminomethyl)methylcyclopentanes to produce two dimethylmethylenecyclopentanes whose exact structures were not determined. When the reaction between TIBA and butadiene in the bomb was carried out in the presence of added isobutylene, the amounts of 2,2-dimethylhexane, 1,1,3-trimethylcyclopentane, and the two dimethylmethylenecyclopentanes formed increased still further.

Experimental Section

The nmr spectra were obtained from a Varian A-60 spectrometer with tetramethylsilane as internal standard. The infrared spectra were taken on a Perkin-Elmer Model 21. The ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. The mass spectra were obtained with a General Electric 60-deg sector magnetic focusing mass spectrometer.

The gas chromatograph used for analyzing the composition of a certain fraction was the Barber–Coleman capillary gas chromatograph IDS Model 20, with a 200-ft long Ucon 50 H.B. 2000 column, a Strontium 90 detector, a column temperature varying from 50 to 200° and an argon pressure of 35 pounds. The gas chromatograph used for isolating a component from a certain fraction was the Beckman GC-2 analytical gas chromatograph with a packed column containing a UCON-P substrate on firebrick. The amount of material injected varied from 0.03 to 0.05 ml. The desired component was collected by condensation of the effluent from the exit port. Usually the amount collected was sufficient for an infrared or a mass spectral determination. However, in a few cases where the material contained too little of the desired component, collections had to be repeated until a sufficient amount was available. In the case of complex mixtures, where separation by distillation was not successful or not attempted, the yields reported are based on calculations derived from the gas chromatographic spectra. Since the assumption was made that "area %" equals "weight %" yields given are only approximate. Most probably this assumption is fairly valid for similar hydrocarbons.

TIBA–Butadiene Reaction Product and Its Hydrolysis.—Butadiene was bubbled through TIBA (160 g, 0.81 mol) with stirring during a period of 28 hr, while the temperature was maintained between 110 and 120°. The unchanged butadiene together with the displaced isobutylene was collected in a Dry Ice trap and analyzed by mass spectroscopy. It was found that 126 g (93%) of isobutylene had been displaced together with about 410 g of unchanged butadiene. The reaction product, which was very viscous at 110° and a colorless glassy solid at room temperature, weighed 125 g. It was hydrolyzed carefully with ethanol (300 g) to give 34 g of low-boiling material which was collected in a Dry Ice trap and analyzed by mass spectroscopy; it contained 20.2 g (29% yield) of butane, 10.3 g (7.4%) of recovered isobutane derived from unchanged TIBA, 2.3 g of isobutylene, 1.0 g of butadiene and traces of butenes. Then the reaction product was hydrolyzed with dilute hydrochloric acid. The upper layer was separated, washed with water, dried over magnesium sulfate and filtered to give 55 g. The major amount (44 g) of the 55 g was distilled through a short column to give the fractions listed in Table II.

TABLE II

Fraction	Wt, g	Bp, °C (mm)	$n^{30}D$	d^{25}_{25}
1	29	110–120 (1 atm)	1.413	0.757
2	3	120 (atm)–70 (50)	1.426	0.775
3	2	70 (50)–118 (50)	1.443	0.813
4	8	118 (50)–82 (0.3)	1.454	0.833
Residue	4			

Gas chromatography, using a capillary chromatograph at 113°, showed that fractions 1 and 2 contained the four major components given in Table III.

TABLE III

	Peak			
	I	II	III	IV
Retention time, min	5⅛	5½	5¾	6½
% of fraction 1	82	8	5	5
% of fraction 2	20	20	20	40

Since fraction 1 contained 1,*trans*-2,*cis*-3-trimethylcyclopentane (3) as predominant component, this compound could be identified in fraction 1 without difficulty. Gas chromatography afforded an even purer sample. The last three components were separated by gas chromatography from fraction 2. Peak I was found to represent 1,*trans*-2,*cis*-3-trimethylcyclopentane (3), peak II 1,*cis*-2,*trans*-3-trimethylcyclopentane (4), peak III 1,*cis*-2,*cis*-3-trimethylcyclopentane (5), and peak IV the unknown cyclic C_8H_{14} olefin as has already been discussed. Fraction 3 contained mostly $C_{12}H_{22}$ and $C_{12}H_{24}$ hydrocarbons (highest mass units 166 and 168). Fraction 4 contained probably C_{12} and C_{16} hydrocarbons. The yield of 1,2,3-trimethylcyclopentanes was about 27%.

For comparison, the physical constants of the three 1,2,3-trimethylcyclopentanes, which have been reported previously,[19] are given in Table IV.

None of the two dimethylmethylenecyclopentanes, 2,2-dimethylhexane (9), and 1,1,3-trimethylcyclopentane (10) found in various runs could be obtained pure by distillation.

TABLE IV

	Bp, °C	$n^{20}D$	d^{20}_4
1,*trans*-2,*cis*-3	110.2–110.3	1.4140	0.7540
1,*cis*-2,*trans*-3	118–118.2	1.4216	0.7695
1,*cis*-2,*cis*-3	122–122.1	1.4250	0.7766

(19) A. V. Koperna and B. A. Kazanskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 302 (1948); *Chem. Abstr.*, **43**, 155 (1949).

TABLE V

Compound	Bp, °C
2,2-Dimethylhexane	106.8[a]
1,1,3-Trimethylcyclopentane	104–104.2[b]
1,*trans*-2,*cis*-3-Trimethylcyclopentane	110.2–110.3[c]
1,*cis*-2,*trans*-3-Trimethylcyclopentane	118–118.2[c]
1,*cis*-2,*cis*-3-Trimethylcyclopentane	122–122.1[c]
Dimethylmethylenecyclopentane "A"	~117
Dimethylmethylenecyclopentane "B"	~120
Unknown cyclic olefin (C_8H_{14})	>122
2-Methyl-1,3-dimethylenecyclopentane	120–121°

[a] C. B. Willingham, W. J. Taylor, J. M. Pignocco, and F. D. Rossini, *J. Res. Nat. Bur. Stand.*, **35**, 219 (1945). [b] H. Pines and J. T. Arrigo, *J. Amer. Chem. Soc.*, **79**, 4958 (1957). [c] See ref 19.

However by repeated distillations we were able to enrich certain fractions with the desired components so that isolation in a fairly pure state by gas chromatography was possible. In Table V are the nine components found in the C_8 fraction in the order of increasing retention times using the Barber–Coleman capillary gas chromatograph with a UCON column. Some of the boiling points are only approximate.

2-Methyl-1,3-dimethylenecyclopentane and 3-Methyl-1,2-dimethylenecyclopentane.—Butadiene was bubbled through TIBA (768 g, 3.87 mol) under conditions similar to those described in the previous experiment to give 612 g of a colorless polymer. Of this polymer 215 g, which is equivalent to 1.36 mol of initial TIBA, was used for the following run.

A mixture of TIBA–butadiene polymer (215 g), benzene (350 g), phenylacetylene (0.3 ml), and nickel acetylacetonate (0.1 g) was charged under nitrogen to a 3-l. stainless steel bomb. After the addition of ethylene (276 g, 9.86 mol) the bomb was heated with rocking to 71° within 35 min to give a pressure of 860 psi. Heating with rocking between 71 and 78° was continued for 21 hr. The pressure had dropped to 420 psi at 75°. The bomb was connected to two Dry Ice traps and vented at room temperature. A 44-g sample of material was collected in cold traps. This material was analyzed by mass spectroscopy and found to contain about 12 g of benzene, 28 g of butenes, and 4 g of butadiene. The contents of the bomb were transferred under nitrogen to a distillation flask. The bomb was rinsed with some benzene, and the distillation was continued. All of the product was now soluble in benzene. The vacuum was gradually reduced to 200 mm at room temperature, and another 82 g was collected in a Dry Ice cold trap that contained 6 g of benzene, 65 g of butenes, and 11 g of butadiene. Finally, the vacuum was reduced to 3 mm at room temperature to give 566 g of distillate, which according to gas chromatography consisted of only two compounds. The major one was benzene, the other one (38 g based on gas chromatographic calculations, 17% yield based on initial TIBA) was methyldimethylenecyclopentane. The 566-g portion was washed with water. Most of the benzene was removed by distillation through a 4-ft long column. Then the distillation was continued on a 20-in. long spiral wire column to give 23 g of methyldimethylenecyclopentane, bp 118–121°. The remainder of the methyldimethylenecyclopentane distilled over with the benzene. The major fraction (12 g) had the following physical properties: bp 120–121°; $n^{20}D$ 1.4621; d^{20}_4 0.8172 [ϵ_{max} (2480 Å) 1900 in methanol].

Anal. Calcd for C_8H_{12}: C, 88.32; H, 11.18; mol wt, 108; MD for pure 1,3-dimethylene compound, 36.02. Found: C, 88.61; H, 11.41; mol wt (largest parent peak), 108; MD, 36.40.

The capillary gas chromatograph showed the presence of only one major peak (several smaller peaks corresponded to a total of 5%), when the sample was sent through a 200-ft long UCON column at 49°. Despite this it is believed that the material contains about 20% of the 2,3-dimethylene compound; this assumption would explain the uv absorption, the slightly high molecular refractivity caused by exaltation, and the shoulder at 6.14 μ in the infrared spectrum. The nuclear magnetic resonance spectrum was in agreement with the 1,3-dimethylene compound as the predominant structure.

After removal of benzene and methyldimethylenecyclopentane there was obtained 119 g (77% yield), bp 65 (3 mm)–78° (1 mm), of fairly pure triethylaluminum. Hydrolysis of this cut produced ethane as almost the only hydrocarbon. The residue (57 g) was not identified.

Reduction of Methyldimethylenecyclopentane.—The starting material is believed to have contained about 80% of the 2-methyl-1,3-dimethylenecyclopentane (6) and 20% of the 1-methyl-2,3-dimethylenecyclopentane (7).

This methyldimethylenecyclopentane (3 ml) was hydrogenated over platinum oxide in a Parr hydrogenator at 40 psi and room temperature. After 50 min the pressure had decreased to 37.5 psi. The gas chromatographic spectrum showed the presence of four peaks: 8% of peak I, 25% of peak II, 52% of peak III, and 15% of peak IV. The infrared spectrum of the product showed all the significant features of 1,*cis*-2,*cis*-3-trimethylcyclopentane (5). Peaks I and III had the same retention times as the authentic 1,*trans*-2,*cis*-3 and 1,*cis*-2,*cis*-3 isomers (3 and 5), respectively. The products representing peak II and IV were isolated by gas chromatography and investigated by infrared and mass spectroscopy. The compound representing peak II was identical with the 1,*cis*-2,*trans*-3 isomer (4) which was obtained from TIBA and butadiene after hydrolysis. The compound representing peak IV was a C_8H_{14} hydrocarbon (highest mass unit 110). The infrared spectrum showed weak C=C absorption at 5.95 μ, but no absorption indicating the attachment of a hydrogen to the double bond. It is believed to be 1,2,3-trimethylcyclopentene (8).

When the hydrogenation was repeated with methyldimethylenecyclopentane (3 ml) dissolved in ethanol (3 ml), the same result was obtained. However, addition of 2 drops of concentrated hydrochloric acid followed by hydrogenation for 50 min converted all of the compound representing peak IV into 1,2,3-trimethylcyclopentane. The reaction product was washed with water, dried over magnesium sulfate and then investigated by gas chromatography again. This time only compounds representing peaks I, II, and III were present in 8, 26, and 66%, respectively.

Registry No.—Triisobutylaluminum, 100-99-2; butadiene, 106-99-0; **3**, 19374-46-0; **4**, 19374-47-1; **5**, 19374-48-2; **6**, 15890-38-7; **7**, 15890-39-8.

Acknowledgment.—The authors wish to express thanks to Messrs. H. R. Harless, C. M. Lovell, and C. B. Strow of Union Carbide Corp. for interpretations of spectral data.

Organolithium Compounds and Acetylenes. VII.[1] Effect of N,N,N′,N′-Tetramethylethylenediamine on Reactivity and Products

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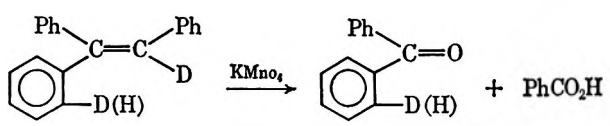
The activating effect of N,N,N′,N′-tetramethylethylenediamine (TMEDA) on addition–metalation reactions of phenyllithium and *n*-butyllithium with diphenylacetylene (DPA) is reported. Phenyllithium and *n*-butyllithium react much more rapidly with DPA—in the presence of TMEDA—to give products arising from addition plus metalation. Whereas *t*-butyllithium and DPA in hydrocarbon solvent react to the extent of 50% after 72 hr, the addition of TMEDA causes quantitative conversion to an addition product in less than 20 min. No metalation of the addition product occurs. The stereochemistry of the addition products (6:1 *cis*:*trans*) was determined by the stereospecific conversion of the carboxylic acid derivative, having a phenyl group and a carboxyl *cis*, into an indone using sulfuric acid at 0°.

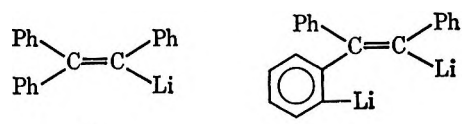
In previous papers organolithium compounds have been reported to yield various combinations of addition, metalation and electron transfer products with acetylenes.[3] A number of workers have recently reported the activating effect of N,N,N′,N′-tetramethylethylenediamine (TMEDA) on a variety of reactions of organolithium compounds.[4] We describe here the activating effect of TMEDA in organolithium and diphenylacetylene (DPA) reactions.

Phenyllithium in ethyl ether reacts slowly (24 hr) with DPA to give after carbonation an 11% yield of triphenylacrylic acid.[5,6] A mixture of 1.0 mol of DPA and 2.5 mol of a 1:1 phenyllithium–TMEDA complex in hexane was heated under reflux for 6 hr and after treatment with deuterium oxide yielded 80% (glpc) of triphenylethylene containing 1.62 D/molecule. One deuterium atom was obviously vinylic because of the absence of an nmr signal in that area, and the second deuterium atom was found by oxidation of the product with basic permanganate to benzophenone-*o*-*d* containing 0.8 D/molecule. The *ortho* position of deu-

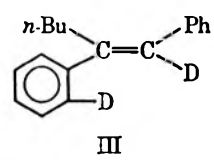


terium was apparent because the nmr spectrum of the ketone revealed only 3.2 *ortho* hydrogens (which appear at τ 2.3 in contrast to the *meta* and *para* protons at a higher field). Thus in the absence of TMEDA only addition occurs to product I, whereas the use of TMEDA results not only in considerably more rapid addition but in metalation as well (II).

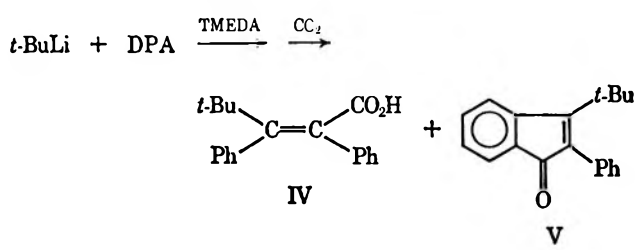
n-Butyllithium and DPA in pentane do not react over a period of many hours,[6] but in the presence of a



1:1 *n*-butyllithium–TMEDA complex in hexane at room temperature DPA gave a 69% yield of *trans*-α-*n*-butylstilbene containing 1.91 D/molecule (III). The position of the deuterium atoms was determined as in the case of the triphenylethylene (above) by oxidation and nmr.[6b]



t-Butyllithium and DPA in hydrocarbon solvents give a quite complex series of reaction products involving polyaddition, metalation and electron transfer.[7] Again, using a 1:1 TMEDA–*t*-butyllithium complex in hexane, DPA yielded after carbonation 41% (isolated) of *cis*-4,4-dimethyl-2,3-diphenyl-2-pentenoic acid (IV) and only a trace of 2-phenyl-3-*t*-butylindone (V).



The stereochemistry of IV was unequivocally determined as follows. Treatment of IV with sulfuric acid resulted only in the recovery of the starting material. However, IV could be photoisomerized to a 45:55 mixture of the *cis*–*trans* isomers, the quantities of each being determined by the integrated intensities of the different *t*-butyl groups in the nmr spectrum of the isomers. When a mixture of the isomers was treated with sulfuric acid, there was obtained 2-phenyl-

(1) For paper VI, see J. E. Mulvaney and L. J. Carr, *J. Org. Chem.*, **34**, 1177 (1969).

(2) Research supported by AFOSR(SRC)-OAR, USAF Grant No. 720-67. From the Ph.D. Thesis of D. J. N., 1968.

(3) See ref 1 and also J. E. Mulvaney and L. J. Carr, *J. Org. Chem.*, **33**, 3286 (1968).

(4) (a) G. G. Eberhardt and W. A. Butte, *ibid.*, **29**, 2928 (1964); (b) G. G. Eberhardt and W. R. Davis, *J. Polym. Sci., Part A*, **3**, 3753 (1965); (c) A. W. Langer, *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965); (d) H. E. Ziegler and E. M. Laski, *Tetrahedron Lett.*, 3801 (1966). See also the technical literature on organometallic–amine complexes, Foote Mineral Co.

(5) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **84**, 1501 (1962).

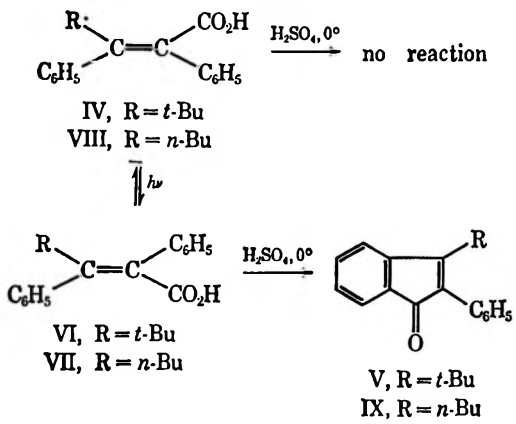
(6) (a) J. E. Mulvaney, Z. G. Gardlund, and S. L. Gardlund, *ibid.*, **85**, 3897 (1963); (b) J. E. Mulvaney, Z. G. Gardlund, S. L. Gardlund, and D. J. Newton *ibid.*, **88**, 476 (1966).

(7) J. E. Mulvaney, S. Groen, L. J. Carr, Z. G. Gardlund, and S. L. Gardlund, *J. Amer. Chem. Soc.*, **91**, 388 (1969).

3-*t*-butylindone. The nmr spectrum revealed that only the isomerized acid had reacted and, therefore, must have had a carboxyl group and a phenyl group *cis* to one another.

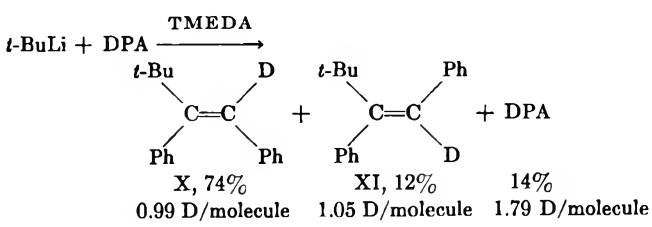
The stereospecificity of the sulfuric acid catalyzed ring closure was further demonstrated by the fact that only *trans* isomer VII of both *cis*- and *trans*-2,3-diphenyl-2-heptenoic acid[3] formed indone IX when treated with sulfuric acid[8] (Scheme I).

SCHEME I

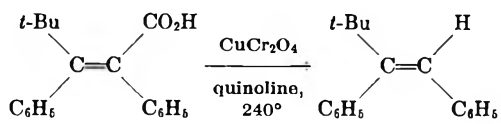


It is interesting that both IV and VIII are converted into their corresponding indones by thionyl chloride.[3,9] Therefore, sulfuric acid catalyzed cyclization of cinnamic derivatives at 0° is a very useful probe for stereochemistry, whereas, thionyl chloride is not.

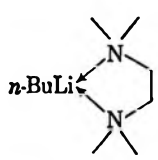
Deuterolysis of a reaction mixture containing 1.0 mol of DPA, 2.5 mol of TMEDA, and 2.5 mol of *t*-butyllithium enabled us to make a quantitative determination of the product composition by glpc. There was obtained 14% DPA, 74% *cis*-α-*t*-butylstilbene (X), and 12% *trans*-α-*t*-butylstilbene (XI). This reaction is complete in less than 20 min at room temperature. This is in sharp contrast to the same reaction in the absence of TMEDA under which conditions only about 50% of the reactants are consumed after 74 hr. Each of the three components was isolated and identified by comparison of glpc retention times, nmr spectra, and/or mixture melting points with authentic samples.[7] Deuterium analyses of the products revealed that DPA contained 1.79 D/molecule, *cis*-α-*t*-butylstilbene contained 0.99 D/molecule, and *trans*-α-*t*-butylstilbene contained 1.05 D/molecule. Control experiments showed that the products did not exchange hydrogen under the work-up conditions.



The stereochemistry of the α-*t*-butylstilbenes was assigned on the basis of the following arguments. As was just pointed out, carbonation of the *t*-butyllithium–DPA–TMEDA reaction mixture resulted in the isolation of 41% yield (pure) of *cis* carboxylic acid IV. *trans*-Carboxylic acid was surely present in the reaction mixture, but the products were too high boiling for a glpc analysis. When the same reaction mixture was terminated by deuteriolysis, two α-*t*-butylstilbenes were shown by glpc to be present in the ratio of 6:1. Because carbonation and hydrolysis of vinylic lithium compounds proceed with retention of configuration,[10] *cis*-carboxylic acid IV must have been the major product of the carbonation. Because IV was the major carbonation product, the major deuteriolysis product must also have had *cis* stereochemistry. Furthermore, IV was decarboxylated with quinoline and copper chromite to a quantitative yield of α-*t*-butylstilbene identical with the major component of *t*-butyllithium–DPA deuteriolysis product. This decarboxylation reaction has been shown to proceed with a high degree of stereospecificity.[3,11]

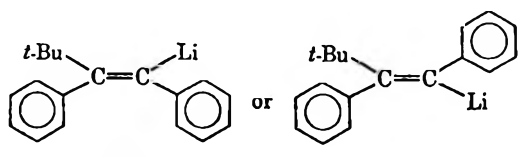


In the case of all other organolithium compounds and DPA which have been discussed in this paper, addition plus ring metalation occurs predominantly, if not exclusively, but with *t*-butyllithium no addition metalation occurs. However, when no TMEDA is present metalation does occur even in the *t*-butyllithium case.[7] This probably represents simply a steric effect. The isolation of a 1:1 butyllithium–TMEDA complex having structure XII has been reported.[4c]



XII

If *t*-butyllithium has the same structure, nucleophilic attack on a hydrogen atom of the benzene ring in XIII or XIV should be difficult, especially if one considers



XIII XIV

that the vinyllic lithium atoms in XIII or XIV are also probably coordinated with TMEDA.

The *t*-butyllithium–DPA–TMEDA reaction is complete in less than 20 min at room temperature and gives the composition indicated above. This composition remains constant for at least 24 hr after mixing. In view of the lack of configurational stability of organo-

(8) In the case of the isomers of α,β-dimethylcinnamic acids, only the isomer with phenyl and carboxyl *cis* to one another undergoes sulfuric acid catalyzed indone formation at 0°: L. M. Jackman and J. W. Lown, *J. Chem. Soc.*, 3776 (1962).

(9) No stereospecificity was observed in the case of thionyl chloride cyclization of the isomeric α,β-dimethylcinnamic acids: J. A. Kampmeier and R. M. Fantazier, *J. Amer. Chem. Soc.*, **88**, 1959 (1966).

(10) D. Seyferth and L. G. Vaughan, *ibid.*, **86**, 883 (1964).

(11) D. Y. Curtin and E. E. Harris, *ibid.*, **73**, 2716 (1951).

lithium compounds under these conditions[12] the deuteriolysis products most likely arise from the thermodynamically more stable vinyllic lithium compound which in this case is the *cis* isomer.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus or a Mel-Temp and are uncorrected. Nuclear magnetic resonance spectra were determined using a Varian Model A-60 (60 MHz) spectrometer, with tetramethylsilane as an internal standard. Either a Perkin-Elmer Infracord or a Beckman IR-4 spectrophotometer was used to determine infrared spectra; a polystyrene film was used to calibrate the instruments.

Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Deuterium analyses reported as "atom % excess deuterium" were performed by Joseph Nemeth, Urbana, Ill., using the falling drop method; those reported as "deuterium atom per molecule" were calculated from mass spectral data. Gas–liquid partition chromatography (glpc) was carried out on a F & M Model 609 flame ionization instrument using columns packed with GE-SE-30 on Chromosorb W. For analytical glpc determinations, correction factors for mole ratio/area ratio data were determined with standards containing the same compounds as in the unknown mixture. For irradiation experiments a quartz jacketed, Hanovia Type L mercury arc lamp was used.

Solvents and reagents were purified as described previously.[3,6b] Eastman Grade N,N,N′,N′-tetramethylethylenediamine (TMEDA) was purified by distilling from calcium hydride and storing over potassium hydroxide. Deuterium oxide was obtained from Stohler Isotope Chemicals and contained 99.8 atom % deuterium. Lithium wire and *t*-butyllithium in pentane were obtained from the Lithium Corp. of America. *n*-Butyllithium in hexane was obtained from Foote Mineral Co. *n*-Butyllithium in ethyl ether was synthesized from *n*-butyl bromide and lithium. All organolithium reactions were run under a nitrogen atmosphere in a flame-dried apparatus protected by calcium chloride drying tubes.

Phenyllithium, TMEDA, and DPA.—*n*-Butyllithium (0.35 mol) in 220 ml of hexane was added slowly to a stirred solution of benzene (78.0 g, 1.00 mol) and TMEDA (40.6 g, 0.35 mol) followed by 6 hr of reflux (65°). After allowing the dark red solution to cool to room temperature, DPA (25.0 g, 0.14 mol) in 50 ml of anhydrous ethyl ether was added and the solution refluxed (65°) for an additional 12 hr. Termination of the reaction was accomplished with deuterium oxide (14.0 g, 0.70 mol) while maintaining a temperature of 5° by external cooling. Water (100 ml) was added and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to yield 38.4 g of a dark red oil, which was shown by glpc to contain ~80% triphenylethylene. A spinning-band distillation of the oil afforded 22.7 g (63%) of glpc pure yellow product, bp 152–156° (0.15 mm). After two recrystallizations from 95% ethanol, the deuterated triphenylethylene had mp 68.5–69.5°; the mixture melting point with authentic sample was undepressed.

Anal. Calcd for $C_{20}H_{14}D_2$: D, 12.50 atom % excess deuterium. Found: D, 10.15 atom % excess deuterium.

A portion of the deuterated triphenylethylene (5.0 g, 0.019 mol) was oxidized with basic potassium permanganate[13] to give 1.6 g (68%) of benzoic acid and 1.2 g (34%) of benzophenone-*o*-*d*. The nmr spectrum of the benzophenone-*o*-*d* indicated the presence of 3.2 lowfield *ortho* protons.

Anal. Calcd for $C_{13}H_9DO$: D, 10.00 atom % excess deuterium. Found: D, 8.02 atom % excess deuterium.

***n*-Butyllithium, DPA and TMEDA.**—*n*-Butyllithium (0.25 mol) in 150 ml of hexane was added slowly to a stirred solution of DPA (17.8 g, 0.10 mol) and TMEDA (29.0 g, 0.25 mol) at −20°. The solution was allowed to warm to room temperature and stirred for 16 hr. The dark red reaction mixture, containing a considerable amount of yellow precipitate, was cooled to 5° and deuterium oxide (10.0 g, 0.50 mol) was added slowly. The mixture was stirred for an additional 4 hr at room temperature, 100 ml of water was added and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to give 22.1 g of a dark red oil. Distillation through a small Vigreux column yielded 16.4 g (69%) of glpc pure deuterated *trans*-α-*n*-butylstilbene, bp 113–115° (0.25 mm). The nmr spectrum and the glpc retention time of the product were identical with those of *trans*-α-*n*-butylstilbene prepared in ether.[6]

Anal. Calcd for $C_{18}H_{18}D_2$: D, 10.00 atom % excess deuterium. Found: D, 9.55 atom % excess deuterium.

***t*-Butyllithium, TMEDA, and DPA. Termination of Reaction by Carbonation.**—*t*-Butyllithium (0.35 mol) in 250 ml of pentane was added slowly to a stirred solution of DPA (25.0 g, 0.14 mol) and TMEDA (40.6 g, 0.35 mol) while maintaining a temperature of 5° by external cooling. After stirring for 22 hr under reflux (43°), the dark red reaction mixture was carbonated by decantation onto powdered Dry Ice. The mixture was allowed to stand overnight before 1 l. of water was added. The resulting basic solution was extracted with ether and the layers were separated. The neutral ether layer was dried (Na_2SO_4) and concentrated to give 9.3 g of a dark red oil. Distillation of the oil yielded 2.1 g (6%) of *cis*-α-*t*-butylstilbene, mp 49.5–50°; the mixture melting point with an authentic sample was undepressed. There was also obtained 2.6 g of an orange oil [bp 120–150° (0.1 mm)] which glpc analysis showed to contain *cis*-α-*t*-butylstilbene and about 20% 2-*t*-butyl-3-phenylindone.[7] This corresponds to a 1.3% yield of the indone based on DPA. The remaining 4.6 g was undistillable.

The basic aqueous solution was acidified with 6 *M* hydrochloric acid and extracted with ethyl ether. The organic layer was dried (Na_2SO_4) and concentrated to yield 42.0 g of yellow acidic material. Two recrystallizations from hexane gave 16.2 g (41%) of *cis*-4,4-dimethyl-2,3-diphenyl-2-pentenoic acid IV: mp 189–190° (lit.[7] mp 186.5–187.0°); there was no melting point depression with authentic sample.

Proof of Stereochemistry of *cis*-4,4-Dimethyl-2,3-diphenyl-2-pentenoic Acid (IV). A. Photoisomerization of IV.—A solution of *cis*-4,4-dimethyl-2,3-diphenyl-2-pentenoic acid (7.2 g) in 1600 ml of benzene was irradiated under nitrogen with a Hanovia uv lamp for 49 hr. The benzene layer was concentrated to 300 ml and extracted with saturated aqueous sodium carbonate. Upon acidification of the basic layer, extraction with ether, drying (Na_2SO_4) and removal of the ether there remained 6.7 g (93%) of a 45% *cis*–55% *trans* mixture of 4,4-dimethyl-2,3-diphenyl-2-pentenoic acid: nmr (8% $CDCl_3$) τ 2.4–3.0 (m, 10.0, aromatic), 8.8 [s, 4.5, *cis*-$(CH_3)_3C$], 9.1 [s, 5.5, *trans*-$(CH_3)_3C$].[7]

B. Reaction of a *cis*–*trans* Mixture of 4,4-Dimethyl-2,3-diphenyl-2-pentenoic Acid with Thionyl Chloride.—The reaction was run according to the method of Koelsh.[14] A mixture of 52% *cis*- and 48% *trans*-4,4-dimethyl-2,3-diphenyl-2-pentenoic acid (0.87 g, 3.1 mmol) was dissolved in 4.35 ml of carbon tetrachloride with heating. Thionyl chloride (0.87 ml, 8.7 mmol) was added, and the solution was heated under reflux for 6 hr. The yellow reaction mixture was allowed to cool and poured into 100 ml of ice water. The mixture was heated under reflux for 0.5 hr before cooling. Ether was added and the layers were separated. The ether solution was extracted with two 20-ml portions of saturated aqueous sodium carbonate. The neutral organic layer was dried (Na_2SO_4) and concentrated to yield 0.74 g (91%) of yellow 2-phenyl-3-*t*-butylindone. Recrystallization from 80% ethanol gave 0.60 g (74%) of pure indone, mp 133–134° (lit.[7] mp 131.5–132°). The nmr spectrum of the indone was identical with that of an authentic sample.

The combined basic extracts were acidified with 6 *M* hydrochloric acid and extracted with ether. Evaporation of the dried (Na_2SO_4) ether solution yielded an unweighable trace of acid.

C. Cyclodehydration of Butylstilbenecarboxylic Acids with Sulfuric Acid.—The procedure used was that of Jackman and Lown.[8] The powdered acid was added in portions to an excess of stirred concentrated sulfuric acid at 0°. The solution was stirred for 5 min, poured on crushed ice, and extracted with ether. The ether layer was extracted with saturated aqueous sodium carbonate solution and the layers were separated. The neutral ether layer was dried (Na_2SO_4) and concentrated to give the indone.

The basic aqueous layer was acidified with 6 *M* hydrochloric acid and extracted with ether. The ethereal extract was dried (Na_2SO_4) and concentrated to recover unreacted acid.

(12) D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962).

(13) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 250.

(14) C. F. Koelsh, *J. Amer. Chem. Soc.*, **54**, 2487 (1932).

1. Reaction with *cis*-2,3-Diphenyl-2-heptenoic Acid.—Treatment of 0.05 g (0.18 mmol) of *cis*-2,3-diphenyl-2-heptenoic acid[3] with 1 ml of sulfuric acid gave a yellow solution. Work-up afforded the starting *cis* acid in quantitative yield; no 2-phenyl-3-*n*-butylindone was obtained.

2. Reaction with *trans*-2,3-Diphenyl-2-heptenoic Acid.—Treatment of 0.05 g (0.18 mmol) of *trans*-2,3-diphenyl-2-heptenoic acid[3] with 1 ml of sulfuric acid gave a dark green solution. Work-up afforded 0.041 g (86%) of crude 2-phenyl-3-*n*-butyl indone; no acid was obtained.[6]

3. Reaction with *cis*-4,4-Dimethyl-2,3-diphenyl-2-pentenoic Acid (IV).—Treatment of *cis*-4,4-dimethyl-2,3-diphenyl-2-pentenoic acid (1.0 g, 3.6 mmol) with 20 ml of sulfuric acid gave a yellow solution. Work-up afforded 0.97 g (97%) of the starting *cis* acid; no 2-phenyl-3-*t*-butylindone was obtained.

4. Reaction with a *cis*-*trans* Mixture of 4,4-Dimethyl-2,3-diphenyl-2-pentenoic Acid.—Treatment of a 40% *cis*-60% *trans* mixture of 4,4-dimethyl-2,3-diphenyl-2-pentenoic acid (0.454 g, 1.62 mmol) with 20 ml of sulfuric acid gave a dark green solution. After work-up followed by sublimation there was obtained 0.185 g (44%) of 2-phenyl-3-*t*-butylindone, mp 133–134°; the mixture melting point with authentic sample[7] was undepressed. The nmr spectrum was identical with that of an authentic sample.

Sublimation of the recovered acid gave 0.154 g (34%) of a 60% *cis*-40% *trans* mixture of 4,4-dimethyl-2,3-diphenyl-2-pentenoic acid by nmr analysis.

Conversion of *cis*-4,4-Dimethyl-2,3-diphenyl-2-pentenoic Acid (IV) to *cis*-α-*t*-Butylstilbene.[15a]—The following procedure was based on a method described by Fieser[15b] for the stereospecific decarboxylation of *cis*-α-phenylcinnamic acid. *cis*-4,4-Dimethyl-2,3-diphenyl-2-pentenoic acid (0.060 g, 0.21 mmol) was added to a suspension of 0.010 g of copper chromite in 0.50 ml of quinoline. After heating at 240° for 10 min, the mixture was cooled and 10 ml of ethyl ether was added. After filtration the dark ethyl ether solution was extracted with two 10-ml portions of 10% hydrochloric acid and two 10-ml portions of 10% sodium hydroxide. The solution was dried over sodium sulfate and the ether was removed under reduced pressure. A nmr spectrum of the crude product (0.049 g, 100%) was identical with the 49° melting isomer of α-*t*-butylstilbene. In particular, the nmr spectrum revealed no *t*-butyl signal due to the 35° melting isomer. This evidence, in combination with what has been said in the discussion, proves that the 50° melting isomer is the *cis*-α-*t*-butylstilbene.[7]

***t*-Butyllithium–DPA–TMEDA. Termination by Deuteriolysis.**—*t*-Butyllithium (0.35 mol) in 227 ml of pentane was added slowly to a stirred solution of DPA (25.0 g, 0.14 mol) and TMEDA (40.6 g, 0.35 mol). After stirring under reflux (43°) for 6 hr the reaction mixture was treated slowly with deuterium oxide (20.0 g, 1.0 mol) while maintaining a temperature of approximately 5° by external cooling. The mixture was stirred for an additional 12 hr at room temperature, 100 ml of water added and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to give 34.2 g of a dark red oil, which was shown by glpc to contain 14% DPA, 74% *cis*-α-*t*-butylstilbene, and 12% *trans*-α-*t*-butylstilbene. The addition of a seed crystal of *cis*-α-*t*-butylstilbene caused solidification of the oil. The solid was filtered, recrystallized twice from 95% ethanol and sublimed to give 16.2 g (49%) of glpc pure deuterated *cis*-α-*t*-butylstilbene: mp 50.5°; mixture melting point with authentic sample[7] was undepressed; nmr (30% $CDCl_3$) τ 2.65–3.45 (m, 10.0, aromatic), 8.83 (s, 9.0, *t*-Bu).

Anal. Calcd for $C_{18}H_{19}D$: D, 5.00 atom % excess deuterium. Found: D, 4.95 atom % excess deuterium.

A portion of the filtrate was fractionated through a preparative scale gas–liquid partition chromatograph. The first and third components were collected to give deuterated DPA and deuterated *trans*-α-*t*-butylstilbene.

The deuterated DPA was recrystallized twice from 95% ethanol to yield glpc pure product, mp 59–60°; the mixture melting point with authentic sample was undepressed.

Anal. Calcd for $C_{14}H_8D_2$: D, 2.00 atom per molecule. Found: D, 1.79 atom per molecule.

The deuterated *trans*-α-*t*-butylstilbene was recrystallized from 95% ethanol and sublimed to yield glpc pure product: mp 41°; the mixture melting point with authentic sample[7] was undepressed; nmr (30% CCl_4) τ 2.80 (s, 9.7, aromatic), 9.00 (9.0, *t*-Bu).

Anal. Calcd for $C_{18}H_{19}D$: D, 5.00 atom % excess deuterium. Found: D, 5.25 and 5.06 atom % excess deuterium.

Osmium Tetroxide Periodate Oxidative Cleavage of Deuterated *o*-*n*-Butylstilbene.—The procedure was similar to that used by Pappo, *et al.*,[16] to cleave oxidatively *trans*-stilbene. *trans*-α-*n*-Butylstilbene (9.0 g, 0.038 mol), prepared by deuteriolysis of an *n*-butyllithium DPA reaction mixture, was oxidatively cleaved according to the method previously described.[6b] There was obtained 3.0 g (74%) of benzaldehyde-α-*d* and 3.2 g (52%) of valerophenone-*o*-*d*. The benzaldehyde contained 0.91 D per molecule and the valerophenone contained 1.03 D per molecule. The *ortho* position of the deuterium was determined by nmr.[6b]

Registry No.—TMEDA, 19289-58-8; DPA, 501-65-6; phenyllithium, 591-51-5; *n*-butyllithium, 109-72-8; *t*-butyllithium, 594-19-4; *trans*-α-*n*-butylstilbene, 5041-39-4; IV, 19289-60-2.

(15) (a) We are grateful to Dr. L. J. Carr for this experiment. (b) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass, 1957, p 186.

(16) R. Pappo, O. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

Some Chemistry of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate[1]

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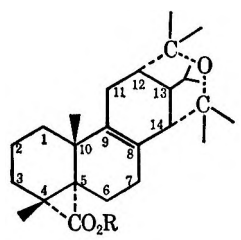
Received December 5, 1967

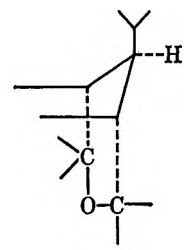
In an earlier paper, some reactions of 12α-hydroxymethylabiet-7,8-enoic acid with formaldehyde were described. The major product when the reaction was run in acetic acid with sulfuric acid present was believed to be 12,14-(2-oxapropano)abiet-8,9-enoic acid (**1a**). In the present paper, consideration is given to the stereochemistry and oxidative studies needed for chemical evidence to support the structure initially assigned. Treatment of **1b** with N-bromosuccinimide gave the transoid diene methyl 12,14-(2-oxapropano)abiet-7,9(11)-dienoate (**3a**). Reduction of the 7-keto derivative (prepared by CrO_3 oxidation and ozonolysis of **1b**) and cleavage of the 8,9 epoxide both gave diene **3a**, which by a series of degradation oxidation steps gave a tetrahydropyran substituted by isopropyl, aldehyde, and hydroxyl (hydroxymethyl) groups and is depicted as **7**.

In studies on the preparation of polyols from resin acids derivatives[4,5] 12,14-(2-oxapropano)abiet-8,9-enoic acid (**1a**) was obtained from the condensation of 12-hydroxymethylabiet-7,8-enoic acid with paraformaldehyde in acetic acid containing sulfuric acid.[4] Similar products may be formed in reactions of resin acids and rosin used commercially. At the time the results of this reaction were published, structural assignments were based on elemental analyses and spectral data. There was an increase in the neutral equivalent of **1a** and in the infrared (ir) spectrum there were no absorbance bands for hydroxyl, ketone, or acetate groups. The purpose of this report is to consider the stereochemistry of the molecule as it relates to the isopropyl-substituted pyran ring, **1a**, and describe the results of some oxidative studies made involving the 8,9 double bond to obtain chemical evidence in support of the structure initially assigned.

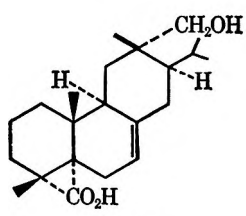
To assign a configuration to the pyran ring and isopropyl group in **1a**, consideration of the stereochemistry of the starting material **2** is necessary since it was not described clearly in the initial publication. Parkin and Hedrick[6] synthesized hydroxymethylabietic acid and from the method of synthesis and spectral data concluded the hydroxymethyl group had an α configuration. Herz and coworkers[7] demonstrated preference for α attack when 12α-hydroxyabietic acid was reduced catalytical with Adam's catalyst. The same hydrogenation of 12-hydroxymethylabietic acid would be expected to proceed in an analogous manner leading to a structure with α-hydroxymethyl- and β-isopropyl groups as in **2**. In the mechanism initially proposed by Black and Hedrick[4] the methylene carbonium ion attacked the C-14 carbon forming an α-pyran ring. This is the only possibility if **2** has the structure depicted. There is strong evidence for a β-oriented isopropyl group in the nuclear magnetic resonance (nmr) spectrum. The observed difference in chemical shift for the two methyls of the isopropyl group together with the change in shift of one methyl with alterations in ring B require this configuration. An α-isopropyl group would be in an essentially symmetrical environment well removed from the rest of the molecule.



1a, R = H
b, R = CH_3



1c



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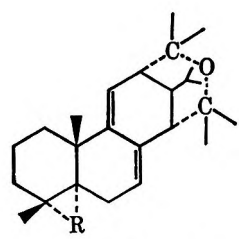


3a, R = CO_2Me
b, R = CH_2OH

Chemical evidence to support the assigned structure was obtained by degradative studies of **1b** using three different oxidation reactions which gave the transoid diene structure **3a**. The pyran **7** was obtained from cleavage of **3a** by ozonolysis and subsequent reactions of the ozonide.

Treatment of **1b** with N-bromosuccinimide resulted in allylic bromination and dehydrobromination to give the transoid diene methyl 12,14-(2-oxapropano)abiet-7,9(11)-dienoate (**3a**), the nmr spectrum of which showed a broad signal at 5.41 ppm for the H-7 and H-11 vinyl protons.

Oxidation of **1b** with chromic acid in acetic acid[8] gave methyl 7-keto-12,14-(2-oxapropano)abiet-8,9-enoate (**4**) as the major product,[9] the presence of the α,β-unsaturated ketone chromophore being shown by the uv maximum at 249 mμ and ir bands at 1610 and 1660 cm^{-1}. That oxidation had occurred at the less hindered C-7 site rather than at C-11 is apparent from the nmr spectrum which showed the AB portion of an ABX pattern in the region 1.90–2.60 ppm, attributed to the coupling of the two protons adjacent to the carbonyl group with the angular C-5 proton.[10] A broad doublet centered at 2.12 ppm is assigned to the geminal coupling ($J \sim 12$ cps) of the equatorial 6α

(1) Presented at the American Chemical Society Southeastern Regional Meeting, Atlanta, Ga., Nov 1967.

(2) National Research Council Posdoctoral Resident Research Associate.

(3) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(4) D. K. Black and G. W. Hedrick, *J. Org. Chem.*, **32**, 3763 (1967).

(5) D. K. Black and G. W. Hedrick, *ibid.*, **32**, 3758 (1967).

(6) B. A. Parkin and G. W. Hedrick, *ibid.*, **30**, 2356 (1965).

(7) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *ibid.*, **30**, 3190 (1965).

(8) L. Ruzicka, E. Rev, and A. C. Muhr, *Helv. Chim. Acta*, **27**, 472 (1944).

(9) Intermediate chromatographic fractions showed ultraviolet (uv) maxima at approximately 260 mμ, suggesting the presence of some enedione.

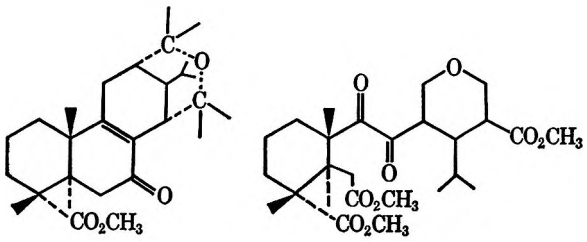
(10) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 73.

proton, the broadening being due to axial–equatorial coupling with the 5α proton. The 6β axial proton gives rise to a pair of doublets, centered at 2.36 and 2.58 ppm, the larger coupling ($J \sim 13$ cps) again corresponding to the geminal interaction, and the smaller splitting ($J \sim 10$–11 cps) being due to the axial–axial coupling with the 5α proton. Although no deuterium incorporation experiments were carried out, these assignments are in agreement with examples found in the literature for 7-keto steroids.[11]

Lithium aluminum hydride reduction of **4** gave 12,14-(2-oxapropano)abiet-7,9(11)-dienol (**3b**), formed by 1,4-dehydration of the unstable intermediate allylic alcohol.

Ozonolysis of **1b** gave a complex mixture of products. The major component was found to be the 7-keto compound **4**, suggesting preferential allylic attack rather than oxidation of the hindered double bond. However, some epoxide formation was observed. Enzell and Thomas[12] obtained epoxides from the anomalous ozonolysis of araucarolene diacetate, containing a 7,8 double bond.

Epoxidation of methyl 12,14-(2-oxapropano)abiet-8,9-enoate with *m*-chloroperbenzoic acid gave a low yield of an epoxide which on hydrolysis, using lithium iodide in collidine,[13] was accompanied by opening of the oxirane ring and elimination[14] to give the corresponding 7,9(11)-diene (**3a**).



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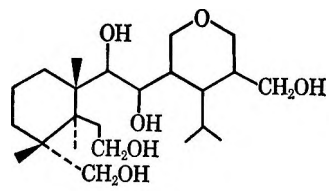

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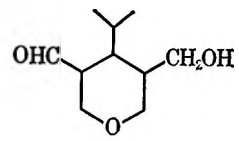

7

Ozonolysis of **3a** followed by esterification gave, presumably, the diketone (**5**) which was reduced with lithium aluminum hydride to the corresponding pentaol (**6**). Lead tetraacetate cleavage indicated the presence of a 1,2-diol system and gave the pyran (**7**), isolated by preparative glpc and characterized by ir and nmr.

Experimental Section[15]

Methyl 12,14-(2-Oxapropano)abiet-7,9(11)-dienoate (3a).—Methyl ester **1b** (2.0 g) in dry carbon tetrachloride (50 cc) was refluxed 2 hr with recrystallized N-bromosuccinimide (2.0 g). The mixture was filtered cold; the filtrate was washed with 5% aqueous sodium hydroxide solution and water, dried, and concentrated *in vacuo* to give a resinous solid (1.6 g). Chromatography over alumina (50 g) and elution with *n*-hexane ether (19:1) gave ester **3a** as a colorless solid (1.5 g, 76%): mp 106–108°; λ_{max} 237, 244 mμ (ε 15,000), and 253; $[\alpha]^{24}D$ +103° (*c* 1.33); glpc showed a single peak at *t* 4.8 min; nmr ($CDCl_3$) signals appeared at 0.86 and 0.76 and 0.99 and 0.88 (doublets for isopropyl group, J = 6.5 cps), 1.02 (C-10 Me), 1.20 (C-4), 3.63 (ester Me), and a broad signal centered at 5.41 ppm (H-7 and H-11).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 79.49; H, 9.86. Found: C, 79.41; H, 9.81.

Methyl 7-Keto-12,14-(2-oxapropano)abiet-8,9-enoate (4).—Ester **1b** (2.3 g) in glacial acetic acid (120 cc) was heated to 40°, chromium trioxide (1.5 g) in 90% aqueous acetic acid (15 cc) was added, and the mixture was heated at 45° for 4 hr. Methanol (10 cc) was added; the mixture was poured into water and ether extracted. The extracts were washed with aqueous $NaHCO_3$ solution and water then dried. Removal of solvent gave a low melting solid (2.0 g, 83%). Chromatography over neutral alumina and elution with ether gave the **enone** (**4**) as colorless needles: mp 115°; λ_{max} 249 mμ (ε 12,900); ν_{max} ($CHCl_3$) 1730 (ester C=O), 1660 and 1610 cm^{-1} (αβ-unsaturated C=O); glpc showed a major peak at *t* 5.5 min (*ca.* 95%) together with unreacted material at *t* 4.0 min; nmr signals appeared at 0.87 and 0.76 and 0.97 and 0.85 (doublets for isopropyl group, J = 6.5 cps), 1.13 (C-10 Me), 1.25 (C-4 Me), 3.65 (ester Me), and doublets centered at 2.12 (J = 12 cps) and 2.37 ppm (H-5 and H-6); mass spectrum *m/e* (rel intensity) 374 (100), 329 (26), 314 (20), 298 (28), 223 (28), 158 (37), 145 (40), 119 (31), 107 (22), 105 (38), 91 (54), 77 (22), 55 (35), 43 (44), and 41 (46).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.73; H, 9.15. Found: C, 73.64; H, 9.07.

The **enone** gave a 2,4-dinitrophenylhydrazone derivative as an orange-red solid: mp 212–214°; λ_{max} 384 mμ (ε 22,000).

Anal. Calcd for $C_{29}H_{38}N_4O_7$: C, 62.80; H, 6.91; N, 10.10. Found: C, 62.37; H, 6.78; N, 9.97.

Lithium Aluminum Hydride Reduction of 4.—Ketone **4** (0.60 g) in ether (50 cc) was refluxed for 2 hr with lithium aluminum hydride (0.5 g). Addition of water followed by dilute HCl (1:1) to pH 2.0, ether extraction, washing with aqueous $NaHCO_3$ and water, concentration, and filtration gave 12,14-(2-oxapropano)-abiet-7,9(11)-dienol (**3b**, 0.4 g, 73%): mp 204–205°; λ_{max} 238, 244.5 mμ (ε 13,600), and 255; ν_{max} 3300 cm^{-1} (OH).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.93; H, 10.37. Found: C, 79.95; H, 10.37.

Epoxidation of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate.—Ester **1b** (0.4 g) in dry chloroform (50 cc) was refluxed for 48 hr with *m*-chloroperbenzoic acid. The resulting solution was washed with aqueous potassium iodide solution, aqueous sodium thiosulphate solution, and water and then dried. Removal of solvent gave a semisolid mass. Addition of ether precipitated a colorless solid (*m*-chlorobenzoic acid). Concentration of the filtrate gave a viscous liquid (0.3 g) which on glpc showed two major components at *t* 4.0 (starting material) and 7.0 min, with minor components having longer retention times. Chromatography of the mixture (0.3 g) over alumina (20 g) and elution with hexane–ether (9:1) gave unreacted ester followed by the epoxidized product as a viscous liquid (60 mg, 20%): nmr signals appeared at 0.87 and 0.77 and 0.92 and 0.82 (doublets for isopropyl group, J = 6.5 cps), 1.15 (C-10 Me), 1.26 (C-4 Me), and 3.65 ppm (ester Me).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.35; H, 9.64. Found: C, 72.98; H, 9.54.

Hydrolysis of the Above Epoxide.—The epoxidized material (0.2 g) and anhydrous lithium iodide (1.5 g) in collidine (15 cc) was refluxed for 18 hr in a nitrogen atmosphere, cooled, acidified, and ether extracted. The extracts were washed, decolorized, dried, concentrated, and reesterified with excess ethereal diazo-

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1966, p 63.

(12) C. R. Enzell and B. R. Thomas, *Tetrahedron Lett.*, No. **4**, 225 (1965).

(13) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960); E. Wendert, P. Peak, R. W. J. Carney, J. W. Chamberlin, D. R. B. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1965).

(14) W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).

(15) Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were determined as neat liquids or in solution; uv spectra and rotations were determined in 95% ethanol. Nmr spectra were run in CCl_4, unless otherwise stated, using a Varian A-60 spectrometer. Frequencies are given in parts per million (ppm) measured downfield from tetramethylsilane as internal standard. J values are in cycles per second. Mass spectra were obtained with A CEC 21-104 spectrometer using a direct insertion probe. Gas–liquid partition chromatography (glpc) was carried out on a 10 ft. × $\frac{3}{16}$ in. column 10% Dow Corning silicone grease on 60–80 mesh Diatoport S (F & M Scientific Division of Hewlett-Packard, Avondale, Pa.) at 280° using a Loenco, Inc., Model 15B instrument and a helium flow of 110 cc min. Alumina for chromatography was Alcoa F-20.

methane. Removal of solvent and chromatography over alumina, eluting with hexane–ether (19:1), gave **7,9(11)-diene 3a** (0.15 g): mp 106–108°; λ_{max} 237, 244 mμ (ε 12,000), and 253; glpc showed a major component (~90%), *t* 4.8 min.

Ozonolysis of Diene 3a.—Ozonized oxygen (from a Welsbach ozonizer) was passed into a solution of **3a** (0.8 g) in chloroform (50 cc) at 0° until no further ozone was absorbed. Hydrogen peroxide 20% (20 cc) was added to the concentrated solution (residue taken up in methanol) and left at 20° for 24 hr. Water (50 cc) was added, the mixture was concentrated to remove methanol, and the mixture was ether extracted. The extracts were washed with aqueous ferrous sulfate solution and water and then dried. Removal of solvent gave a colorless resinous solid (0.9 g), neut equiv 231 (theory for diacid 227).

The above diacid was esterified with excess ethereal diazomethane to give the triester **5** as a viscous liquid: ν_{max} 1735 (ester C=O), 1715 (1,2 diketone), 1710–1715 (CH_2CO), and 1430 cm^{-1} (CH_2 deformation); glpc showed a major peak, *t* 8.5 min, with two impurities having shorter retention times.

Anal. Calcd for $C_{25}H_{38}O_9$: C, 62.10; H, 7.92. Found: C, 61.80; H, 7.65.

Lithium Aluminum Hydride Reduction of Triester 5.—Triester (0.3 g) was refluxed 2 hr with lithium aluminum hydride (0.5 g) in dry ether (50 cc). Addition of water and dilute hydrochloric acid (1:1) to pH 2.0, ether extraction, and concentration *in vacuo* gave the crude pentaol **6** as a resinous solid (0.21 g), which was not purified.

Lead Tetraacetate Oxidation of 6.—The crude pentaol (0.20 g) was left at room temperature with lead tetraacetate (0.2 g) in acetic acid (10 cc) for 3 hr. Addition of a few drops of ethylene glycol, standing 10 min, dilution with water, ether extraction, and washing gave a viscous liquid (0.2 g). Glpc showed the presence of three major components, *t* 4.5, 7.5, and 12.5 min. Preparative glpc (similar conditions) gave the component having *t* 7.5 min as a viscous liquid (65 mg) identified as the pyran (**7**): ν_{max} (CCl_4) 3400 (OH), 2800 (CHO), 1720 (aldehyde C=O), 1360 and 1380 (Me_2CH), and 1090 cm^{-1} (COC); nmr signals appeared at 0.98 and 0.85 (broad, isopropyl group, J = 7.0 cps), 2.95 (OH), and a doublet centered at 9.56 ppm (J = 2 cps, CHO).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.12; H, 9.64.

Ozonolysis of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate (1b).—Ester **1b** (2.0 g) in dry chloroform (100 cc) was cooled in ice and ozonized oxygen was passed through for 30 min (progress of the reaction was followed directly by glpc). Concentration *in vacuo* gave a viscous liquid (2.6 g) which on glpc showed a major peak, *t* 6.5 (~60%), and another peak at *t* 4.0 min (ester **1b**) with minor components having longer retention times.

Chromatography over alumina (50 g) and elution with hexane–ether (4:1) gave a forerun of starting material (0.3 g) followed by a mixture (0.7 g) of two components, *t* 7.0 and 7.2 min. Preparative glpc gave the component with *t* 7.0 min as a viscous liquid (0.3 g): ν_{max} ($CHCl_3$) 1725 (ester C=O) and 875 cm^{-1} (epoxide); end absorption only in the uv region; nmr spectrum very similar to that of the epoxide of **1b**.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.35; H, 9.64. Found: C, 73.21; H, 9.59.

Elution with ether gave a colorless crystalline solid (1.0 g): mp 115°; λ_{max} 249 mμ (ε 12,750); ν_{max} 1730 (ester C=O), 1660, and 1610 cm^{-1} (α,β-unsaturated C=O); glpc gave a major peak, *t* 5.5 min, identical with that of the product **4** from CrO_3 oxidation of **1b**.

Registry No.—**1b**, 19206-15-6; **1b** (8,9-epoxy), 19206-20-3; **3a**, 19206-16-7; **3b**, 19206-17-8; **4**, 19206-18-9; **4** (2,4-dinitrophenylhydrozone), 19237-74-2; **5**, 19206-19-0; **7**, 19203-28-2.

Acknowledgments.—The authors wish to thank Mr. G. S. Fisher of the Naval Stores Station and Dr. Werner Herz, Florida State University, for helpful discussions, and to thank Mr. Robert T. O'Conner, Southern Utilization Research and Development Division, New Orleans, La., for the provision of mass spectra.

Conformational Studies. II. Consequences of the Conjugate Addition of Cyanide Ion to Rigid Bicyclic Systems. A. Hexahydro-1,4a-dimethyl-2-naphthalenone[1]

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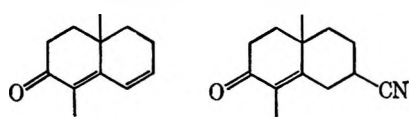
Received July 24, 1968

The unsaturated ketone named in the title underwent conjugate addition when treated with potassium cyanide in ethanol. In the absence of ammonium chloride, the main products were two isomeric lactamols, while in the presence of this salt the reaction yielded two epimeric ketonitriles. The structure proofs of the products entailed the use of dipole moment measurements, infrared intensity studies, and nuclear magnetic resonance spectroscopy, as well as classical chemical correlations.

Several years ago a series of publications appeared describing the introduction of a nitrile group at an angular position by the conjugate addition of potassium cyanide to an α,β-unsaturated ketone system.[2,3] In studies originally directed toward the total synthesis of certain sesquiterpenes, this reaction was likewise encountered in our laboratory at that time. The potential synthetic applications of such a cyanation procedure encouraged us to examine it in some detail as to yield, stereoselectivity, and reversibility. Our initial studies were concerned with the addition of potassium cyanide to dienone **1** for the purpose of effecting a 1,6 addition, yielding adduct **2**. The



1 **2**

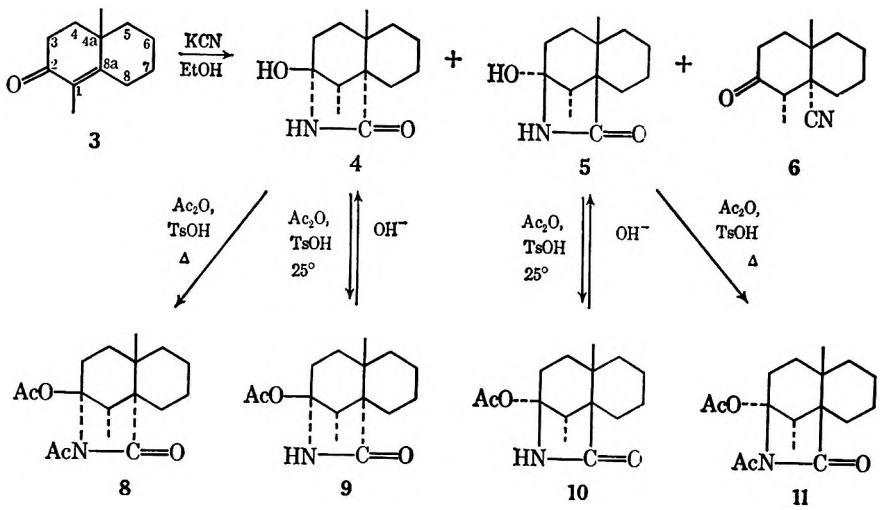
products obtained from this reaction were sufficiently complex, however,[4] that the elucidation of their struc-

(1) (a) Taken in part from the dissertation of Norman J. Johnston submitted for the Doctor of Philosophy Degree, University of Virginia, 1963. (b) This is part of a series of conformational studies; for earlier work, see O. R. Rodig and L. C. Ellis, *J. Org. Chem.*, **26**, 2197 (1961).

(2) Some of the more influential contributions in this field have been made by Nagata and coworkers. For a lead reference to their work, see W. Nagata, M. Narisada, and T. Sugasawa, *J. Chem. Soc., C*, 648 (1967). We wish to thank W. Nagata for sending us prior to their publication copies of some of the papers describing the work of the Shionogi group.

(3) Some other significant references are (a) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961); (b) J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.*, **84**, 1485 (1962); (c) W. L. Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962); (d) W. L. Meyer and J. F. Wolfe, *ibid.*, **29**, 170 (1964).

(4) This reaction is described in detail in the following paper: O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, **34**, 1949 (1969).



SCHEME I

tures was greatly facilitated by studying the addition reaction on the simpler α,β-unsaturated ketone **3**. Our findings on this phase of the work are discussed in this paper.

When ketone **3** was treated with ethanolic potassium cyanide (Scheme I), the main products were lactamols **4** (20%) and **5** (55%), together with a small amount of cyano ketone **6** (1%) and a compound (**7**) of unknown structure (1% by weight).[5] To determine the structures of lactamols **4** and **5**, attempts were made to hydrolyze the lactam ring. However, this function was found to be stable even under the most severe hydrolytic conditions, including 10 and 50% aqueous sulfuric acid at reflux temperatures, concentrated sulfuric acid at room temperature and 85°, and refluxing 10 and 40% aqueous potassium hydroxide.[6] When the hydrolysis method of Hauser and Hoffenberg[7] using boron trifluoride in glacial acetic acid was tried, lactamol **5** yielded 45% of monoacetate **10** whereas, interestingly enough, lactamol **4** failed to react.

Nevertheless, the assigned lactamol structures are supported by spectroscopic data. The substances exhibited no significant ultraviolet absorption above 220 mμ and lacked the $n \rightarrow \pi^*$ transitions at 270–285 (unconjugated) or 300–350 mμ (conjugated) characteristic of the ketone group. The infrared spectrum confirmed the lack of ketone carbonyl absorption and also contained no amide II bands at 1570–1515 cm^{-1}.[8a]

Selected solid state infrared absorption bands of the lactamols are shown in Table I. The assignments given in the first column are supported by dilution studies in chloroform,[8b,9] and by acetylation experiments described below.

When the two lactamols were heated at reflux in acetic anhydride containing molar quantities of *p*-toluenesulfonic acid, diacetylation occurred to yield

TABLE I
SELECTED INFRARED ABSORPTION BANDS OF LACTAMOLS 4 AND 5

Assignment	Lactamol 5	Lactamol 4	Ref
Bonded OH	3284 b[a]	3257 b	8b
Bonded NH	3189 b		8c
Lactam	3086 sh[a]	3096 sh	8c
Bonded lactam C=O	1658 b	1664 b	8d

[a] b = broad, sh = shoulder.

products **8** and **11**. The replacement of two hydrogens with acetyl groups was confirmed by the lack of infrared absorption in the N–H and O–H regions at 3300–3000 cm^{-1}. The two acetyl groups showed carbonyl absorption which overlapped into one broad band at 1736–1734 cm^{-1} and the original lactam carbonyl was shifted from 1658–1664 cm^{-1} to 1705 cm^{-1} due to the elimination of intermolecular hydrogen bonding.

Room temperature acetylation of the lactamols **4** and **5** by the acetic anhydride–*p*-toluenesulfonic acid method[10] yielded monoacetyl derivatives **9** and **10**, respectively. The infrared spectra of these compounds confirmed that O acetylation had occurred because of the retention of the 3086–3096-cm^{-1} lactam absorption which now appeared as a defined peak[8c] along with the expected bonded NH absorption. Saponification equivalents of both monoacetates were in excellent agreement with the theoretical values, the parent lactamols being recovered from the hydrolysis media.

Proofs of structure for lactamols **4** and **5** came largely from their preparations through the hydrolyses of ketonitriles **6** and **12** (Scheme II).[11] The latter were obtained in 42 and 18% yields, respectively, when ammonium chloride was added to the cyanide addition reaction and a shorter reaction time was employed.[12]

(5) The yields given are those obtained before final purification.

(6) The lack of hydrolysis under these conditions is in keeping with the observations on the reported stabilities of similar lactamol structures; for example, see W. Nagata, S. Harai, H. Itazaki, and K. Takeda, *Ann.*, **641**, 184, 196 (1961); W. Nagata, S. Hirai, T. Aoki, and K. Takeda, *Chem. Pharm. Bull. Jap.*, **9**, 837 (1961).

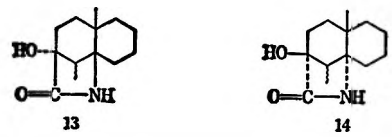
(7) C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1448 (1955).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., Ltd., London, 1958: (a) p 216 ff; (b) p 96; (c) pp 205, 208; (d) p 213.

(9) Dilution in chloroform is accompanied by the appearance of a band in the 1600-cm^{-1} region which might be a primary amide II band arising from lactam ring opening;[8a] also *cf.* ref 3c.

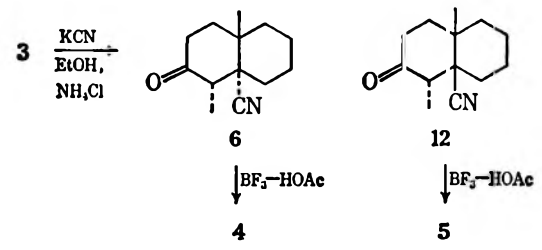
(10) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *J. Amer. Chem. Soc.*, **74**, 5394 (1952).

(11) This sequence thus ruled out the alternate, but less likely, structures **13** and **14**. Such products could arise by 1,2 addition of cyanide ion, yielding epimeric cyanohydrins, followed by hydrolysis to amidohydrins in the basic media and cyclization with the $\Delta^{1(8a)}$-double bond. The latter would be analogous to the cyclization of β,γ-unsaturated acids to γ-lactones.



(12) W. Nagata, *Tetrahedron*, **13**, 278 (1961).

SCHEME II



In addition, small amounts of lactamols **4** and **5** as well as some starting ketone **3** were obtained.

Hydrolysis Studies.—A number of hydrolysis conditions were tried to convert ketonitriles **6** and **12** into the corresponding lactamols. Interestingly, lactamol formation could be effected under mildly basic conditions, a fact which has also been affirmed by other workers.[13] However, in every case employing basic media, an appreciable quantity of ketone **3** was formed, presumably by β elimination of hydrogen cyanide. This result obviously vitiated the use of such hydrolyses in a structure proof sequence since cyanide ion could re-add to give the alternate isomer.

Actually, the conditions in the cyanide addition reaction in the absence of ammonium chloride are sufficiently basic to cause this reversibility.[14] This was nicely demonstrated by heating *trans* epimer **6** at reflux for 48 hr in a 2% solution of potassium cyanide in aqueous ethanol. Careful chromatography of the reaction mixture yielded a trace of ketone **3**, lactamol **4** (30%), lactamol **5** (25%), ketonitrile **6** (13%), ketonitrile **12** (6%), and the compound of unknown structure **7** (4% by weight).

To avoid side reactions arising from the reversal of the cyanide addition reaction, acidic hydrolysis conditions were investigated. Boron trifluoride in acetic acid[7] afforded good yields of the lactamols without the observed formation of ketone **3**, and these reactions therefore unequivocally established the structures of **4** and **5**.

Each ketonitrile contains three asymmetric centers (C-1, C-4a, and C-8a); however, if the C-1 methyl group (and boat or twist forms) is ignored for the moment, the conformations possible are those shown in Figure 1. The *trans*-decalin ring system is rigid and so can exist in but one conformation, A. The *cis*-decalin system, on the other hand, is flexible and can have two different conformations, B and B′.[15] The structures of the two ketonitriles were determined by infrared, nuclear magnetic resonance and dipole moment studies.

The elegant method of using infrared intensity measurements recently reported by Nagata and coworkers[16] was used to determine the stereochemistry at the ring junctures. This method is based on the principle that the intensity of the stretching frequency of a nitrile group is directly related to the number of

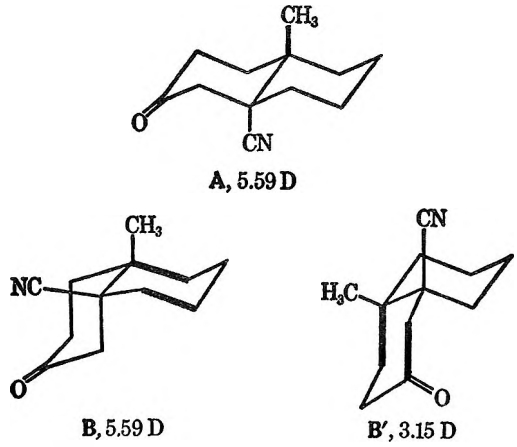


Figure 1.—Calculated dipole moments.

parallel β–γ carbon–carbon bonds. These bonds are shown as heavy lines in Figure 1, *cis* structures B and B′ having two such bonds while *trans* structure A has only one. The observed molar extinction coefficients for ketonitriles **6** and **12** are 19.9 and 33.8, respectively, which clearly indicate that **6** possesses the *trans* structure while **12** has the *cis* configuration. Still, these studies do not allow a distinction between *cis* conformations B and B′.

Inspection of molecular models shows, however, that *cis* form B should have the same dipole moment as *trans* form A (the two strong dipoles, the keto and nitrile groups, have equivalent mutual spacial orientations in each), whereas *cis* form B′ should possess a smaller dipole moment (the two dipoles are oriented at a dihedral angle approximately twice as great as that in A or B). Theoretical dipole moments for the three forms were calculated by a vector analysis method, employing the Corey and Sneen cartesian coordinate values for the cyclohexylidene ring,[17] and the carbonyl and nitrile vector moments of Lehn, Levisalles, and Ourisson.[18a] These values, which are expressed in Debye units, are shown in Figure 1.[18b] The experimentally determined dipole moments for the two ketonitriles **6** and **12** were 5.59 ± 0.06 and 3.08 ± 0.03 D, respectively, which confirm the *trans* assignment of ketonitrile **6** and establish the B′ conformation for compound **12**. In addition, they tend to rule out any appreciable distortion of the ketone-containing ring from the normal chair form. It has been suggested that such distortions, a result of dipole–dipole repulsions, may be present in 5-cyano-3-keto steroids.[19]

Theoretically, a differentiation between structures A and B or B′ should also be possible by observing the chemical shift of the C-4a methyl group protons in the nuclear magnetic resonance spectrum. In conformations B and B′ the nitrile groups are identically oriented with respect to the C-4a methyl groups, the dihedral angle being nearly 60° in each case. In *trans* structure A, however, the dihedral angle between these two groups is approximately 180°. Thus, one might anticipate a significant difference in the chemical shifts of the C-4a methyl groups in A and B or B′.[20] As seen from Table II the C-4a methyl group in ketonitrile **6**

(13) *Cf.* W. Nagata, S. Hirai, H. Itayaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).

(14) The reversible nature of this reaction has also been noted by other investigators: for example, W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Lett.*, 461 (1962), and ref 13.

(15) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 231 ff.

(16) W. Nagata, M. Yoshioka, M. Narisada, and H. Watanabe, *Tetrahedron Lett.*, 3133 (1964).

(17) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).

(18) (a) J. M. Lehn, J. Levisalles, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1096 (1963). (b) For the theoretical and experimental dipole moment calculations, see ref 4.

(19) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3223 (1963).

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR THE KETONITRILES AND LACTAMOL ACETATES[a]

Compound	C-4a methyl,[c] ppm	(angle, deg)	C-1 methyl,[b] ppm	(angle, deg)	C-1 hydrogen,[b] ppm	(angle, deg)
Ketonitrile 6	1.24	(180)	1.16	(60)	2.50	(180)
Ketonitrile 12	1.48	(60)	1.16	(60)	3.05	(60)
Lactamol acetate 9	1.07	(180)	0.88	(60)	2.40	(180)
Lactamol acetate 10	1.03	(60)	0.95	(180)	2.63	(60)

[a] The absorption spectra were determined at 60 Mc in deuteriochloroform solutions using tetramethylsilane as an internal reference. The chemical shifts are reported in parts per million measured from TMS (0 ppm) in the direction of decreasing field. [b] The geometrical center positions of the C-1 methyl doublet and the C-1 hydrogen quartet are reported. [c] The angle reported in each parenthesis is the approximate dihedral angle between that respective atom or group and the C-8a nitrile group in the ketonitriles or the bond at C-8a in the lactamol acetates.

exhibits a 0.24 ppm upfield shift from its position observed in the spectrum of **12**. Since this trend was also observed for the cyano steroid C-19 methyl groups,[19] the nmr evidence provides further support for the configurational assignments made for **6** and **12**.[21]

The configurations of the C-1 methyl groups were also determined from the nmr spectra. The two possible structures for *cis*-ketonitrile **12** are shown in Figure 2 as C and D (compare with structure B'). Of these, one might expect that structure C should be the less stable since it contains a severe 1,3-diaxial interaction between the two methyl groups.[22-24] Nonetheless, both C and D must be considered since the conditions of the reaction are not necessarily equilibrating, and it is well known that reactions of this type may yield the less stable isomer.[25]

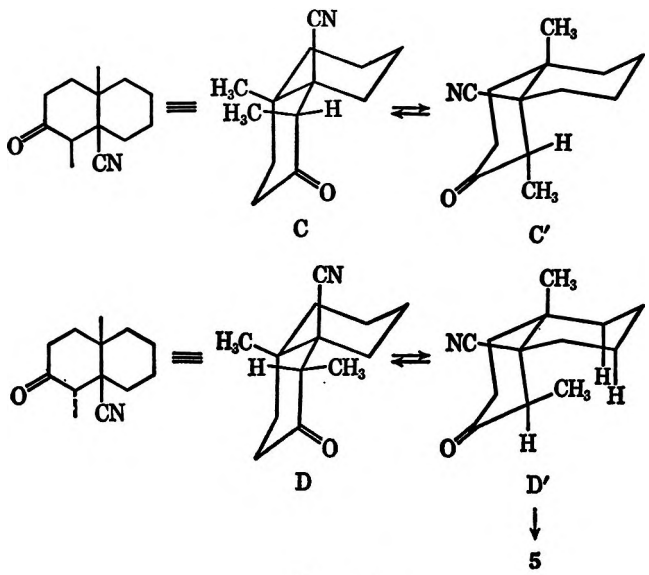
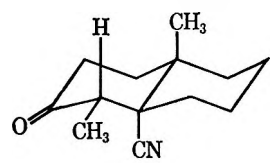


Figure 2

Since structures C and D have the flexible *cis*-decalin ring system, each can exist in the alternate conformations C' and D'. Fairly accurate estimates of the energy differences between these conformers can be obtained by considering the 1,2 and 1,3 interactions present in each. By applying values reported previously for such interactions,[24] it can be calculated that form C' should be about 2.2 kcal more stable than C, a value of sufficient magnitude to ensure almost complete exclusion of the latter conformation in an equilibrium mixture.[23] Thus, if C were the end product of the reaction, it would adjust itself to the more stable conformer C'. But C' (compare with structure B) has been ruled out by the dipole moment data; therefore, ketonitrile **12** must be represented by D.

Once the stereochemistry of ketonitrile **12** was established, it was possible to use this compound as a model to determine the shielding effects of the nitrile and carbonyl groups on the C-1 methyl and hydrogen substituents.[26] This information aided in the elucidation of stereochemistry of the *trans*-ketonitrile **6** as well as of compounds described in the subsequent publication.[4]

The fact that the C-1 methyl groups for both ketonitriles have essentially the same chemical shift (Table II) suggests that these groups probably lie in closely similar environments. Only if the C-1 methyl group in **6** is in an equatorial position as shown in E are such environmental conditions met with respect to the strongly anisotropic keto and nitrile groups.



E

These arrangements, on the other hand, necessarily place the two axial C-1 hydrogen atoms in different environments (compare D and E). Their relationships to the respective carbonyl groups remain the same, but in **6** the dihedral angle between the C-1 hydrogen atom and the nitrile group is 180°, while in **12** it is 60°. Consequently, the hydrogen atoms might reasonably be expected to exhibit different chemical shifts. A downfield shift of the C-1 hydrogen quartet in *cis*-ketonitrile

(20) Although it should be possible to calculate the magnitude of this difference from the known anisotropic shielding characteristics of the nitrile group [G. S. Reddy, J. H. Goldstein, and L. Mandell, *J. Amer. Chem. Soc.*, **83**, 1300 (1961)], recent work with 5-cyano steroids of established structure showed that additional factors of as yet undetermined origin are apparently involved.

(21) The observed chemical shift for the C-4a methyl group in the *cis* structure is also supported by dipole moment measurements on compounds discussed in the following paper (ref 4).

(22) The energy of a 1,3-diaxial dimethyl interaction has been reported to be about 3.7 kcal/mol [N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961)]. Since structure D contains a 1,3 interaction between the C-1 methyl group and the equatorial C-8 hydrogen atom which is absent in C, the actual energy difference involved will be 3.7 kcal minus one 1,3-diaxial methyl–hydrogen interaction, or about 2.9 kcal. The 2-alkyl ketone effect was assumed to be negligible (see references cited in ref 23).

(23) It can be likewise calculated that D is about 0.6 kcal more stable than C'. In these treatments, the 2- and the 3-alkyl ketone effects were considered to be negligible [B. Rickborn, *J. Amer. Chem. Soc.*, **84**, 2414 (1962); N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961), and ref 24a], as was possible dipole interaction between the nitrile and keto groups.

(24) (a) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962); (b) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962); B. Rickborn and F. R. Jensen, *ibid.*, 4606 (1962).

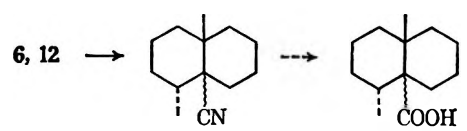
(25) For example, see (a) H. E. Zimmerman and T. W. Cutshall, *J. Amer. Chem. Soc.*, **81**, 4305 (1959); H. E. Zimmerman and A. Mais, *ibid.*, **81**, 3644 (1959); (b) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

(26) The C-1 hydrogen is easily identified because it is split into a quartet having the same *J* value as the C-1 methyl doublet.

12 as compared with that in the *trans* isomer is indeed observed in the spectra of these compounds (Table II).

With respect to the lactamols, the equatorial C-1 methyl group in ketonitrile **6** would be expected to retain this configuration during the hydrolysis to **4**.[27] On the other hand, ketonitrile **12** which also has the C-1 methyl group equatorial (structure D in Figure 3) must shift to conformer D′ in order to cyclize to the lactam. In doing so, however, severe interactions between the C-1 methyl group (which has now become axial) and the C-5 and C-7 hydrogen atoms arise. Should the methyl group epimerize before lactam formation takes place, then such interactions would be alleviated. Nevertheless, the conformation of the C-1 methyl group in lactamol **5** appears to be axial. Evidence for this assignment comes from the nuclear magnetic resonance spectra of lactamol acetates **9** and **10**, wherein the C-1 hydrogen peak in the former appears further upfield than does its counterpart (Table II). These hydrogens thus appear to be in different magnetic environments in the two compounds. Molecular models show that the only way that this condition is fulfilled ensues when the C-1 methyl group of **10** (and therefore of **5**) assumes an axial position.

In the course of this work, an attempt was made to elucidate the structures of ketonitriles **6** and **12** by converting them into the isomeric carboxylic acids **16a** and **b** and determining the structures of the latter by the method of Sommer and coworkers.[28] Although it was possible to remove the keto groups by Clemmensen reduction, subsequent hydrolysis of nitriles **15a** and **b** was unsuccessful, even under rather drastic conditions.



15a, b **16a, b**

These results, contrasted with the mild conditions required for the hydrolysis of the nitrile group in the ketonitriles themselves, demonstrate the importance of carbonyl participation in the hydrolysis reaction.[3c]

Experimental Section[29]

Potassium Cyanide Addition to 4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-2(3H)-naphthalenone (3). A. In Aqueous Ethanol.—A solution of 20.0 g (0.11 mol) of enone **3**[30] (n^{25}D 1.5250), 40.0 g (0.62 mol) of potassium cyanide, 800 ml of 95% ethanol and 80 ml of water was heated at reflux with stirring for 12 hr.[31] The reaction rate was monitored by periodic sampling and observing the decrease of the 248-mμ peak in the uv spectrum of **3**. The solvent was removed *in vacuo* and water was added to the remaining yellow semisolid. This mixture was extracted with ether and ethyl acetate, and the aqueous layer was acidified and further extracted in like manner. The combined extracts were dried and concentrated *in vacuo*, yielding 22.6 g of a colorless solid which was chromatographed on 600 g of florisil.[32]

Elution with benzene and benzene–ether (10:1, 5:1) afforded 0.63 g (3%) of enone **3** followed by 0.05 g (0.2%) of *trans*-ketonitrile **6** as colorless crystals, mp 90–100°, further raised to 100.5–102° by recrystallization from benzene–petroleum ether. Continued elution yielded an additional 0.21 g (0.9%) of impure ketonitrile **6** as an oil.

Benzene–ether (1:1) eluents gave 0.25 g (1% by weight) of solid **7** of unknown structure which was recrystallized from benzene, yielding colorless crystals, mp 203.5–204.5°, ir 3441, 3195, 3080, 1718, 1705 and 1685 cm^{-1}, the latter three bands as a broad triplet. Substance **7** was readily soluble in dilute sodium hydroxide solution but insoluble in hot water; it did not react with dinitrophenylhydrazine reagent[33a] on standing for 3 days.

Anal. Found: C, 67.90, 68.04; H, 8.48, 8.49; N, 5.81, 6.10; mol wt, 332 (Rast).[34]

Further elution with benzene–ether (1:1) gave 0.35 g of a mixture of compounds **4** and **7**, followed by a series of fractions totaling 4.9 g (20%) of lactamol **4** with melting points in the range 175–185°. Recrystallization of this product from benzene furnished colorless crystals: mp 191.5–192.5°, ir (chloroform) 3534 (OH), 3378 (NH), 1701 (sh) and 1689 (b, associated lactam C=O) and 1597 cm^{-1} (weak, $CONH_2$ amide II).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.79; H, 9.25; N, 6.25.

Continued elution with benzene–ether (1:1), ether and ether–ethyl acetate (9:1) afforded 2.09 g (8%) of a mixture of lactamols **4** and **5**, mp 148–167°, which could not be separated by recrystallization from benzene.

Additional elution with ether–ethyl acetate mixtures yielded fractions containing 13.7 g (55%) of lactamol **5** in various states of purity, most of which had mp 170–173°. Recrystallization of this material from benzene readily afforded colorless crystals, mp 172–173.5°, ir (chloroform) 3584 (OH), 3425 (NH), 1701 (sh) and 1686 (b, associated lactam C=O) and 1592 cm^{-1} (weak, $CONH_2$ amide II).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.08; H, 9.30; N, 6.54.

Lactamols **4** and **5** were insoluble in cold water, cold dilute sodium bicarbonate and hydrochloric acid solutions but soluble in hot water and cold aqueous sodium hydroxide. They gave negative tests for unsaturation.[33b] Lactamol **5** gave a negative xanthydrol test for primary amides[33c] and failed to absorb hydrogen at 60 psi with 10% palladium–carbon. Lactamol **5** could not be hydrolyzed with concentrated sulfuric acid at 25 and 85°, refluxing 10 and 50% aqueous sulfuric acid, refluxing 10 and 40% aqueous sodium hydroxide and 20% sodium hydroxide in ethylene glycol–water (6:1). With nitrous acid at 0°, lactamol **5** afforded a nitrogen-containing solid of unknown structure in 31% yield, having a melting point of 245–248° (decomposes with gas evolution) after several recrystallizations from ethyl acetate: ir 3125 (b), 3008, 1763 (b), 1700 (b) and 1683 cm^{-1} (sh, b).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.81, 61.45; H, 7.71, 7.51; N, 5.40.

Treatment of lactamols **4** and **5** with polyphosphoric acid at 180° gave a vigorous evolution of hydrogen cyanide and produced enone **3**, 29% from **5** and 17% from **4**, as well as a mixture of unsaturated hydrocarbons resulting from the action of the reagent on **3**.

A solution of lactamol **5** and 2,4-dinitrophenylhydrazine reagent,[33a] upon standing 2 days at room temperature, deposited yellow needles (54%) which were recrystallized from ethyl acetate: mp 221–223° (dec); uv max (chloroform) 276, 383 mμ (log ε = 4.294, 3.449) inflex 315 mμ (log ε = 3.214); ir 3311, 3086, 1721, 1613, 1589 (sh), 1526 (NO_2), 1493, 1464 and 1343 cm^{-1} (NO_2). The elemental analysis is in agreement with a

(27) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956); D. H. R. Barton, *Chem. Ind.* (London), 664 (1953); *J. Chem. Soc.*, 1027 (1953).

(28) P. F. Sommer, C. Pascual, V. P. Arya, and W. Simon, *Helv. Chim. Acta*, 1734 (1963).

(29) All melting points were determined in a heated oil bath and are corrected, while boiling points are uncorrected. The nmr spectra were determined in deuteriochloroform solution (unless specified otherwise) on a Varian A-60 spectrometer and chemical shift values are given in parts per million (ppm) measured downfield from tetramethylsilane used as an internal standard. The infrared spectra were determined in the solid state in a potassium bromide matrix (unless indicated otherwise) on a Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were obtained with a Perkin-Elmer Model 4000A Spectracord. Magnesium sulfate was usually employed to dry organic extracts, and the microanalyses were performed by Mrs. D. Ellis and Mrs. W. Coyne of this laboratory.

(30) M. Yanagita, M. Hirakura and F. Seki, *J. Org. Chem.*, **23**, 841 (1958).

(31) No reaction was observed when the solution temperature was maintained at 30° for 12 hr or when the water was omitted from a solution which was heated at reflux for 21 hr.

(32) Floridin Co., Talahassee, Fla., 60–100 mesh.

(33) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y. 1964: (a) p 126; (b) pp 121, 149; (c) p 256; (d) p 292.

(34) Althoubg the observed molecular weight value is low, the elemental analysis conforms to a dimer, $C_{26}H_{38-46}N_2O_4$. Dimeric species also have been isolated by other workers.[5,6,13]

TABLE III

HYDROLYSIS CONDITIONS FOR KETONITRILES 6 AND 12

		Hydrolysis conditions				Yields[a]		
			Media, ml		Reflux	Recovered	Ketone 3,	Lactamol	
Nitrile	Wt, mg	Reagent	EtOH (95%)	H_2O	time, hr	nitrile, mg (%)	mg (%)	mg (%)	Total %
6	261	3% KOH	32	1	1		110 (49)	43 (15)	64[b]
	250	3% $KHCO_3$	24	9	23		68 (31)	92 (34)	65[c]
	251	3% K_2CO_3	19	14	2	63 (25)	20 (9)	51 (19)	53[d]
	251	Concd. H_2SO_4[e]	0	0	0.7	182 (73)		40 (15)	88[c]
	251	3% HCl[f]	33	0	20	227 (91)			91[c]
	250	BF_3–HOAc[g]	0	0.8	2			168 (62)	62[b]
12	253	3% KOH	32	1	1		60 (27)	83 (30)	57[d]
	207	3% K_2CO_3	19	15	2	95 (46)	17 (9)	73 (32)	87[d]
	253	BF_3–HOAc[g]	0	0.8	2	34 (13)		225 (82)	95[c]

[a] Blanks indicate that none of that compound could be detected. Yields reported are those obtained before final purification. [b] Products isolated by chromatography on florisil. [c] Products isolated by fractional crystallization. [d] Products isolated by a combination of fractional crystallization and florisil chromatography. [e] 1.5 ml of concentrated sulfuric acid containing one drop of concentrated hydrochloric acid. Reaction conducted at 90°. [f] 3 ml of concentrated hydrochloric acid. [g] 7 ml of glacial acetic acid saturated with gaseous boron trifluoride.

formula obtained by combining **5** and 2,4-dinitrophenylhydrazine with the loss of *2* mol of water.

Anal. Calcd for $C_{19}H_{28}N_5O_4$: C, 59.21; H, 6.01; N, 18.17; mol wt, 385. Found: C, 58.99, 59.10; H, 6.01, 6.13; N, 18.04; mol wt, 383 (Rast).

No reaction was observed when the experiment was repeated with lactamol **4**.

One other reaction served to distinguish lactamol **5** from lactamol **4**. Only the former reacted with hot absolute ethanol containing a trace of concentrated sulfuric acid. The 3α-ethoxy derivative was formed in 60% yield and was recrystallized from ether: mp 158.5–160°; ir 3165 (NH), 3058 (lactam), 1686 (C=O) and 1078 cm^{-1} (C–O–C).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.62; H, 9.87; N, 5.61.

This substance was separated from unreacted lactamol **4** (30% recovery) by chromatography on florisil[32] and could be quantitatively hydrolyzed to the parent lactamol **5** in acetic acid containing a trace of concentrated hydrochloric acid.

B. In Aqueous Ethanol with Ammonium Chloride.[12]—A solution of 7.3 g (0.11 mol) of potassium cyanide and 5.3 g (0.098 mol) of ammonium chloride in 38 ml of water was added to 10.0 g (0.056 mol) of enone **3** in 35 ml of ethanol. The mixture was heated at reflux for 4 hr with stirring, the rate of the reaction being monitored by periodic ultraviolet sampling as described above for the untempered reaction. The solvent was removed *in vacuo* and the red residue was extracted with ethyl acetate then diluted with water and further extracted with ethyl acetate. The combined extracts were dried and concentrated, yielding 11.2 g of orange oil which was only partly resolved when chromatographed on Woelm[35] neutral or acidic alumina.

Nevertheless, separation was sufficient to allow the isolation of 0.04 g of starting material **3**, 1.70 g of *trans*-ketonitrile **6**, mp 99–101°, and 0.04 g of epimeric *cis*-ketonitrile **12**, mp 106.5–108°, by the fractional crystallization of certain fractions. The remaining fractions and mother liquors were combined and rechromatographed in two equal portions on florisil.[32] Elution with petroleum ether–benzene (9:1) gave 0.57 g of **3** (total recovery, 0.61 g, 6%) while petroleum ether–benzene (4:1, 1:1) eluted 2.01 g of *cis*-ketonitrile **12** for a total yield of 2.05 g (18%). Recrystallization from petroleum ether–benzene afforded colorless crystals: mp 107–108.5°; uv max 286 mμ (ε 20), ir 2232 (C≡N) and 1710 cm^{-1} (C=O); nmr[36] δ 1.16 (d, 3, J = 7 Hz, C-1 CH_3), 1.48 (s, 3, C-4a CH_3), 3.05 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.19; H, 9.55; N, 6.79.

Continued elution with petroleum ether–benzene (1:1), benzene and benzene–ether (9:1) produced 3.09 g of *trans*-ketonitrile **6** (total yield 4.79 g, 42%). Recrystallization of this material from petroleum ether–benzene yielded colorless crystals: mp 101–102°; uv max 286–288 mμ (ε 18); ir 2227 (C≡N) and 1706 cm^{-1} (C=O); nmr[36] δ 1.16 (d, 3, J = 7 Hz, C-1 CH_3), 1.24 (s, 3, C-4a CH_3), 2.50 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.28; H, 9.29; N, 6.58.

Final eluents composed of ethyl acetate and ethanol afforded 0.47 g (4%) of a mixture of lactamols **4** and **5**.

Hydrolyses of *cis*- and *trans*-Ketonitriles 6 and 12. General Procedures.—Table III presents the pertinent data for nine hydrolyses of two ketonitriles **6** and **12**. The reaction mixtures were processed as follows. The aqueous ethanol solutions were evaporated to dryness under reduced pressure and water was added to the residues prior to extraction. The concentrated sulfuric acid solution was diluted sevenfold with cold water before being extracted, while the boron trifluoride–acetic acid mixtures were made basic with 8 ml of 6 *N* sodium hydroxide solution prior to extraction. All extractions were made with both ether and ethyl acetate; the extracts were dried and concentrated *in vacuo* and the resulting residues were fractionated by either crystallization, chromatography on florisil[32] or by a combination of these two methods. The products of each reaction were carefully identified by comparison of their infrared spectra with those of authentic samples and by mixture melting points.

The Reaction of *trans*-Ketonitrile 6 with Potassium Cyanide in Ethanol.—A clear solution of 138 mg of ketonitrile **6**, 280 mg of potassium cyanide, 11.2 ml of absolute ethanol and 2.1 ml of water was heated at reflux with stirring for 48 hr. To follow the hydrolysis, infrared spectra were taken of aliquots removed from the reaction mixture at periodic intervals. The reaction mixture was extracted with ether and ethyl acetate and the combined extracts were dried and evaporated to dryness under reduced pressure. The colorless residue was chromatographed on florisil.[32] Benzene eluents afforded initially a trace of the enone **3**, then 7 mg (6%)[37] of *cis*-ketonitrile **12** contaminated with a trace of **3**. Further elution with benzene–ether (20:1) gave 15 mg (13%) of starting material **6**, also containing a trace of **3**. Benzene–ether (5:1) then furnished 6 mg (4% by weight) of the dimeric substance **7** of unknown structure. Continued elution with ether gave 38 mg (30%) of lactamol **4** and, finally, elution with ethyl acetate afforded 31 mg (25%) of the corresponding lactamol **5**.

Isomeric Naphthalenecarbonitriles 15a and b.—To 10 g of washed zinc amalgam, made from 10 g of granulated zinc, 15 ml of water, 0.5 ml of concentrated hydrochloric acid and 1.0 g of mercuric chloride,[38] were added in order 7.5 ml of water, 17.5 ml of concentrated hydrochloric acid, 10 ml of toluene and 0.93 g of a mixture consisting of approximately two parts of **6** and three parts of **12** (infrared). The reaction mixture was heated at reflux for 25 hr with the addition of 5-ml portions of concentrated hydrochloric acid after 13, 19 and 23 hr. The aqueous layer was separated from the cooled reaction mixture and extracted with ethyl acetate, saturated with sodium chloride and again extracted with ethyl acetate. These extracts were combined with the toluene layer and washed with 5% sodium

(35) Alupharm Chemicals, New Orleans, La.

(36) The chemical shift values for all doublets and quartets were measured at the geometrical midpoint between the peaks.

(37) The yields in this experiment are adjusted to correct for the removal of 21 mg of solid from the reaction medium during the infrared sampling. All products were identified by comparing their infrared spectra with those of authentic samples.

(38) E. L. Martin, *J. Amer. Chem. Soc.*, **58**, 1438 (1936).

hydroxide solution until the washings remained basic. The organic phase was dried and concentrated *in vacuo*, affording 0.82 g (95%) of a mixture of epimeric nitriles **15a** and **b** as a semisolid which showed strong nitrile absorption in the infrared spectrum and which readily dissolved in petroleum ether (bp 30–60°). No further purification was attempted.

Attempted Hydrolyses of Nitriles 15a and b.—Seven unsuccessful attempts were made to hydrolyze nitrile mixture **15a** and **b**. Hydrolysis conditions included 5% potassium hydroxide in ethanol–water (3:1), 29 hr reflux; concentrated hydrochloric acid, 25 hr reflux; 40% aqueous potassium hydroxide solution, 49 hr reflux; concentrated sulfuric acid, 15 min at 75°, then diluted with ethanol–water (1:4) to 10% acid concentration, followed by 34 hr reflux; anhydrous boron trifluoride–glacial acetic acid, 10 min at 120°, also 90 min at 120° followed by 30 min at 135°;[7] and 75% aqueous sulfuric acid, 1 hr at 155–180°. From each run only unreacted nitrile (infrared identification) was obtained in 82% average recovery. None of the procedures afforded acidic products.

Treatment of Lactamol 5 with Acetic Anhydride. A. At Room Temperature.[10]—A solution of 7 ml of acetic anhydride, 130 mg of *p*-toluenesulfonic acid monohydrate and 157 mg of lactamol **5** was stirred for 21 hr at 35°, then poured onto crushed ice and allowed to warm to room temperature. The resultant clear solution was extracted with ether, saturated with sodium chloride and again extracted with ether. The combined extracts were washed with saturated sodium bicarbonate solution until evolution of gas had ceased, dried and evaporated to dryness *in vacuo*. The colorless residue was chromatographed on florisil[32] whereby benzene–ether (20:1 to 1:1) eluents yielded 127 mg (68%) of lactamol acetate **10**, mp 160–162.5°, raised to 162–163° by one recrystallization from benzene. The product from a similar reaction exhibited mp 164–164.5°; ir 3205 (N–H), 3077 (lactam), 1744 ($CH_3C{=}O$), 1692 (lactam C=O), 1268 and 1229 cm^{-1} (b, –COO–); nmr[36] δ 0.95 (d, 3, J = 6.5 Hz, C-1 CH_3), 1.03 (s, 3, C-4a CH_3), 2.05 (s, 3, CH_3CO), 2.63 (qr, 1, J = 6.5 Hz, C-1 H).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.87; H, 8.74; N, 5.28. Found: C, 68.05; H, 8.57; N, 5.18.

Further elution with ether and ethyl acetate gave 23 mg (15% recovery) of starting material **5**, mp 135–160°, raised to 167.5–170.5° by one recrystallization from benzene.

The hydrolysis of acetate **10** was effected by refluxing 105.4 mg for 12 hr in 25.13 ml of 0.0393 *N* potassium hydroxide solution. Titration of the cooled mixture with 11.82 ml of 0.0488 *N* hydrochloric acid solution to a phenolphthalein end point furnished a saponification equivalent of 252 (theoretical 265). To isolate the reaction product, the solution was further acidified and extracted with ether and ethyl acetate prior to and after some concentration of the aqueous phase under reduced pressure. The combined extracts were washed with saturated sodium bicarbonate solution, dried and evaporated *in vacuo*. The residual oil crystallized when triturated with benzene–petroleum ether and afforded 52 mg (59%) of lactamol **5**, mp 169–172°, the ir spectrum of which was identical with that of an authentic sample.

Monoacetate **10** was also obtained during an attempt to hydrolyze lactamol **5** by heating it with anhydrous boron trifluoride–glacial acetic acid for 10 min at 120–125°.[7] The reaction mixture was processed as described above for the similar hydrolyses of ketonitriles **6** and **12**. Accordingly, from 109 mg of **5**, 58 mg (45%) of colorless monoacetate **10** was obtained, mp 150–156°, raised to 163–164.5° after two recrystallizations from benzene. A mixture melting point of this product with an authentic sample, mp 164–164.5°, was undepressed, and the infrared spectra of the two samples were identical.

B. At Reflux Temperature.—A mixture of 25 ml of acetic anhydride, 800 mg of *p*-toluenesulfonic acid monohydrate and 507 mg of lactamol **5** was heated at reflux for 24 hr. The resulting deep red reaction mixture was processed in the manner described above for the room temperature acetylation and yielded a brown oil which solidified on standing. The solid was chromatographed on florisil[32] whereby elution with benzene and benzene–ether (4:1) yielded 642 mg (92%) of lactamol diacetate **11** in several fractions having melting points in the range 119–125°. The fractions were combined and recrystallized from petroleum ether–benzene, yielding an analytical sample: mp 126–127°, ir 1751 (sh, CH_3CON–), 1736 (b, CH_3COO–), 1705 (lactam C=O), 1276, 1260, 1239 and 1217 cm^{-1} (b, –COO–); nmr[36] δ 0.89 (d, 3, J = 7 Hz, C-1 CH_3), 1.03 (s, 3, C-4a CH_3), 2.22 (s, 3, CH_3COO), 2.66 (s, 3, CH_3CON), 3.33 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.47; H, 7.92; N, 4.52.

Treatment of Lactamol 4 with Acetic Anhydride. A. At Room Temperature.—By employing the same conditions described above for the monoacetylation of lactamol **5**, 149 mg of lactamol **4** yielded 154 mg of monoacetate **9** as colorless crystals, mp 143–150°. On recrystallization from benzene, 133 mg (76%) of **9**, mp 155–160°, was recovered. Two additional recrystallizations from benzene raised the melting point to 158.5–160°: ir 3185 (NH), 3067 (lactam), 1736 ($CH_3C{=}O$), 1689 (lactam C=O), 1275, 1254 and 1229 cm^{-1} (b, –COO–); nmr[36] δ 0.88 (d, 3, J = 6.5 Hz), 1.07 (s, 3, C-4a CH_3), 2.08 (s, 3, CH_3CO), 2.40 (qr, 1, J = 6.5 Hz, C-1 H).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.87; H, 8.74; N, 5.28. Found: C, 68.12; N, 8.68; N, 5.43.

Another run employing 404 mg of **4** afforded 393 mg (82%) of **9**, mp 154–157°, which gave 306 mg (64%), mp 157.5–159.5°, when recrystallized from benzene.

The hydrolysis of monoacetate **9** was effected by the same procedure employed for monoacetate **10**. Thus, 101.5 mg of **9**, when heated at reflux for 12 hr in 25.12 ml of 0.0393 *N* potassium hydroxide solution and titrated with 12.35 ml of 0.0488 *N* hydrochloric acid solution to a phenolphthalein end point, furnished a saponification equivalent of 259 (theoretical 265). From this solution, 67 mg (78%) of lactamol **4** was recovered, mp 191–192.5°, which gave an undepressed mixture melting point with an authentic sample of **4**. The infrared spectra of the two were identical.

When lactamol **4** was treated with anhydrous boron trifluoride–glacial acetic acid[7] in the same manner described above for lactamol **5**, no acetylated products were obtained and the starting material was recovered.

B. At Reflux Temperature.—Under the same conditions employed for the diacetylation of lactamol **5**, 511 mg of lactamol **4** gave a dark oil which solidified on standing and was chromatographed on florisil.[32] Elution with benzene yielded a combined 620 mg (88%) of diacetate **8** as colorless crystals, mp 74–81°. When recrystallized from petroleum ether–benzene, this material afforded 496 mg (71%) of **8**: mp 82–85°; ir 1751 (sh, CH_3CON–), 1734 (b, CH_3COO–), 1706 (lactam C=O), 1282, 1264, 1247 (sh), 1233 (b) and 1214 cm^{-1} (b, –COO–); nmr δ 0.83 (d, 3, J = 7.5 Hz, C-1 CH_3), 1.19 (s, 3, C-4a CH_3), 2.20 (s, 3, CH_3COO), 2.65 (s, 3, CH_3CON), 3.01 (qr, 1, J = 7.5 Hz, C-1 H).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.62; H, 8.08; N, 4.36.

Further elution with benzene–ether (1:1) yielded no additional identifiable material.

TABLE IV

INFRARED INTENSITY MEASUREMENTS

Compd	Concn, mol/l. of $CHCl_3$	I_0	I	ϵ
6	1.226	89.2	45.9	18.7
6	0.768	93.1	59.7	19.9
6	0.360	95.1	76.3	21.1
12	1.292	91.9	29.2	30.6
12	0.813	91.2	40.3	34.6
12	0.380	96.1	64.6	36.1

Infrared Intensity Measurements.—Molar extinction coefficients were obtained for the C≡N stretching vibration of the two ketonitriles **6** and **12** using the data presented in Table IV. For each compound, three concentrations in chloroform were measured using a Perkin-Elmer Model 521 infrared spectrophotometer and a 0.0126-cm sodium chloride cavity cell[39] matched against a cavity cell containing chloroform in the reference beam. The region from 2300–2200 cm^{-1} was scanned at 14 cm^{-1}/min using a 10:1 scale expansion. The $\nu_{max}^{C\equiv N}$ for **6** and **12** is 2231 cm^{-1}.

Registry No.—Cyanide ion, 57-12-5; **3**, 878-55-7; **4**, 19292-09-2; **5**, 19292-10-5; 3α-ethoxy derivative of **5**, 19291-70-4; **6**, 19292-04-7; **8**, 19292-13-8; **9**, 19292-14-9; **10**, 19292-15-0; **11**, 19292-16-1; **12**, 19292-17-2.

(39) Connecticut Instrument Corp., Stamford, Conn.

Conformational Studies. III. Consequences of the Conjugate Addition of Cyanide Ion to Rigid Bicyclic Systems. B. Tetrahydro-1,4a-dimethyl-2-naphthalenone[1]

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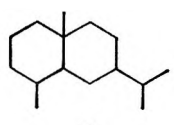
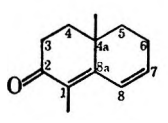
The dienone named in the title underwent both 1,6 and 1,4 addition when treated with potassium cyanide in aqueous ethanol. In the absence of ammonium chloride, the reaction yielded two lactamols; while in the presence of this salt the major products were three isomeric ketodinitriles. The structures of these substances were determined from their dipole moments and nuclear magnetic resonance spectra, used in conjunction with classical chemical correlations.

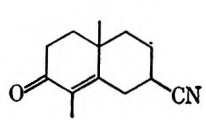
In studies conceived to investigate an improved route for the total synthesis of sesquiterpenes having eudesmane ring structure **1**, the feasibility of adding potassium cyanide in a 1,6 fashion across the tetrahydro-1,4a-dimethyl-2-naphthalenone system (**2**) was examined. The product from such an addition would be ketonitrile **3**, an interesting intermediate for the conduct of further transformations. Although 1,6 additions with ketone **2** have been reported previously, the yields have often been poor.[2] Furthermore, the nucleophiles were of the malonate type whereas our approach required the attachment of an intrinsically positive carbon to position 7. Thus the sterically small cyanide ion appeared to be an ideal nucleophile for our purposes.



1



2



3

The dienone and enone systems represented in **2** and **3**, respectively, have highly characteristic ultraviolet absorption spectra which provided a convenient method for monitoring the addition reactions. The 1,6 addition of potassium cyanide to ketone **2** was attempted in media both with and without the addition of ammonium chloride. In each case, the disappearance of the dienone chromophore signaled the occurrence of a reaction, but the expected enone absorption never appeared, indicating that ketonitrile **3** was not present in appreciable amount at any one time. Furthermore, the reactions were accompanied by considerable decomposition, but the products could nevertheless be easily isolated by careful chromatography.

In the absence of ammonium chloride, the reaction yielded lactomols **4** (42%) and **5** (6%), the structures (Scheme I) of which were supported by their infrared spectra (see Experimental Section).[3] Additional information on the structures of **4** and **5** was forthcoming from acetylation studies. By a method described previously,[1b] using an acetic anhydride–*p*-toluenesulfonic acid mixture, cyanolactamol **4** could be either mono- or diacetylated to give **7** and **8**, respectively. Amidolactamol **5** yielded monoacetyl derivative **9** when treated with this reagent at 35°. Under reflux temperatures however (diacetylation conditions), dehydration of the amide group occurred as well, giving diacetyl derivative **8**.

Two methods were used to hydrolyse the C-7 nitrile group of lactamol **4** to an amide function. The first employed boron trifluoride in acetic acid[4] and yielded the same acetylated amidolactamol **9** obtained from **5**. The second method used 90% sulfuric acid and gave a new amidolactamol **6**.[5]

To aid in the further elucidation of the above structures, it was desirable to obtain the corresponding dinitrile precursors. Dienone **2** was therefore treated with potassium cyanide in the presence of ammonium chloride.[6] Five substances were isolated: three ketodinitriles (**10**, **11** and **12**) in 3, 8 and 18% yields, respectively, 1% ketonitrile **13**, a trace of a ketonitrile of unknown structure, and 29% (by weight) uncrystallizable oil.[7] Unfortunately, ketonitrile **13** was obtained in sufficient quantity to allow its complete structural characterization.[8]

Each of the ketonitriles was hydrolyzed in 3% aqueous potassium carbonate. *trans* compounds **10** and **11** both gave the previously obtained lactamol **4** while *cis*-ketodinitrile **12** yielded a new cyanolactamol **17**. In addition, compound **11** was converted into ketal **16** which was then treated with potassium carbonate. Acid hydrolysis of the reaction product yielded ketodinitrile **10**. No epimerization at C-7 occurred during

(1) (a) Taken in part from the dissertation of Norman J. Johnston submitted for the Doctor of Philosophy degree, University of Virginia, 1963; (b) for part A of this series, see O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, **34**, 1942 (1969).

(2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Amer. Chem. Soc.*, **78**, 1416, 1422 (1956); P. Dutta, J. K. Chakrabarti, and P. C. Dutta, *Chem. Ind.* (London), 170 (1955); F. J. McQuillin, *ibid.*, 311 (1954); J. K. Chakrabarti, P. Dutt, and P. C. Dutta, *J. Chem. Soc.*, 4978 (1956); F. J. McQuillin, *ibid.*, 528 (1955); F. D. Gunstone and A. P. Tulloch, *ibid.*, 1130 (1955); J. R. Mahajan, P. Dutt, and P. C. Dutta, *ibid.*, 5069 (1957); T. Miki, *J. Pharm. Soc. Jap.*, **75**, 395 (1955); T. Harukawa, *ibid.*, **75**, 521 (1955); M. Matsui, K. Toki, S. Kiyamara, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Jap.*, **27**, 7 (1954); M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958).

(3) The spectrum of **4**, taken in dilute chloroform solution, exhibits what appears to be a concentration-dependent band in the amide II region, which may indicate a partial opening of the lactamol system. Lactamol **5** was found to be too insoluble to permit such a study.

(4) C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1448 (1955).

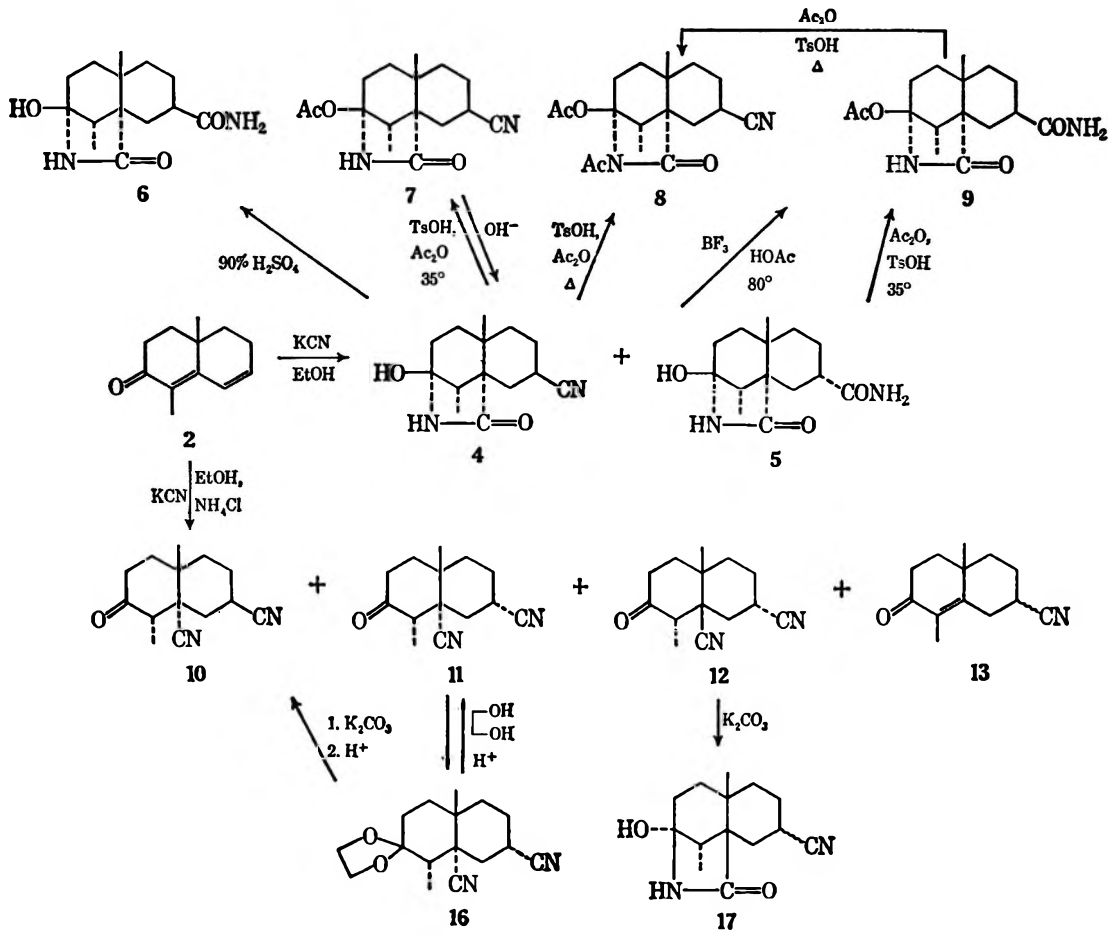
(5) Attempts to convert the amide group in lactamol **5** to a nitrile group using either phosphorus pentoxide or thionyl chloride were unsuccessful.

(6) W. Nagata, *Tetrahedron*, **13**, 278 (1961).

(7) Yields given have been corrected for 51% of recovered ketone **2**.

(8) This compound was isolated from the mother liquors obtained from the recrystallization of ketodinitrile **10** which contains an equatorial C-7 nitrile group. It is possible that **13** may have been formed from **10** by the β elimination of hydrogen cyanide, in which case the C-7 nitrile group should retain its equatorial configuration. Attempts to prepare **13** by heating **10** with silver nitrate in aqueous ethanol were unsuccessful.

SCHEME I



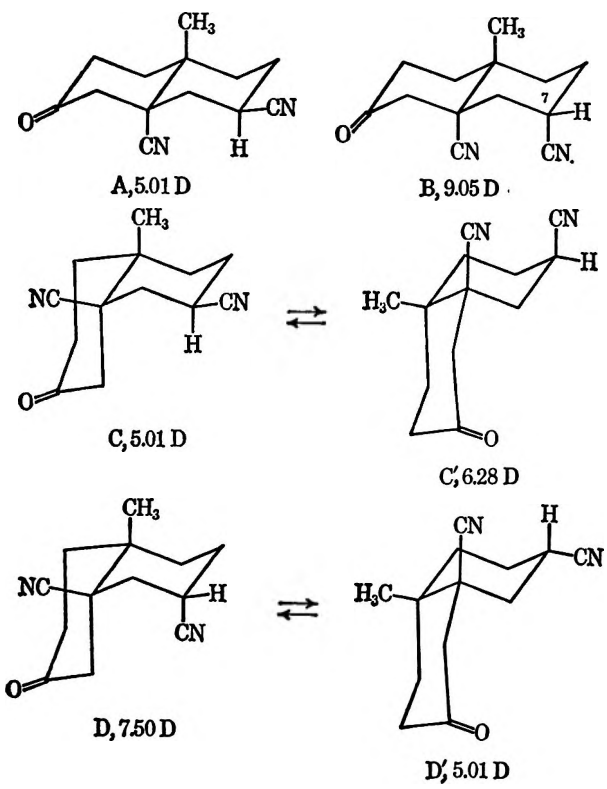


Figure 1

the ketalization process as was shown by the acid hydrolysis of **16** back to ketodinitrile **11**.

The ease with which the angular nitrile group is hydrolyzed in relation to the one at C-7 demonstrates the important role the carbonyl group plays in this reaction.[9] This is further illustrated in the epimerization study involving structure **16** which lacks the carbonyl group. The conditions used for this isomerization were the same as those which effected hydrolysis in the ketodinitriles.

Stereochemistry of Ketodinitriles 10, 11 and 12.—The elucidation of the stereochemistry of the products obtained from the cyanide addition reactions discussed above pivoted on the structure proofs of the ketodinitriles. The stereochemistry of each ketodinitrile was determined by nuclear magnetic resonance and dipole moment measurements. The structures possible for these compounds (neglecting for the moment the C-1 methyl group and boat or twist conformations of the cyclohexane rings) are shown in Figure 1.

The two isomers possible for the rigid *trans*-fused ring system are A and B, but for their counterparts in the flexible *cis*-fused systems (C and D) it is necessary to consider the alternate conformational forms C′ and D′ as well.[10]

The shielding effects of the carbonyl and C-8a nitrile groups on the C-1 hydrogen and the C-1 and C-4a methyl groups had been previously observed on ketonitriles **14** and **15** and a correlation was established between the chemical shifts of these groups and their

(9) *Cf.* ref 1b and references cited therein.

(10) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 231 ff.

TABLE I

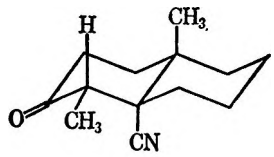
NMR DATA FOR THE KETODINITRILES AND KETONITRILES[a]

Compound	Ring juncture	C-4a methyl, ppm (angle, deg)[c]	C-1 methyl,[b] ppm (angle, deg)[c]	C-1 hydrogen,[b] ppm (angle, deg)[c]
Ketodinitrile **10**	*trans*	1.30 (180)	1.20 (60)	2.51 (180)
Ketodinitrile **11**	*trans*	1.23 (180)	1.18 (60)	2.49 (180)
Ketodinitrile **12**	*cis*	1.50 (60)	1.18 (60)	3.08 (60)
Ketonitrile **14**[d]	*trans*	1.24 (180)	1.16 (60)	2.50 (180)
Ketonitrile **15**[d]	*cis*	1.48 (60)	1.16 (60)	3.05 (60)

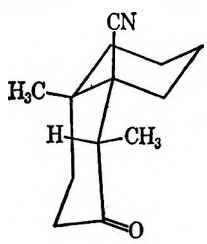
[a] The spectra were determined at 60 Mc in deuteriochloroform solutions using tetramethylsilane as an internal reference. The chemical shifts are measured from TMS (0 ppm) in the direction of decreasing field. [b] The geometrical center positions of the C-1 methyl doublet and the C-1 hydrogen quartet are reported. [c] The angle reported in each parentheses is the approximate dihedral angle which that respective atom or group makes with the C-8a nitrile group. [d] See ref 1b.

orientations with respect to the keto and nitrile groups (Table I).[1b] A similar analysis of the C-4a methyl positions in the three ketodinitriles **10, 11** and **12** thus makes it possible to determine whether they have a *cis*- or *trans*-fused ring system.

The data in Table I show that the C-4a methyl peaks of ketodinitriles **11** and **12** agree closely with those observed in *trans*- and *cis*-ketonitriles **14** and **15**,



14



15

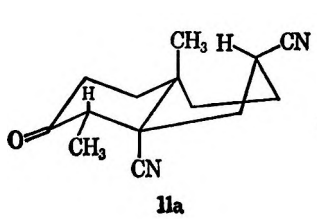
respectively, and thus allow the ring-juncture assignments to be made as shown. The agreement is less precise for ketonitrile **10**, but its value nevertheless corresponds considerably more closely with that of the *trans* rather than the *cis* structure (*cf.* also the C-1 proton values). That **10** and **11** do indeed have the same ring juncture stereochemistry has already been shown by the correlation of their structures through the ketal **16**, and by the conversion of both substances to lactamol **4**.

The configurations of the C-7 nitrile groups in compounds **10, 11** and **12** were determined by dipole moment measurements. The calculated dipole moments expressed in Debye units for the structures shown in Figure 1 are given below the formulas.[11] The experimentally determined dipole moments for the two *trans* compounds **10** and **11** were 4.96 ± 0.05 and 8.06 ± 0.08 D, respectively. Thus structure A is confirmed for ketonitrile **10**.

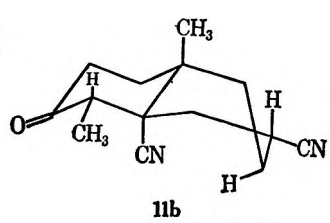
The low dipole moment value obtained for ketodinitrile **11** remains to be explained. If the ring containing the two nitrile groups exists in the traditional chair conformation, the nitrile groups are oriented 1,3 diaxially. Should sufficient dipole–dipole repulsion exist between these two groups, it may cause appreciable ring distortion or may even force the ring into a boat form.[12]

The two boat forms possible, **11a** and **11b**, should have similar free energies. Unfortunately, insufficient information is available on the energy parameters required for these systems to allow an accurate assessment of their relative stabilities. However, an *a priori* estimate might favor **11b** over **11a**, because the latter has the more severe bow–stern interaction (CH_3:H in **11a** *vs.* CN:H in **11b**). In support of this is a calculated[13] dipole moment of 8.10 D for conformation **11b**, in excellent agreement with the observed value. Nevertheless, definitive conclusions cannot be drawn as to the conformation of ketodinitrile **11** because of existing uncertainties as to the effects of mutual interactions of parallel dipoles in close proximity with each other.[14]

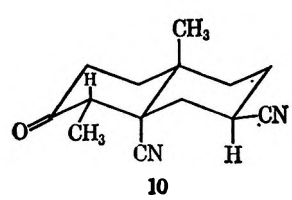
For ketodinitriles **10** and **11** the stereochemistry at C-1 remains to be assigned. This was made by comparing the chemical shifts of the C-1 hydrogen and methyl peaks with those of the corresponding *trans*-ketonitrile **14** where the C-1 methyl group has been shown to be equatorial.[1b] The values (Table I) clearly indicate that this group is also equatorial in ketonitriles **10** and **11**, allowing one to make the structural assignments shown in Scheme I.



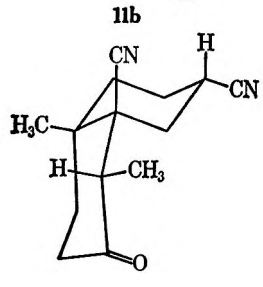
11a



11b



10



12

For *cis*-ketodinitrile **12**, the experimental dipole moment of 4.98 ± 0.05 D effectively eliminates structures C′ and D from consideration.[15] From the nmr spectrum of this compound (Table I), the peaks for

(11) The dipole moments were calculated using the cartesian coordinate values for the cyclohexylidene ring system as determined by E. J. Corey and R. A. Sneen [*J. Amer. Chem. Soc.*, **77**, 2505 (1955)] and the carbonyl and nitrile vector moments reported by J. M. Lehn, J. Levisalles, and G. Curisson [*Bull. Soc. Chim. Fr.*, 1096 (1963)] (see Experimental Section).

(12) Dreiding models show that if this ring is in a *twist* conformation, it involves some angle strain. It has also been calculated that in decalins having one ring a boat or twist form, the former should be more stable than the latter [J. Levisalles and J. C. N. Ma, *Bull. Soc. Chim. Fr.*, 1597 (1962)].

(13) This dipole moment was calculated using the atom positions as measure from a Dreiding model and is therefore probably less accurate than those obtained using the coordinate system method.

(14) *Cf.* C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, **28**, 1632 (1963).

(15) The ring containing the two 1,3-diaxial nitrile groups in structure C′ could prefer a boat conformation so as to relieve the dipole–dipole repulsion between these groups. However, the most stable structure should actually be C where both rings are in chair forms and the C-7 nitrile group is equatorial.

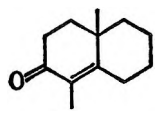
the C-1 methyl group (1.18 ppm) and the C-1 hydrogen (3.08 ppm) indicate that the dihedral angle each of these makes with the angular nitrile group is approximately 60°. Molecular models readily shown that only structure D′ (C-1 methyl equatorial *or* axial) satisfies these arrangements. Furthermore, only when the C-1 methyl group is assigned an equatorial position in D′ is its relationship to the carbonyl group the same as that in the other compounds cited in Table I. Hence, ketodinitrile **12** can be assigned the structure shown above.

Stereochemistry of Lactamols 4 and 17.—The hydrolysis of *trans* compounds **10** and **11** established the *trans* ring juncture of cyanolactamol **4.** Since the C-7 nitrile group in **4** would be expected to retain the more stable equatorial position, hydrolysis must have involved the epimerization of the axial C-7 nitrile group in **11.**[16] Likewise, the C-1 methyl group which is equatorial in both **10** and **11** would be expected to remain so in product **4.** This assignment is in accord with the nmr spectrum of the acetyl derivative **7** which exhibits the C-1 methyl and C-1 hydrogen multiplets centered at 0.91 and 2.41 ppm, respectively.[17]

Cyanolactamol **17** obtained from the hydrolysis of ketodinitrile **12** is assumed to have an axial C-1 methyl group by analogy with the corresponding lactamol obtained in the enone series.[1b] The configuration of the C-7 nitrile function in **17** remains uncertain. Molecular models show that if this group retains its original configuration, it will be axial and extremely close to the axial methyl group at C-1. In view of the slightly larger steric requirement for a nitrile group as compared to hydrogen[18] and the fact that the hydrolysis conditions are sufficient to cause expimerization at C-7, one is encouraged to favor an equatorial conformation for this group in this case.

Stereochemistry of Derivatives of Lactamols 4 and 5.—The stereochemistry at C-1, C-2, C-4a and C-8a is the same in both **4** and **5** as was shown by their conversion to the same acetate **9.** The hydrolysis product **6** obtained from cyanolactamol **4** should also have the same stereochemistry at these centers. Therefore, compounds **5** and **6** must be epimeric at C-7. In the hydrolysis using 90% sulfuric acid, the relatively bulky amido group in **6** would be expected to retain its equatorial configuration. On the other hand, the conditions employed during the acetylation of amidolactamol **5** can be expected to effect epimerization of an amido group axial at C-7.[19] Hence, this group in lactomol **5** is assigned an axial configuration.[20]

Mechanistic Notes.—The products obtained from the addition of potassium cyanide to conjugated dienone **2** show that 1,6 addition must occur first, followed by a rapid 1,4 addition. The observed disappearance of the dienone chromophore in the ultraviolet spectrum of the reaction mixture as addition proceeded without concomitant increase in the absorption of the enone chromophore supports such a mechanism.[21] A rough measure of the rates of the potassium cyanide additions to both dienone **2** and enone **18** was obtained by quantitatively



18

sampling the reaction mixtures at periodic intervals and observing the respective decreases of the absorption peaks with time (247 mμ for the enone and 287 mμ for the dienone). The results indicate that under the conditions investigated, the rates of addition to the enone **18** were about the same in both the presence and absence of ammonium chloride, being approximately 0.4 l. mol^{-1} hr^{-1}. Furthermore, the rates of 1,6 addition to dienone **2** in the presence and absence of ammonium chloride were 10 and 2.5 times slower, respectively, than were the 1,4 additions to enone **18.** Consequently, the 1,6 addition step appears to be the rate-determining one. The reversibility of the steps in this sequence precludes any discussion of the stereochemistry of these conjugate additions.

Experimental Section[22]

Potassium Cyanide Addition to 4,4a,5,6-Tetrahydro-1,4a-dimethyl-2-(3H)-naphthalenone (2). A. In Aqueous Ethanol.—A solution of 4.0 g (0.023 mol) of dienone **2** ($n^{25}D$ 1.5660),[23] 8.0 g (0.123 mol) of potassium cyanide, 160 ml of 95% ethanol and 16 ml of water was heated at reflux with stirring for 12 hr. The solvent was removed *in vacuo* and the remaining orange oil was diluted with water, extracted with ethyl acetate, saturated with sodium chloride and extracted continuously for 24 hr with ethyl acetate. The combined extracts were dried, the solvent was removed *in vacuo* and the 4.5 g of orange semisolid remaining was chromatographed on Florisil.[24]

Benzene and benzene–ether (10:1) eluents yielded 0.42 g (4%) of unreacted dienone **2** while benzene–ether (1:1), ether and ether–ethyl acetate (5:1) eluted 2.37 g (42%) of cyanocal-

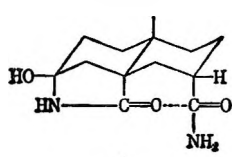
(16) As indicated previously, such an epimerization occurs under these conditions in the conversion of ketodinitrile **11** to **10** *via* the ketal **16.**

(17) Compare with the values observed for these groups in the monoacetates of lactamols **4** and **5** in ref 1b.

(18) N. L. Allinger and W. Sykrybalo, *J. Org. Chem.*, **27**, 4601 (1962); B. Rickborn and F. R. Jensen, *ibid.*, 4606 (1962).

(19) B. Rickborn and F. R. Jensen, *J. Org. Chem.* **27**, 4608 (1962), and references cited therein.

(20) The stereochemistry given for the C-7 substituents in all compounds except **10, 11, 12** and **16** is that which is considered to be the most likely from the available evidence and partly rests on the assumption that the substituent is the more stable in an equatorial position. It is conceivable, however, that an axial C-7 amido group might be stabilized through intramolecular bonding of the type shown in i. A similar argument can be applied to lactamol **4.** Infrared dilution studies carried out on amidolactamols **5** and **6** in dioxane were inconclusive with respect to this point.



i

(21) Patents issued to A. Bowers and H. J. Ringold describe the 1,6 addition of cyanide ion to a variety of 3-keto $\Delta^{4,6}$ steroids. It is reported that potassium cyanide in absolute or 95% ethanol at reflux for 2.5 hr afforded the 7α- and 7β-cyano epimers. No other reaction products or yields are described [U.S. Patents 3,050,534 (August 21, 1963) and 3,099,664 (July 30, 1963).

(22) All melting points were determined in a heated oil bath and are corrected, while boiling points are uncorrected. The nmr spectra were determined in deuteriochloroform solution (unless specified otherwise) on a Varian A-60 spectrometer and chemical shift values are given in parts per million (ppm) measured downfield from tetramethylsilane used as an internal standard. The infrared spectra were determined in the solid state in a potassium bromide matrix (unless indicated otherwise) on a Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were obtained with a Perkin-Elmer Model 4000A Spectracord. The microanalyses were performed by Mrs. D. Ellis and Mrs. W. Coyne of this laboratory.

(23) D. K. Banerjee and V. B. Angadi, *J. Org. Chem.*, **26**, 2988 (1961).

(24) Floridin Company, Tallahassee, Fla., 60–100 mesh.

tamol **4** which was recrystallized from ethyl acetate to give 1.46 g (26%) of colorless crystals, mp 210–214°. Further recrystallization from ethyl acetate raised the melting point to 215–216°; ir 3420 (OH), 3176 (NH), 3058 (sh, b, lactam), 2232 (C≡N) and 1681 cm^{-1} (lactam C=O); ir (chloroform) 3534 (OH), 3390 (NH), 2232 (C≡N), 1698 (lactam C=O) and 1597 cm^{-1} ($-CONH_2$ amide II); no selective ultraviolet absorption was observed above 220 mμ with a 1% ethanol solution.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28; mol wt, 248. Found: C, 67.65; H, 8.25; N, 11.47; mol wt, 248 (Rast).

Cyanolactamol **4** was insoluble in hot water, hot 5% sodium bicarbonate solution, and hot 10% hydrochloric acid solution but was soluble in cold 10% sodium hydroxide solution, and failed to react with dinitrophenylhydrazine reagent.[25a]

Further elution with ethyl acetate gave 0.08 g (2% by weight) of a water-soluble solid of unknown structure, mp 220–248° dec, which crystallized from ethyl acetate as a colorless solid: mp 248–256° dec; ir 3441, 3349, 3199, 3090 (sh), 2247, 1723 (sh, b) and 1678 cm^{-1} (b); unsaturation tests were negative.[25b]

Anal. Found: C, 60.87; H, 7.19; N, 10.42; mol wt, 297 (Rast).

Finally, elution with acetone yielded a water-soluble brown solid which was washed with ethyl acetate, yielding 0.20 g (3%) of amidolactamol **5** as colorless crystals: mp 250–252° dec; ir 3391 (OH, NH_2), 3206 (NH, NH_2), 3102 (lactam), 1690 (lactam C=O), 1657 (b, C=O amide I) and 1599 cm^{-1} (NH_2 amide II); no selective ultraviolet absorption was observed above 220 mμ with a 1% ethanol solution; nmr[26] (DMSO-d_6) δ 0.78 (d, 3, J = 7 Hz, C-1 CH_3), 0.97 (s, 3, C-4a CH_3), 6.50 (s, 1, NH), 7.27 (s, 2, NH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.42; H, 8.51; N, 10.56.

Recrystallization of amidolactamol **5** from isopropyl alcohol–petroleum ether gave a colorless solid containing alcohol of crystallization. Its melting point in an open capillary was below 200° but on further heating the sample resolidified and melted again at 251–252.5° dec. Drying *in vacuo* at 140° for 24 hr removed the solvent of crystallization.

A combined 0.66 g (16.5% by weight) of unidentifiable highly colored oils were also obtained at several points in the elution spectrum of the above chromatogram.

When the above experiment was scaled up 2.5 times and a 19.5-hr reflux period was employed, the following yields were obtained: dienone **2**, 8%; cyanolactamol **4**, 26%; amidolactamol **5**, ≤%; a lactamol derived from enone **18**,[27] 0.7%; and unidentifiable highly colored oils, 14% by weight. The reaction rate was monitored by removing aliquot parts of the reaction solution at periodic intervals and observing the decrease of the 288-mμ absorption maximum in the ultraviolet spectrum of dienone **2**.

B. In Aqueous Ethanol with Ammonium Chloride.—A solution of 10.00 g (0.0567 mol) of dienone **2**, $n^{28}D$ 1.5660, in 100 ml of 95% ethanol was added to a solution of 14.75 g (0.227 mol) of potassium cyanide and 10.60 g (0.198 mol) of ammonium chloride in 100 ml of water. The mixture was heated to the reflux temperature and clarified with an additional 50 ml of ethanol–water (3:2 v/v). After 6 hr, the concentrations of both salts were doubled and the heating at reflux was continued for another 8.5 hr. The rate of conjugate addition was followed by periodic ultraviolet sampling as previously described for the untempered reaction. The solvent was removed *in vacuo* and the brown residue was extracted with ethyl acetate, diluted with water and extracted continuously with ethyl acetate for 24 hr. The combined extracts were dried and the solvent was removed *in vacuo* leaving 10.8 g of dark oil which was chromatographed on Florisil.[24] Elution with benzene and benzene–ether (20:1) yielded 4.04 g of starting material **2**. Benzene–ether (20:1, 5:1) eluents gave 2.17 g of white semisolid which was separated by crystallization from benzene into 1.04 g of dienone **2** (51% total recovery) and 1.13 g (18%)[28] of ketodinitrile **12**, mp 149.5–151°. A recrystallization of **12** from benzene yielded the substance as colorless needles: mp 152–152.5°; uv max 287.5 mμ (ε 19); ir 2242 (C≡N) and 1721 cm^{-1} (C=O); nmr[26] δ 1.18 (d, 3, J = 7 Hz, C-1 CH_3), 1.50 (s, 3, C-4a CH_3), 3.08 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.98; H, 7.94; N, 12.14.

Continued elution with benzene–ether (5:1) and ether produced a white solid which was recrystallized from benzene, giving 0.21 g (3%)[28] of ketodinitrile **10**, mp 214–226°. Further recrystallization from benzene raised the melting point to 225–228°; ir 2237 (C≡N) and 1706 cm^{-1} (C=O); nmr[26] δ 1.20 (d, 3, J = 7 Hz, C-1 CH_3), 1.30 (s, 3, C-4a CH_3), 2.51 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.90; H, 8.13; N, 11.99.

The mother liquor yielded 68 mg (1%)[28] of cyanoenone **13**, mp 90–150°. Recrystallization of this material from carbon tetrachloride gave colorless crystals: mp 97–98°, uv max 244.5 mμ (log ε = 4.119); ir 2237 (C≡N), 1664 (C=O) and 1612 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.87; H, 8.29; N, 7.06.

Elution with ether and ether–ethyl acetate (7:1) yielded 0.18 g of colorless crystals which, after recrystallization from ethyl acetate, gave 30 mg of a ketonitrile of unknown structure: mp 203–204°; ir 3483, 3344, 2235 and 1700 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.82; H, 8.24; N, 6.24.

It formed a yellow dinitrophenylhydrazone the infrared and qualitative uv spectra of which were similar to those expected of a dinitrophenylhydrazone of a saturated ketone.

After ether–ethyl acetate (7:1, 1:1) had removed 0.44 g (4% by weight) of dark red oil which resisted all attempts at crystallization, ether–ethyl acetate (1:1) and acetone eluted 0.76 g of brown solid which was recrystallized several times from ethanol, yielding 0.48 g (8%)[28] of ketodinitrile **11** as colorless plates: mp 182.5–183.5°; ir 2237 (C≡N) and 1704 cm^{-1} (C=O); nmr[26] δ 1.18 (d, 3, J = 7 Hz, C-1 CH_3), 1.23 (s, 3, C-4a CH_3), 2.49 (qr, 1, J = 7 Hz, C-1 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.83; H, 7.90; N, 12.20.

Further elution with acetone gave 1.00 g (10% by weight) of dark red oil which failed to crystallize.

Hydrolysis of Ketodinitrile 12.—Ketodinitrile **12** (250 mg) was added to a boiling solution of 1.0 g of potassium carbonate in 20 ml of 95% ethanol and 14 ml of water. The mixture was heated at reflux for 2 hr, evaporated *in vacuo* and extracted with ethyl acetate. When the combined extracts were dried and evaporated *in vacuo*, 207 mg (77%) of solid remained which was triturated with ether yielding 178 mg (66%) of cyanolactamol **17**, mp 208–230°. Recrystallization of this material from ethanol raised the melting point to 254–257° dec; ir 3333 (OH), 3190 (b, NH), 2242 (C≡N) and 1664 cm^{-1} (b, lactamol C=O).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.41; H, 8.39; N, 11.25.

Hydrolysis of Ketodinitrile 10.—Using the procedure given above for ketodinitrile **12**, 34 mg of **10** produced 33 mg of solid which was chromatographed on Florisil.[24] Elution with benzene gave 4.4 mg (15%) of impure ketonitrile **13**, uv max 244 mμ (ε 5900). Ethyl acetate eluents afforded 18 mg (49%) of cyanolactamol **4**, mp 208–211°, whose infrared spectrum was identical with that of authentic **4**. Recrystallization of this material from ethyl acetate raised the melting point to 214–215° and a mixture melting point with authentic **4** was undepressed.

Hydrolysis of Ketodinitrile 11.—Following the above procedure, 84 mg of **11** gave 70 mg of oil which was chromatographed on Florisil.[24] Again, two major fractions were obtained. Elution with benzene yielded 17 mg (23%) of ketonitrile **13**, uv max 244 mμ (ε 8400), the infrared spectrum of which indicated that about 20% starting material **11** was also present. Ether and ethyl acetate eluents gave 36 mg (40%) of cyanolactamol **4** whose infrared spectrum was identical with that of authentic **4**. One recrystallization of this material from ethyl acetate raised the melting point to 214–215° and a mixture melting point with authentic **4** was undepressed.

Treatment of Cyanolactamol 4 with Acetic Anhydride. A. At Room Temperature,[29] Cyanolactamol Acetate (7).—A solution

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964: (a) p 126; (b) pp 121, 149.

(26) The chemical shift values for all doublets and quartets were measured at the geometrical midpoint between the peaks.

(27) This material was formed from a small amount of enone **18** impurity in the starting material ($n^{28}D$ 1.5651), and is lactamol **5** in ref 1b.

(28) Yields are adjusted for recovered starting material.

(29) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *J. Amer. Chem. Soc.*, **74**, 5394 (1952).

of 99 mg of cyanolactamol **4**, 90 mg of *p*-toluenesulfonic acid monohydrate and 5 ml of acetic anhydride was stirred at 35° for 24 hr, cooled, poured onto crushed ice and allowed to warm to room temperature. The resultant clear solution was extracted with ether, saturated with sodium chloride and further extracted with ether. The combined extracts were washed with saturated sodium bicarbonate solution until evolution of gas had ceased, dried and the solvent removed *in vacuo*. The residue consisted of 114 mg of cyanolactamol acetate **7** as colorless crystals, mp 180–185°. When this material was recrystallized from benzene 88 mg (76%) was recovered: mp 185.5–186.5°; ir 3333 (N–H), 2237 (C≡N), 1730 (CH_3C=O), 1709 (lactam C=O), 1259, 1225 and 1212 cm^{-1} (CH_3COO–); nmr[26] δ 0.91 (d, 3, J = 7 Hz, C-1 CH_3), 1.10 (s, 3, C-4a CH_3), 2.07 (s, 3, CH_3CO), 2.41 (qr, 1, J = 7 Hz, C-1 H), 5.15 (s, 1, NH).

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65; mol wt, 290. Found: C, 65.89; H, 7.51; N, 9.85; mol wt, 286 (Rast).

Hydrolysis was carried out by heating at reflux 109.6 mg of **7** for 12 hr in 25.24 ml of 0.0393 *N* potassium hydroxide solution. Titration of the cooled mixture with 12.12 ml of 0.0488 *N* hydrochloric acid solution to a phenolphthalein end point furnished a saponification equivalent of 268 (theoretical 290). To isolate the reaction product, the solution was acidified and extracted with ethyl acetate both before and after concentration *in vacuo*. The combined extracts were washed with saturated sodium bicarbonate solution, dried and the solvent removed *in vacuo*. Upon trituration with ethyl acetate–petroleum ether (bp 30–60°), the residual oil gave 34 mg (36% recovery) of cyanolactomol **4** mp 214–215°, the infrared spectrum of which was identical with that of an authentic sample of **4**.

B. At Reflux Temperature. Cyanolactamol Diacetate (8).—A solution of 0.51 g of cyanolactamol **4**, 0.80 g of *p*-toluenesulfonic acid monohydrate and 25 ml of acetic anhydride was heated at reflux for 24 hr. The resulting dark solution was processed in the manner described above for the room temperature acetylation, yielding a dark oil which solidified on standing. This material was chromatographed on Florisil[24] where elution with benzene and benzene–ether (1:1) gave 0.48 g (71%) of the cyanolactamol diacetate **8** in several fractions melting over a range of 149–156°. Recrystallization from ethyl acetate–petroleum ether gave **8** as light yellow plates: mp 156–157°; ir 2242 (C≡N), 1739 (sh, CH_3CON–), 1727 (b, CH_3COO–), 1708 (b, lactam C=O) and 1274, 1261, 1245 (sh), 1235–1217 (b, doublet) and 1203 cm^{-1} (sh, CH_3COO–).

Hydrolysis of Cyanolactamol 4. A. With 90% Sulfuric Acid.[30] Amidolactamol 6.—A solution of 510 mg of **4** and 15 ml of 90% sulfuric acid was heated with stirring for 1 hr at 125°. The yellow reaction mixture was poured onto crushed ice, warmed to room temperature and the resultant solution extracted with ethyl acetate. The aqueous layer was then carefully neutralized with dilute base, extracted with ethyl acetate, evaporated to dryness *in vacuo* and again extracted with ethyl acetate. The combined extracts were dried and evaporated *in vacuo* yielding an oil. Trituration of the oil with acetone yielded 100 mg (19%) of amidolactamol **6** as colorless crystals, mp 238–242° dec, with gas evolution, and also gave a filtrate containing 150 mg of oil (further treated as described below). Recrystallization of the former product from isopropyl alcohol gave crystalline **6**: mp 244–245° dec; ir 3448 (OH), 3226 (very b, NH_2, NH, lactam), 1717 (lactam C=O), 1656 (b, amide I C=O) and 1609 cm^{-1} (sh, amide II NH_2); nmr[26] (DMSO-d_6) δ 0.78 (d, 3, J = 7 Hz, C-1 CH_3), 0.97 (s, 3, C-4a CH_3), 7.37 (s, 2, NH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.29; H, 8.34; N, 10.61.

The dry salt remaining from the above trituration was extracted with acetone giving 0.29 g of oil which was combined with the oil from the above filtrate and triturated with isopropyl alcohol. An additional 184 mg (34%) of **6** was obtained in several crops having melting point ranges from 232–238° dec.

B. With Boron Trifluoride–Acetic Acid.[4] Amidolactamol Acetate (9).—Cyanolactamol **4** (0.15 g) was added to 2 ml of glacial acetic acid saturated with boron trifluoride. The solution was heated for 10 min at 120°, cooled, carefully neutralized with 10% sodium hydroxide solution, extracted with ethyl acetate, then made alkaline with dilute base and again extracted with ethyl acetate. The combined extracts were dried and the solvent was evaporated *in vacuo* yielding an oil. When this material was triturated with ethyl acetate–petroleum ether, 0.14 g (75%) of the amidolactamol acetate **9** was obtained as a colorless solid, mp 214–222°. Recrystallization of this solid from acetone followed by filtration through Florisil[24] in ethyl acetate gave rise to apparently less pure material, mp 200–207°, the infrared spectrum of which was poorly resolved. However, when this material was recrystallized from acetone–petroleum ether, colorless crystals were obtained: mp 216–219°; ir 3465 (OH), 3367 (b, NH_2), 3185 (NH_2, NH), 3086 (lactam), 1734–1704 (b, lactam C=O, CH_3C=O), 1664 (amide I C=O), 1621 (amide II NH_2), 1254, 1221, 1213 and 1202 cm^{-1} (CH_3COO–).

Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.31; H, 7.84; N, 9.09. Found: C, 62.07; H, 7.72; N, 9.25.

Acetylations of Amidolactamol 5.—A solution of 0.23 g of **5**, 0.17 g of *p*-toluenesulfonic acid monohydrate and 10 ml of acetic anhydride was stirred at 35° for 24 hr,[29] then poured onto crushed ice and allowed to reach room temperature. The solution containing suspended crystalline material was extracted with ethyl acetate, saturated with sodium chloride and again extracted with ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate solution, dried, and the solvent evaporated *in vacuo*, yielding 0.22 g of a yellow solid. This was recrystallized from ethyl acetate giving 0.13 g (46%) of compound **9** (ir spectrum), mp 211–220°. This colorless solid could not be purified by further recrystallization from ethyl acetate so 91 mg of the substance were heated at reflux for 24 hr with 200 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of acetic anhydride. The reaction mixture was poured onto crushed ice, allowed to warm to room temperature and extracted with ethyl acetate. The extracts were washed with 5% sodium hydroxide solution, dried and the solvent removed *in vacuo*. There remained 90 mg of yellow solid which was recrystallized several times from ethyl acetate, giving 21 mg (21%) of the diacetate **8**, mp 157.5–158°. A mixture melting point of this material with **8**, mp 156–157°, produced by the action of refluxing acetic anhydride on cyanolactamol **4**, was undepressed, and the infrared spectra were identical.

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.85; H, 7.32; N, 8.36.

Preparation of the Ketodinitrile Ketal 16.—A mixture of 68.0 mg of ketodinitrile **11**, 500 mg of ethylene glycol, a few small crystals of *p*-toluenesulfonic acid, and 5 ml of benzene was placed in a flask attached to a Dean–Stark water trap filled with benzene and heated at reflux for 5 hr. The mixture was cooled, 5 ml of ethyl acetate was added, and the solution was then washed in a centrifuge tube with saturated sodium bicarbonate solution and with water. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. There remained 81.2 mg (98%) of crude ketal **16**, mp 204–209°. Repeated recrystallization from benzene raised the melting point to 220–224° with previous sintering at 216°: ir 2850, 2210 (C≡N), 1440, 1100, 1080, 1045, 953, 927, 900 and 685 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.98; H, 8.68; N, 11.00.

A mixture of 6 mg of the ketal **16**, 3 ml of ether and 3 ml of 3 *N* hydrochloric acid was stirred magnetically for 15 min. The mixture was transferred to a centrifuge tube and the aqueous layer removed with a dropper. The organic layer was washed thoroughly with water and dried over anhydrous sodium sulfate. Removal of the ether *in vacuo* left 3 mg of solid, the infrared spectrum of which was identical with that of ketodinitrile **11**.

Conversion of the Ketodinitrile Ketal 16 into the Ketodinitrile 10.—Potassium carbonate (1 g) was dissolved in a boiling solution of 20 ml ethanol and 14 ml water. A 5-ml sample of this solution was added to 47.6 mg of ketal **16** and the homogeneous mixture was heated at reflux for 2 hr. The solvent was removed *in vacuo* and the residue was triturated with water and filtered. The colorless solid remaining on the filter was washed several times with water and dried, yielding 32.1 mg of material, the infrared spectrum of which indicated that a small amount of ketal hydrolysis had occurred.

Therefore, this product was not further purified but rather was dissolved in 10 ml of ether and hydrolyzed with 7 ml of 3 *N* hydrochloric acid using the procedure described earlier. A colorless solid was obtained which was chromatographed on Florisil. Pure benzene eluted a small amount of oil which was not further identified, while elution with 100% ether yielded a combined

(30) W. J. Hickenbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1957, pp 382–383.

TABLE II

THEORETICAL DIPOLE MOMENT CALCULATIONS[a]

	Coordinates[b]			Factor	Directed moments		
	x_i	y_i	z_i	k_i	k_ix_i	k_iy_i	k_iz_i
Carbonyl oxygen	−0.732	0	0.258	3.8524	−2.8200	0	0.9939
Axial nitrile at c or e (as in **10a** or **12**, form D)	−0.031	±0.049	1.09	3.4538	−0.1071	±0.1692	3.7646
Equatorial nitrile at c, c′ or e (as in **10a**)	0.577	±0.886	−0.300	3.4302	1.9792	±3.0392	−1.0291
Axial nitrile at d′ (as in in **12**, form D)	−1.04	0	−0.313	3.4712	−3.6100	0	−1.0865

[a] All values except coordinates are in Debye units. [b] Origin at carbon atom bearing the substituent. Coordinates refer to those of attached hydrogen atoms and therefore define the bond directions necessary for the calculation of the dipole moments by the described method.

weight of 28.1 mg (72%) of colorless solid which proved to be identical with ketodinitrile **10** as evidenced by their infrared spectra and melting points. Further elution with 100% acetone gave an additional small amount of noncrystalline material, the infrared spectrum of which indicated that it was possibly a mixture of ketodinitriles **10** and **11**.

Theoretical Dipole Moment Values. A. Method.—Theoretical dipole moments were calculated for all the possible configurations of the two ketonitriles **14** and **15** and the three ketodinitriles **10**, **11** and **12**.[31] The bond moments (μ_i) are the magnitudes of the individual group dipoles ($\vec{\mu_i}$). For each group, a vector ($\vec{p_i}$) can be defined in terms of the local coordinates of Corey and Sneen[11] (x_i, y_i, z_i) for substituents on a cyclohexylidene ring. This vector acts parallel to the dipole vector ($\vec{\mu_i}$) and the magnitude of $\vec{p_i}$ is related to the magnitude of $\vec{\mu_i}$ by

$$|\vec{\mu_i}| = k_i |\vec{p_i}| \quad (1)$$

The factor k_i is calculated (for each group) from the relationship

$$k_i = \frac{|\vec{\mu_i}|}{|\vec{p_i}|} = \left(\frac{\mu_i^2}{x_i^2 + y_i^2 + z_i^2}\right)^{1/2} \quad (2)$$

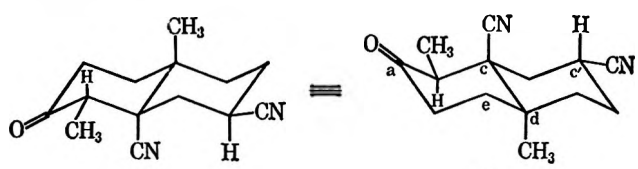
The components of $\vec{\mu_i}$ along the coordinate axes (directed moments) are then given by (k_ix_i, k_iy_i, k_iz_i) and the magnitude of the resultant dipole moment (μ) for the molecule is given by[32]

$$\mu = [(\sum_i k_ix_i)^2 + (\sum_i k_iy_i)^2 + (\sum_i k_iz_i)^2]^{1/2} \quad (3)$$

B. Calculations.—The bond moments (μ_i) of Lehn, Levisalles, and Ourisson[11] were employed, *i.e.*, carbonyl, 2.99 D, and nitrile, 3.77 D. The Corey and Sneen[11] coordinates for the axial and equatorial substituents of all pertinent carbon atoms (see **10a**, atoms a, c, d, e) are listed in Table II along with the calculated values of k_i and directional moments.

The dipole moments (μ) of the various configurations of nitrile-containing ketones were calculated substituting the proper directional moment values from Table II into eq 3. Two examples will illustrate the facile application of this technique for calculating μ from any number of separate group moments.[33]

ketodinitrile **10**

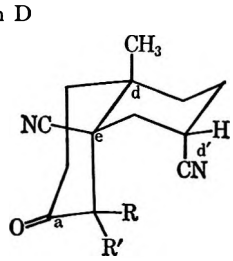


10 **10a**

The directional moments of the carbonyl carbon a, the axial nitrile group on carbon c and the equatorial nitrile on carbon c′ are employed. Thus

$$\sum k_ix_i = -2.8200 - 0.1071 + 1.9792 = -0.9479 \text{ D}$$
$$\sum k_iy_i = 0 - 0.1692 - 3.0392 = -3.2084 \text{ D}$$
$$\sum k_iz_i = 0.9939 + 3.7646 - 1.0291 = 3.7294 \text{ D}$$
$$\mu = [(-0.9479)^2 + (-3.2084)^2 + (3.7294)^2]^{1/2}$$
$$\mu = 5.010 \text{ D}$$

ketodinitrile **12**, form D



12 (form D), R = H; R′ = CH_3
or R′ = H; R = CH_3

$$\sum k_ix_i = -2.8200 - 0.1070 - 3.6100 = -6.5371 \text{ D}$$
$$\sum k_iy_i = 0 + 0.1692 + 0 = 0.1692 \text{ D}$$
$$\sum k_iz_i = 0.9939 + 3.7646 - 1.0865 = 3.6720 \text{ D}$$
$$\mu = [(-6.5371)^2 + (0.1692)^2 + (3.6720)^2]^{1/2}$$
$$\mu = 7.500 \text{ D}$$

TABLE III

EXPERIMENTAL DIPOLE MOMENT DATA

	$\omega_{12} \times 10^{-3}$	ϵ_{12}	ΔN
Ketodinitrile **10**	1.19	2.2860	4.63
	1.75	2.2924	5.03
	2.85	2.3053	5.32
Ketodinitrile **11**	1.21	2.3097	0.50
	2.48	2.3474	1.50
	3.55	2.3816	2.30
Ketodinitrile **12**	1.07	2.2855	0.36
	2.19	2.2990	0.80
	2.75	2.3052	1.10
Ketonitrile **14**	1.08	2.2896	4.54
	2.03	2.3053	5.37
	2.82	2.3180	6.04
	3.41	2.3283	6.19
Ketonitrile **15**	0.73	2.2758	4.82
	1.45	2.2786	5.71
	3.15	2.2873	6.75
	4.10	2.2929	7.90

TABLE IV

EXPERIMENTAL DIPOLE MOMENT CALCULATIONS

Compd	α	ν	M_2	μP_2	μ_2
10	11.63	0.0272	230.3	502	4.96 ± 0.05 D
11	30.73	0.0503	230.3	1329	8.06 ± 0.08 D
12	11.73	0.0288	230.3	507	4.98 ± 0.05 D
14	16.61	0.0463	205.3	640	5.59 ± 0.06 D
15	5.07	0.0598	205.3	194	3.08 ± 0.03 D

(31) N. J. Johnston, Ph.D. Dissertation, University of Virginia, Charlottesville, Va., 1963.

(32) A similar treatment has been reported by N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegell, *J. Org. Chem.*, **28**, 780 (1963); however, in their case k_i was not evaluated from a local coordinate system.

(33) For additional examples in this series, see ref 31.

Ketodinitrile 11 in Form 11b.—Corey and Sneen[11] do not furnish the cartesian coordinates of the atoms in a boat conformation of the cyclohexylidene ring, therefore the directional moments k_ix_i, k_iy_i and k_iz_i of the C-7 nitrile group for this form were determined from measurements on a Dreiding model. An orthogonal coordinate system was constructed with string and the C-7 carbon atom of the model for form **11b** was inserted at the origin such that the coordinate system with respect to the remaining atoms was identical with that employed by Corey and Sneen.[11] The angles the C-7 nitrile group made with the x, y and z axes were carefully measured to be 83, 40 and 52°, respectively. The product of the cosine of the angle times the nitrile group moment gave a new set of directional moments for the C-7 nitrile group in this conformation: 0.46, −2.89 and 2.32 D for the x, y and z coordinates, respectively. These data along with the directional moments of the carbonyl group and the axial nitrile group on carbon c allowed a calculation of 8.1 D for the dipole moment of **11b**.

C. **Experimental Dipole Moment Values.**—The DMOl dipolemeter manufactured by Wissenshaftlich-Technische Werkstatten was used for the dielectric constant measurements (ϵ_{12}) at various weight fraction (weight of sample/weight of solution) concentrations (ω_{12}). This apparatus was thermostated to 25 ± 0.01° and has been described elsewhere.[34] Measurements were made in benzene, n_{5460}^{25} 1.49790, d^{25} 0.87368, ϵ_1^{25} 2.2725. Refractive indices (ΔN_{12}) were measured at the same concentrations (ω_{12}) in a 2.5-cm cell on a Rayleigh interferometer operating at 25° on a wavelength of 0.546×10^{-4} cm. This instrument is described elsewhere.[35] The ϵ_{12}, ΔN_{12} and ω_{12} values are presented in Table III.

The calculations were made essentially by the method of Halverstadt and Kumler[36] as modified by Guggenheim,[37] and are fully described by Smith.[38] Details for the calculation of ν are given by Bauer, Kajans and Lewin.[35] The values for α, ν, M_2, $_2P_2$ and μ_2 are listed in Table IV.

Registry No.—Cyanide ion, 57-12-5; **2**, 19291-93-1; **4**, 19291-94-2; **5**, 19291-95-3; **6**, 19291-96-4; **7**, 19291-97-5; **8**, 19291-98-6; **9**, 19291-99-7; **10**, 19292-00-3; **11**, 19292-01-4; **12**, 19292-02-5; **13**, 19292-03-6; **14**, 19292-04-7; **15**, 19292-17-2; **16**, 19292-05-8; **17**, 19292-06-9.

Acknowledgment.—The authors are most grateful to Jean-Marie Lehn, Institut de Chimie, Universite de Strasbourg, France, for supplying the experimental dipole moment data.

(34) N. L. Allinger, H. M. Blatter, M. A. DaRooge, and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).

(35) N. Bauer, K. Kajans, and S. Z. Lewin, "Physical Methods of Organic Chemistry," Vol. I, Part 2, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1960, pp 1254–1270.

(36) I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, **64**, 2988 (1942).

(37) E. A. Guggenheim, *Trans. Faraday Soc.*, **45**, 714 (1949).

(38) J. W. Smith, "Electric Dipole Moments," Butterworth and Co., Ltd., London, 1955.

Dienones Derived from 5-Methoxy[2.2]metacyclophanes[1]

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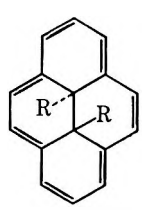
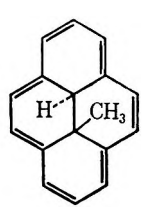
Treatment of 5,13-dimethoxy[2.2]metacyclophane (**4**) under the conditions of the Rieche reaction gives predominantly the corresponding 8-formyl derivative (**5**). Attempts to convert **5** into a methylene-bridged *cis*-[2.2]metacyclophane were unsuccessful. However, **5** could be converted into the corresponding 8-methyl derivative (**7**) and this in turn was oxidized to the corresponding dienone (**8**). Also, it has been shown through the preparation of 5-methoxy-8-methyl[2.2]metacyclophane (**11**) that the Wurtz reaction can be used effectively to prepare "mixed dimeric" products. Oxidation of **11** gave the corresponding dienone **12** and treatment of **12** with acetic anhydride and perchloric acid readily effected a dienone–phenol type of rearrangement to give 2-acetoxy-3-methyl-4,5,9,10-tetrahydropyrene (**13**).

The synthesis of *trans*-15,16-dimethyldihydropyrene[2,3] (**1**) and *trans*-15,16-diethyldihydropyrene[4] (**2**) have demonstrated the possibility of preparing aromatic molecules having substituents within the cavity of the aromatic π cloud of electrons. In a continuation of this study one of the molecules of high interest would be the corresponding *trans*-15-methyldihydropyrene (**3**). Having hydrogen as one of the substituents in the cavity of the π cloud would open the possibility of removal of the "internal" hydrogen to form the corresponding anion, cation, or radical. Such species would not only be inherently interesting but might allow the direct introduction of various other substituents. Also, if the internally substituted hydrogen were labile, it might allow its equilibration to the still unknown *cis*-15,16-dihydropyrene system. For these reasons we undertook a study of the synthesis of *trans*-15-methyldihydropyrene (**3**).



1, R = CH_3
2, R = C_2H_5



3

The synthetic approach envisioned was modeled closely to the route proven successful for **1** and **2**. This required in the first instance the synthesis of 5,13-dimethoxy-8-methyl[2.2]metacyclophane (**7**). Since the Wurtz reaction, which is the standard procedure for preparing [2.2]metacyclophanes, is normally utilized only for the synthesis of symmetrical molecules, a modification of this approach was necessary. One possibility was to subject the readily available 5,13-dimethoxy[2.2]metacyclophane[5] (**4**) to electrophilic substitution in the hope that substitution would occur at the 8 position in reasonable yield. Actually, examination of models or a projection drawing such as

(1) This work was supported in part by the Office of Naval Research and in part by the National Science Foundation.

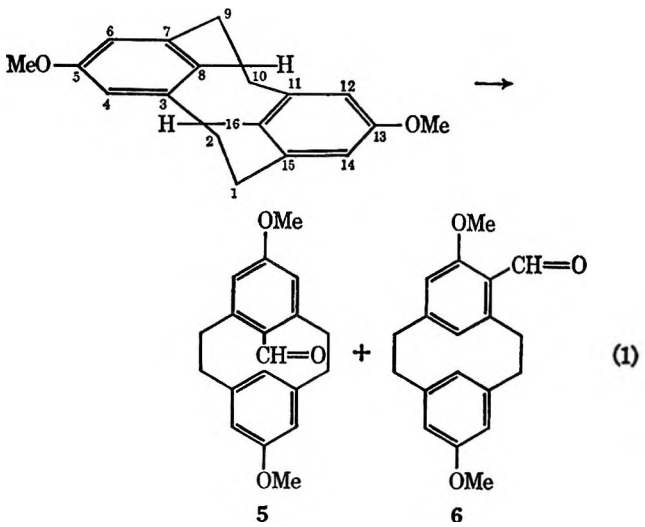
(2) V. Boekelheide and J. B. Phillips, *Proc. Natl. Acad. Sci. U. S.*, **51**, 550 (1964).

(3) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).

(4) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).

(5) V. Boekelheide and R. W. Griffin, Jr., *J. Org. Chem.*, **34**, 1960 (1969).

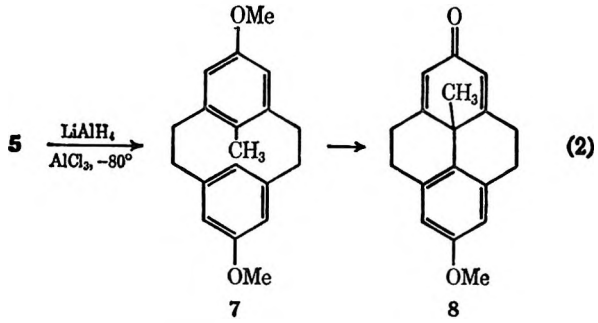
4 clearly suggests that the 8 position is less sterically hindered than the other positions available for reaction. In fact, when 4 was subjected to the conditions of the Rieche procedure[6] there was formed in high yield a mixture of the two aldehydes, 5 and 6 (eq 1), in a ratio of 3:1, as estimated from the nmr spectrum of the mixture. Thus, as predicted, the "internal" 8 position undergoes substitution more readily than the "external" positions even though the external positions are twice as abundant.



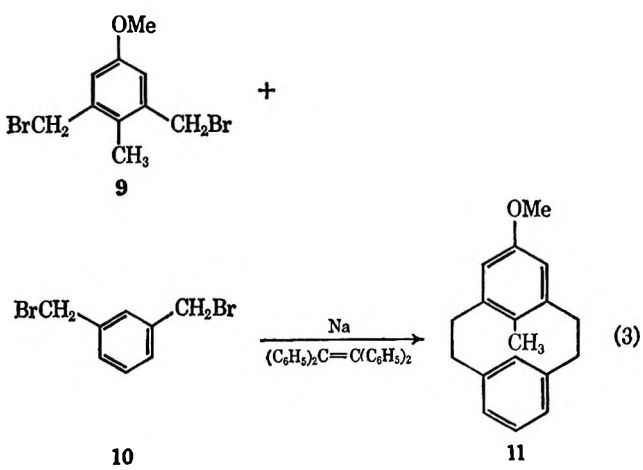
The separation and purification of the two aldehydes 5 and 6 was readily accomplished by chromatography over alumina. Their identification was apparent from examination of their nmr spectra. Substituents at the 8 and 16 positions of [2.2]metacyclophanes are directly over the face of the opposite aromatic ring and show unusual chemical shifts because of the ring current in the opposite aromatic ring. Thus, the signal for the 8 and 16 protons of 4 occurs at τ 5.99, a shift of almost 3 ppm to higher field than the normal region for a benzenoid proton.[5] Similarly, a comparison of 5 and 6 shows that, whereas the signal for the aldehyde proton of 6 is normal, occurring at τ −0.60, the signal for the aldehyde proton of 5 occurs at 1.22, exhibiting the strong shift to higher field to be expected for a proton exposed to the ring current of the opposite aromatic ring.

Reduction of 5 by means of a lithium aluminum hydride–aluminum chloride mixture at −80° proceeded smoothly in good yield to give the desired 5,13-dimethoxy-8-methyl[2.2]metacyclophane (7). In previous studies,[2-4] oxidation of various substituted 5,13-dimethoxy[2.2]metacyclophanes occurred readily in good yield to give the corresponding bisdienones. However, when 7 was subjected to the usual chromic acid oxidation procedure, an unstable product was isolated whose nmr spectrum was in accord with structure 8 (eq 2). Attempts to convert 8 into a stable derivative or to utilize it in subsequent steps of the reaction scheme were not fruitful.

In view of the fact that oxidation of 7 gave a monodienone with retention of the other aromatic ring, our attention turned to possible modifications of our approach that would allow us to take advantage of



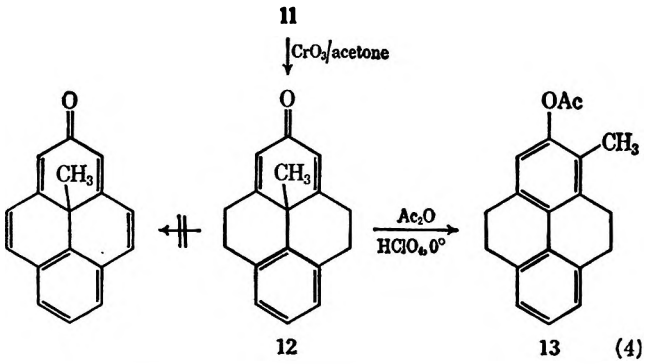
this mode of oxidation. A likely molecule for this purpose was the analogous 5-methoxy-8-methyl[2.2]-metacyclophane (11). However, to employ the Wurtz reaction in a synthesis of 11 seemed feasible only if the Wurtz reaction could be modified to be effective for preparing "mixed dimeric" products. Fortunately, the two partners, 9 and 10, needed for studying such a mixed dimerization were at hand.[3] Obviously, the formation of symmetrical dimers could not be avoided completely. However, since *m*-xylyl dibromide is commercially available, it was used in twofold excess to allow more efficient use of the more costly 3,5-bis-(bromomethyl)-4-methylanisole (9).[3] As expected, the Wurtz reaction under these conditions gave all three possible dimers but these could readily be separated by column chromatography over alumina. The desired "mixed dimer" (11) was isolated in 19% yield (eq 3), based on the amount of 9 employed. This is quite favorable when compared with the usual yields of symmetrical [2.2]metacyclophanes obtained by the Wurtz reaction and establishes the merit of such mixed dimerization experiments.



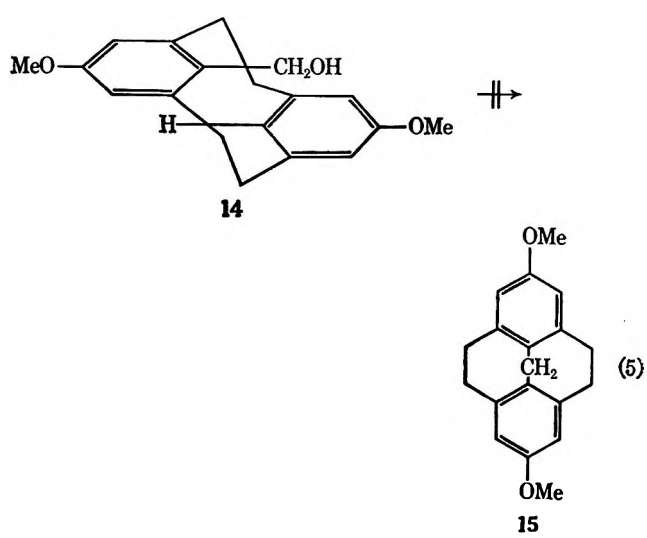
Chromic acid oxidation of 11 proceeded readily to give the corresponding dienone 12 (eq 4) as stable white needles in 50% yield. However, attempts to introduce further unsaturation either by reaction with N-bromosuccinimide or with 2,3-dichloro-5,6-dicyanoquinone were unsuccessful, resulting in mixtures of unstable products in poor yield.

The dienone 12 is somewhat unusual in that for it to undergo a dienone–phenol rearrangement double migration of the methyl group is required. It might be expected, therefore, that the dienone–phenol rearrangement would not occur so readily in this case. In fact, when 12 was treated with a solution of perchloric acid in acetic acid at 0°, rearrangement to 13 was complete in a few minutes.

(6) A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, **93**, 88 (1960).

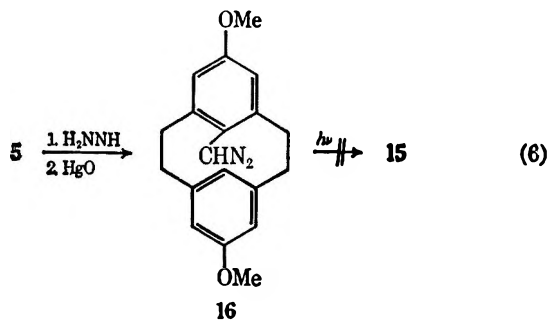


As shown by formula **4** the [2.2]metacyclophanes have a stepwise geometry and X-ray crystallographic analysis of both [2.2]metacyclophane[7] and 8,16-dimethyl[2.2]metacyclophane[8] show the internal carbon atoms at the 8 and 16 positions to be only about 2.8 Å apart. The fact that oxidation[3-5] and electrophilic substitution[9] of these molecules occur with bond formation between the 8 and 16 positions demonstrates that the chemical properties of the [2.2]metacyclophanes are strongly dependent on their special geometry. In view of this it was of interest to explore the question of whether ready interaction might also occur between the aromatic 16 position and a suitably substituted benzylic carbon at C-8. Such a hypothetical reaction is illustrated by the conversion of **14** into **15** (eq 5) and, if successful, would provide an easy route from *trans*-[2.2]metacyclophanes to methylene-bridged *cis*-[2.2]-metacyclophanes. Examination of models suggests that **14** can meet the spatial requirements necessary for either SN1 or SN2 displacement reactions which would give rise to **15.**



Reduction of the aldehyde mixture (**5** and **6**) from the Rieche reaction with sodium borohydride led to a mixture of the corresponding alcohols which, after chromatography over silica gel, gave the desired alcohol **14** in good yield. Several attempts were made to bring about the conversion of **14** into **15** using such conditions as boron trifluoride in ether or toluenesulfonic acid in formic acid, but nothing useful could be isolated that had physical properties corresponding to those to be expected for a methylene-bridged *cis*-[2.2]metacyclophane.[10]

Alternatively, the possibility of effecting the desired transannular ring closure by a carbene insertion reaction was explored. Conversion of **5** into its hydrazone followed by oxidation with mercuric oxide gave the corresponding diazo derivative **16** (eq 6). Irradiation of an ether solution of **16**, as the crude product, caused loss of the diazo absorption band at 2060 cm^{-1}, but nothing recognizable could be isolated from the reaction mixture.



Experimental Section[11]

5,13-Dimethoxy-8-formyl[2.2]metacyclophane (5).—To a solution of 500 mg of 5,13-dimethoxy[2.2]metacyclophane[6] (**4**) in 10 ml of methylene chloride held at 0° under a nitrogen atmosphere there was added dropwise with stirring 294 mg of dichloromethyl *n*-butyl ether.[6] The solution was then allowed to warm to room temperature and stand with continued stirring for 5 hr. It was poured into ice water and the aqueous solution was extracted with ether. After the ether extract had been dried, it was concentrated to give a solid residue. Analysis of the nmr spectrum of this solid residue indicated it to be a 3:1 mixture of **5** and **6**. To separate the two aldehydes the mixture was taken up in benzene and chromatographed over neutral alumina (Woelm, activity II). The first fractions of eluate gave 110 mg of white crystals, mp 214–216°, whose nmr spectrum [singlet at τ −0.60 (1 H), multiplet at 3.5 (3 H), broadened singlet at 5.93 (2 H), and singlets at 6.1 and 6.2 (3 H each), and doublets at 7.0 and 7.9 (8 H)] is in accord with **6**. From the eluate directly following there was isolated 321 mg (58%) of crystals corresponding to **5**. After recrystallization from a benzene–chloroform mixture, **5** was obtained as white crystals: mp 157–159°; nmr ($CDCl_3$) singlet at τ 1.22 (1 H), multiplet at 3.37 (4 H), singlet at 6.01 (1 H), singlets at 6.16 and 6.24 (3 H each), and multiplet at 6.4–8.2 (8 H).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.94; H, 6.75.

5,13-Dimethoxy-8-methyl[2.2]metacyclophane (7).—To 30 ml of a solution of lithium aluminum hydride–aluminum chloride reagent (prepared by boiling a solution of 6 g of aluminum chloride and 2 g of lithium aluminum hydride in 200 ml of ether for 2 hr and then decanting the solution from the residue) held at −80° a solution of 159 mg of 5,13-dimethoxy-8-formyl-[2.2]metacyclophane (**5**) in 5 ml of ether was added dropwise with stirring. The mixture was then stirred an additional 2 hr at −80° and allowed to warm to room temperature. The excess reducing agent was destroyed by cautious addition of moist ether followed by a saturated aqueous solution of sodium sulfate.

(7) C. J. Brown, *J. Chem. Soc.*, 3278 (1953).

(8) A. W. Hanson, *Acta Cryst.*, **15**, 956 (1962).

(9) (a) N. L. Allinger, M. A. Da Rooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1974 (1961); (b) N. L. Allinger, B. J. Gordon, S-E Hu, and R. A. Ford, *J. Org. Chem.*, **32**, 2272 (1967).

(10) H. B. Renfroe, J. A. Gurney, and L. A. R. Hall, *J. Amer. Chem. Soc.*, **89**, 5304 (1967).

(11) Analyses were performed by Micro-Tech Laboratories and Pascher and Pascher Laboratories. Spectra were obtained using a Varian A-60 nmr, Cary 15, and Beckman IR-5 spectrometers. We thank the National Science Foundation for providing the funds for the Varian A-60.

After removal of the precipitate by filtration, the filtrate was dried over magnesium sulfate and concentrated. Recrystallization of the resulting solid from methanol gave 90 mg of white cubes: mp 97.5–98.5°; nmr ($CDCl_3$) multiplet at τ 3.32–3.38 (4 H), singlets at 6.19 and 6.25 (3 H each), singlet at 6.41 (1 H), multiplet at 6.9–8.0 (8 H), and singlet at 9.41 (3 H).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.11; H, 7.77.

Chromic Acid Oxidation of 7.—To a solution of 50 mg of 5,13-dimethoxy-8-methyl[2.2]metacyclophane (**7**) in 5 ml of acetone held at 0° there was added dropwise with stirring 0.05 ml of a 9 *M* solution of chromium trioxide in concentrated sulfuric acid. The solution was stirred at 0° until precipitation occurred and then, after an additional 5 min, the mixture was poured into 20 ml of ice water. The aqueous suspension was extracted with three 30 ml portions of methylene chloride; the methylene chloride extracts were combined, dried, and concentrated. The red-brown oily residue was taken up in a 1:1 mixture of benzene–methylene chloride and chromatographed over neutral alumina (Woelm, activity II). From the eluate there was isolated a yellow oil: ir $\lambda_{max}^{CHCl_3}$ 5.95, 6.08, 6.17, 8.63, 9.50, and 10.97 μ; nmr ($CDCl_3$) singlet at τ 3.54 (2 H), singlet at 3.97 (2 H), singlet at 6.26 (3 H), multiplet at 6.75–7.50 (8 H), and singlet at 8.45 (3 H). On standing the oil underwent resinification and it was not possible to prepare a pure sample for analysis.

5-Methoxy-8-methyl[2.2]metacyclophane (11).—A solution of 15.4 g of 3,5-bis(bromomethyl)-4-methylanisole[3] (**9**) and 26.4 g of *m*-xylyl dibromide in 1.0 l. of dry tetrahydrofuran was added through a Hershberg dropping funnel over a period of 48 hr to a rapidly stirred suspension of 20.0 g of sodium granules and 2.0 g of tetraphenylethylene in 1.0 l. of tetrahydrofuran at room temperature under a nitrogen atmosphere. At the end of the addition the excess sodium was removed by filtration of the mixture through glass wool. The resulting milky-white suspension was then filtered through Celite and concentrated under reduced pressure. The yellow, sticky residue was taken up in 1:1 mixture of benzene–*n*-pentane and chromatographed over 500 g of neutral alumina (Woelm, activity I). From the first eluate fractions there was isolated a mixture of tetraphenylethane and [2.2]metacyclophane. From the next eluate fraction there was isolated 2.4 g (19%) of white solid having spectral properties in accord with **11**. In the final eluate fraction there was a small quantity of 5,13-dimethoxy-8,16-dimethyl[2.2]metacyclophane.[3] Crystallization of **11** from a benzene–methanol mixture gave white cubes: mp 93–95°; nmr ($CDCl_3$) multiplet at τ 2.80–3.00 (3 H), singlet at 3.33 (2 H), broad singlet at 6.05 (1 H), singlet at 6.19 (3 H), multiplet at 6.8–8.0 (8 H), and singlet at 9.51 (3 H).

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.09; H, 8.04.

2-Keto-15-methyl-2,4,5,9,10,15-hexahydropyrene (12).—To a stirred solution of 250 mg of 5-methoxy-8-methyl[2.2]metacyclophane (**11**) in 50 ml of acetone held at 0° there was added dropwise 0.7 ml of an 8 *M* solution of chromium trioxide in concentrated sulfuric acid over a period of 1 hr. The mixture was then stirred for an additional hour at 0° before being poured into 50 ml of ice water. The aqueous solution was extracted with three 50-ml portions of methylene chloride, and then the combined methylene chloride extracts were washed successively with water, aqueous sodium bicarbonate, and water. After the methylene chloride extract had been dried, it was concentrated giving a yellow gummy residue. This was taken up in benzene and transferred to a silica gel column. Elution of the column with a 3:1 benzene–chloroform mixture afforded 119 mg of pale yellow crystals, mp 105–106°. Treatment with charcoal followed by recrystallization from hexane gave white needles: mp 106–107°; ir $\lambda_{max}^{CHCl_3}$ 6.01 and 6.17 μ; nmr ($CDCl_3$) broad singlet at τ 2.98 (3 H), singlet at 3.81 (2 H), multiplet at 6.6–7.6 (8 H), and singlet at 8.51 (3 H).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.53; H, 6.80.

2-Acetoxy-1-methyl-4,5,9,10-tetrahydropyrene (13).—To a solution of 50 mg of 2-keto-15-methyl-2,4,5,9,10,15-hexahydropyrene (**12**) in 25 ml of carbon tetrachloride held at 0° there was added dropwise with stirring a solution of 3 drops of 70% perchloric acid in 1.0 ml of acetic anhydride. The reaction mixture rapidly turned yellow-orange and then faded to a light yellow. The solution was stirred at 0° for 10 min and then poured into 50 ml of water. The organic layer was separated and washed successively with water, a 5% aqueous solution of sodium bicarbonate, and water. It was then dried and concentrated to give a white solid. This was sublimed at 120° (0.5 mm), yielding 45 mg of fine white needles: mp 167–168°; ir $\nu_{max}^{CHCl_3}$ 1740, 1444, 1360, 1200, 1172, and 1068 cm^{-1}; nmr ($CDCl_3$) singlet at τ 2.94 (3 H), singlet at 3.22 (1 H), singlet at 7.17 (8 H), singlet at 7.69 (3 H), and singlet at 7.89 (3 H).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.03; H, 6.76.

5,13-Dimethoxy-8-hydroxymethyl[2.2]metacyclophane (14).—To a solution of 380 mg of the aldehyde mixture (**5** and **6**) from the Rieche reaction in 100 ml of methanol there was added dropwise at room temperature a solution of 400 mg of sodium borohydride in 5 ml of methanol. After the mixture had been stirred at room temperature overnight, 10 ml of a 10% aqueous sodium hydroxide solution was added and the mixture was boiled under reflux for 0.5 hr. Concentration of the mixture gave a white solid which was taken up in methylene chloride and chromatographed over neutral alumina (Woelm, activity II). From the first eluate fractions there was isolated 267 mg of white crystals: mp 153–164°; uv λ_{max}^{EtOH} 247 mμ (ϵ 10,200) and 292 (2760); ir ν_{max}^{KBr} 3560, 1020, 993, 846, and 717 cm^{-1}; nmr ($CDCl_3$) singlet at τ 3.39 (4 H), singlets at 6.20 and 6.27 (3 H each), singlet at 6.41 (1 H), multiplet at 6.90–7.92 (10 H), and singlet at 9.15 (1 H, broadening on dilution indicating it to be the hydroxyl proton). Reduction of a portion of these crystals at −80° with a lithium aluminum hydride–aluminum chloride mixture proceeded in good yield to give a sample of **7**, identical in all respects with the product of the preparation described earlier. Thus the structure of **14** is established.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.31; H, 7.58.

In the above experiment after elution of the silica gel column with methylene chloride, further elution with chloroform afforded 90 mg of white crystals, mp 202–204°, whose spectral properties are in accord with those to be expected for 5,13-dimethoxy-4-hydroxymethyl[2.2]metacyclophane.

Conversion of 5 into 16 and the Irradiation of 16.—A solution of 180 mg of 5,13-dimethoxy-8-formyl[2.2]metacyclophane and 120 mg of 100% hydrazine hydrate in 2 ml of absolute ethanol was boiled under reflux for 2 hr. It was then concentrated under reduced pressure leaving a solid residue. This was dissolved in 5 ml of tetrahydrofuran and 600 mg of sodium sulfate and 10 drops of a saturated alcoholic solution of potassium hydroxide were added. After the mixture had been cooled to 0°, 210 mg of yellow mercuric oxide was added. The mixture was then allowed to warm to room temperature and to stand with stirring for 4 hr. The solution was then concentrated, the residue was taken up in ether, and the ether solution was centrifuged. Examination of the clear ether solution in the ir showed the distinctive diazo absorption band at 2060 cm^{-1} and absence of carbonyl absorption. The ether solution was then diluted to a volume of 100 ml and irradiated under a nitrogen atmosphere with a 150-W Hanovia lamp using a Pyrex filter. The color of the solution changed from orange to a light yellow over a period of 3 hr. After concentration, the residue was taken up in chloroform and examination in the ir showed the complete disappearance of absorption at 2060 cm^{-1}. Removal of the chloroform followed by chromatography over neutral alumina (Woelm, activity I) using benzene for elution gave 100 mg of a yellow oil. This oil showed only a single spot on thin layer chromatography over silica gel. However, its nmr spectrum was complex and not at all in accord with that to be expected for a methylene-bridged *cis*-[2.2]metacyclophane.[10]

Registry No.—**5**, 19289-32-8; **7**, 19289-33-9; **11**, 19289-34-0; **12**, 19289-35-1; **13**, 19289-36-2; **14**, 19289-37-3.

Notes

Synthesis of [2.2]Metacyclophanes[1]

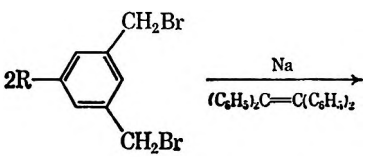
V. BOEKELHEIDE[2a] AND RODGER W. GRIFFIN, JR.[2b]

Department of Chemistry, University of Rochester, Rochester, New York

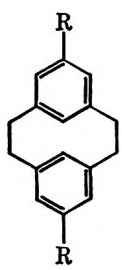
Received August 28, 1968

The successful synthesis of 15,16-dihydropyrene derivatives evolved out of an approach involving intermediate [2.2]metacyclophanes.[3,4] In the preliminary work directed toward this approach extensive studies were made on the synthesis of [2.2]metacyclophanes utilizing model compounds. In the present communication we report on a portion of these preliminary studies because of its relevance to later work currently being published.[5]

Of the various methods that have been reported for the synthesis of [2.2]metacyclophanes,[6] the only generally useful one has been the Wurtz reaction. For our purposes it was of interest to examine the electronic and steric effects of substituent groups on the Wurtz reaction and, because of the over-all plan involving phenolic-oxidation radical coupling,[3] it was of particular interest to prepare 5,13-dimethoxy derivatives.[7] In this study the Wurtz reaction, as modified by Müller and Röscheisen,[8] was utilized to convert *m*-xylyl dibromides, as illustrated by Ia–Id, into the corresponding [2.2]metacyclophanes (IIa–IIe) (eq 1).



Ia, R = OMe
b, R = Me
c, R = NO_2
d, R = F

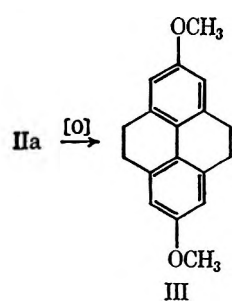


+ 2NaBr (1)

IIa, R = OMe
b, R = Me
c, R = NO_2
d, R = F
e, R = NH_2

The synthesis of the requisite *m*-xylyl dibromides (Ia–Id) was straightforward, is described in the Experimental Section, and requires no special comment. The conditions of the Wurtz reaction are relatively severe and the choice of substituents was made to determine what functional groups, if any, would survive these reaction conditions, permitting the isolation of useful quantities of substituted [2.2]metacyclophanes. In fact, the Wurtz dimerization of 3,5-bis(bromomethyl)anisole (Ia) proceeded smoothly to give the requisite 5,13-dimethoxy[2.2]metacyclophane (IIa) in 27% yield. Likewise, the dimerization of 3,5-bis(bromomethyl)toluene proceeded satisfactorily, but in lower yield, to give IIb. However, the dimerization of 3,5-bis(bromomethyl)nitrobenzene occurred in very poor yield with the production of many side products. Reduction of the crude 5,13-dinitro[2.2]metacyclophane (IIc) did allow the isolation of crystalline 5,13-diamino[2.2]metacyclophane (IIe). Finally, the dimerization of the fluoro analog (IId) was studied. In this case, again, the yield of dimeric product was very low and spectral evidence indicated it to be a mixture of the parent hydrocarbon, [2.2]metacyclophane, and its fluorinated analog (IId). Clearly, the conditions of the Wurtz reaction effect partial elimination of aromatic fluoride.

With the ready availability of 5,13-dimethoxy[2.2]-metacyclophane (IIa), it was of interest to study its oxidation under conditions effecting radical coupling *via* phenolic oxidation. Chromic acid oxidation of 5,13-dimethoxy[2.2]metacyclophane led to its conversion in excellent yield into the corresponding 2,7-dimethoxy-4,5,9,10-tetrahydropyrene (III).[9] The extreme ease with which the metacyclophane structure of IIa is converted into the corresponding pyrene derivative (III) (eq 2) is reminiscent of the studies of Allinger on the nitration of [2.2]metacyclophane.[10,11]



(2)

III

Experimental Section[12]

3,5-Bis(hydroxymethyl)anisole.—In the thimble of a Soxhlett was placed 60 g of 3,5-bis(carbomethoxy)anisole[13] and extraction

(1) Abstracted from the Ph.D. Thesis of R. W. Griffin, Jr., University of Rochester, 1960.

(2) (a) To whom inquiries should be sent: Department of Chemistry, University of Oregon, Eugene, Ore. (b) National Science Foundation Cooperative Graduate Fellow, 1959–1960.

(3) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).

(4) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).

(5) V. Boekelheide, C. Ramey, E. Sturm, T. Miyasaka, and B. A. Hess, Jr., *J. Org. Chem.*, **34**, 1956 (1969).

(6) See B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, for a comprehensive review.

(7) The numbering used for the [2.2]metacyclophanes is that recommended by Smith, ref 6, p 8.

(8) E. Müller and G. Röscheisen, *Ber.*, **90**, 543 (1957).

(9) We are indebted to Dr. E. Sturm for the details of this experiment.

(10) N. L. Allinger, M. A. Da Rooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1974 (1961).

(11) N. L. Allinger, B. J. Gordon, S.-E. Hu, and R. A. Ford, *J. Org. Chem.* **32**, 2272 (1967).

(12) Analyses were performed by Micro-Tech Laboratories and by Miss Annette Smith; nmr spectra were taken by Professor David Wilson using a Varian HR-60 MHz, infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer, and ultraviolet spectra were recorded using a Cary 11 spectrometer.

(13) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954).

was carried out into a suspension of 41.5 g of lithium aluminum hydride in 1.5 l. of ether. After extraction was complete, the excess lithium aluminum hydride was destroyed by addition of methanol followed by aqueous sulfuric acid. The ether layer was separated, dried, and concentrated to give 42 g (93%) of white crystals, mp 66–67°. A sample recrystallized from acetone gave white needles, mp 68.5–69.0°.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.88; H, 7.37.

3,5-Bis(bromomethyl)anisole (Ia).—A mixture of 40 g of 3,5-bis(hydroxymethyl)anisole and 44 g of phosphorus tribromide in 500 ml of benzene was boiled under reflux for 4 hr and allowed to stand at room temperature overnight. Then the benzene solution was decanted from the inorganic residue, washed with water, and concentrated to give 50 g (70%) of white crystals, mp 70–74°. A sample recrystallized from ether melted at 76.0–76.5°.

Anal. Calcd for $C_9H_{10}OBr_2$: C, 36.76; H, 3.43. Found: C, 36.67; H, 3.47.

5,13-Dimethoxy[2.2]metacyclophane (IIa).—A solution of 22.5 g of 3,5-bis(bromomethyl)anisole (Ia) in 1 l. of dry tetrahydrofuran was added dropwise through a Hershberg funnel over a period of 65 hr to a rapidly stirred suspension of 20 g of sodium granules in 1 l. of tetrahydrofuran containing 2 g of tetraphenylethylene and held at room temperature. At the end of the addition the unreacted sodium was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in methylene chloride, passed over a short column of Florisil to remove polymeric material, and concentrated. This residue, in turn, was taken up in benzene and chromatographed over neutral alumina (Woelm, activity I). The first substance to be eluted was tetraphenylethane followed by 2.97 g (27%) of white crystals, mp 169–170°. A sample recrystallized from a benzene–methanol mixture gave white cubes: mp 170.5–171.0°; nmr ($CDCl_3$) multiplet at τ 3.45 (4 H), singlet at 5.99 (2 H), singlet at 6.25 (6 H), and two doublets at 7.11 and 8.01 (8 H); λ_{max}^{KBr} 7.87 μ; λ_{max}^{EtOH} 210 mμ (log ϵ 4.63) and 292 (3.39).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.82; H, 7.60.

5,13-Dimethyl[2.2]metacyclophane (IIb).—The preparation of 3,5-bis(bromomethyl)toluene was carried out in 20% yield by treating mesitylene with N-bromosuccinimide in carbon tetrachloride and the physical properties of the product were in agreement with those reported.[14] Its dimerization to 5,13-dimethyl-[2.2]metacyclophane (IIb) was carried out as described for the dimerization of Ia above. From 6.85 g of 3,5-bis(bromomethyl)-toluene there was isolated, after recrystallization from a benzene–methanol mixture, 226 mg (8%) of white rhombic crystals, mp 153.0–153.5°.[15]

5,13-Diamino[2.2]metacyclophane (Ie).—The dimerization of 5.5 g of 3,5-bis(bromomethyl)nitrobenzene[16] was carried out in a manner similar to that described previously for the preparation of IIa. After removal of the sodium granules and concentration, there remained a brown semisolid residue. This was partially soluble in benzene; chromatography of the benzene solution yielded a mixture of tetraphenylethane and tetraphenylethylene. The benzene-insoluble portion, presumably containing some IIc, was placed in dilute hydrochloric acid, tin shot was added, and the mixture was boiled under reflux for 16 hr. The aqueous solution was decanted, made basic, and extracted with ether. Concentration of the ether extract gave a solid which, after recrystallization from an ether–methanol mixture, yielded 40 mg of light tan crystals: mp 230–240° dec; λ_{max}^{Nujol} 2.95–3.25 (broad absorption with discernible maxima), 11.66, and 13.58 μ.

Anal. Calcd for $C_{16}H_{18}N_2$: C, 81.32; H, 6.83. Found: C, 80.96; H, 6.88.

Dimethyl 5-Fluoroisophthalate.—To a solution of 84 ml of 12 *N* hydrochloric acid containing 33.3 g of dimethyl 5-aminoisophthalate[17] held at 0° was added a cold solution of 11.2 g of sodium nitrite in 50 ml of water. After the diazotized solution had been filtered through a sintered-glass disk, a cold solution of 22 g of sodium fluoroborate in 80 ml of water was added. The light orange precipitate, which separated, was collected and washed successively with cold 5% aqueous sodium fluoroborate, methanol, and ether. It was then dried in a desiccator to give 40.6 g (83%) of crystalline diazonium fluoroborate, mp 139–140° dec. This was placed in a large distilling flask and gently heated with a free flame until a highly exothermic reaction was initiated. After the evolution of boron trifluoride and nitrogen was complete, distillation of the residue was continued until the oil distilling over became highly colored. The distillate solidified and was sublimed to give 14.6 g (52%) of white crystals: mp 55.0–55.5°; λ_{max}^{KBr} 5.79, 11.15, 11.45, and 13.86 μ.

Anal. Calcd for $C_{10}H_9O_4F$: C, 56.60; H, 4.28. Found: C, 56.55; H, 4.26.

3,5-Bis(hydroxymethyl)fluorobenzene.—A solution of 13.6 g of dimethyl 5-fluoroisophthalate in 50 ml of tetrahydrofuran was added dropwise with stirring at room temperature to a solution of 5.3 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. After the solution had been boiled under reflux for 1 hr, it was cooled and decomposed by addition of a saturated aqueous solution of sodium sulfate. The solids, which precipitated, were removed by filtration and the filtrate was concentrated. Recrystallization of the solid residue from ether gave 4.98 g (50%) of white crystals, mp 85–86°.

Anal. Calcd for $C_8H_9O_2F$: C, 61.53; H, 5.81. Found: C, 61.67; H, 6.06.

3,5-Bis(bromomethyl)fluorobenzene (Id).—A mixture of 4.75 g of 3,5-bis(hydroxymethyl)fluorobenzene and 5.65 g of phosphorus tribromide in 40 ml of benzene was boiled under reflux for 30 min. The benzene solution was then separated by decantation, washed with water, and concentrated. The solid residue was recrystallized from hexane to give 4.71 g (55%) of white crystals, mp 56–57°.

Anal. Calcd for $C_8H_7Br_2F$: C, 34.07; H, 2.50. Found: C, 34.17; H, 2.78.

Dimerization of 3,5-Bis(bromomethyl)fluorobenzene (Id).—The Wurtz dimerization of 5.3 g of 3.5-bis(bromomethyl)fluorobenzene (Id) was carried out as described previously for the preparation of IIa. From the elution of the alumina column with benzene there was isolated 126 mg of a sticky white solid. Although this was obviously a mixture, attempts at separation of the mixture were unsuccessful. Elementary analysis and spectral data of this solid suggest that it was a mixture of approximately equal parts of [2.2]metacyclophane and 5,13-difluoro-[2.2]metacyclophane.

Oxidation of 5 13-Dimethoxy[2.2]metacyclophane (IIa) to 2,7-Dimethoxy-4,5,9,10-tetrahydropyrene (III).—Chromic acid reagent was made by adding a solution of 2.67 g of chromium trioxide in 5 ml of water to 2.13 g of concentrated sulfuric acid and diluting the whole to a volume of 10 ml with water; 0.50 ml of this chromic acid reagent was added dropwise with stirring to a suspension of 100 mg of 5,13-dimethoxy[2.2]metacyclophane in 25 ml of acetone. A precipitate formed and the solution became red. After 1 hr, the mixture was poured into ice–water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and concentrated. The residue was taken up in chloroform and chromatographed over neutral alumina (Woelm, activity III). From the first eluate fractions there was isolated a fluorescent solid which, after recrystallization from ethanol, gave 55 mg of white plates: mp 181.0–181.5°; nmr ($CDCl_3$) singlet at τ 3.40 (4 H), singlet at 6.20 (6 H), and singlet at 7.18 (8 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.86; H, 7.05.

Registry No.—Ia, 19254-79-6; Ib, 19294-04-3; Id, 19254-80-9; Ie, 19254-81-0; IIa, 19254-82-1; III, 19254-83-2; 3,5-bis(hydroxymethyl)anisole, 19254-84-3; dimethyl 5-fluoroisophthalate, 17449-48-8; 3,5-bis(hydroxymethyl)fluorobenzene, 19254-86-5.

(14) J. von Braun and O. Engel, *Ber.*, **58**, 283 (1919).

(15) The nmr data for 5,13-dimethyl[2.2]metacyclophane were first recorded using a Varian HR-60 [D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Amer. Chem. Soc.*, **82**, 6302 (1960)]. Subsequently, N. L. Allinger, B. J. Gorden, S.-E. Hu, and R. A. Ford [*J. Org. Chem.*, **32**, 2272 (1967)] have described an independent preparation of 5,13-dimethyl[2.2]metacyclophane and their nmr data showed discrepancies with that which we had recorded earlier. We have recently reexamined the nmr spectra of a number of compounds in the [2.2]metacyclophane series using a Varian A-60 and find that these spectra are very concentration dependent. This we feel is probably responsible for the discrepancies noted by Allinger and his collaborators.

(16) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2819 (1954).

(17) E. I. du Pont de Nemours and Co., British Patent 695,164 (1955); *Chem. Abstr.*, **49**, 755 (1955).

Angular Methylation

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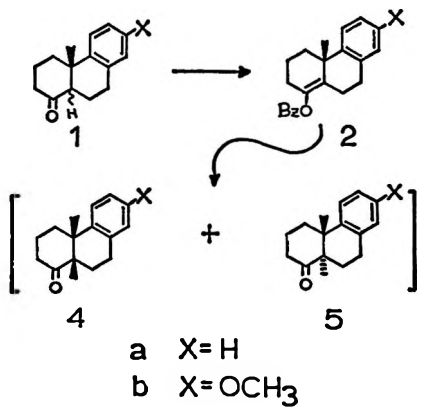
We wish to report one possibly useful solution to the general problem of angular methylation of ketones. It involves reaction between enolate ions, produced in a structurally specific manner by the procedure of House,[1] and iodomethylzinc iodide (Simmons–Smith reagent)[2] and leads directly to the α-methylated ketone.[3]

In the case at hand we were faced with the problem of angular methylation of two ketones **1a** and **1b**.[4]



Enol benzoylation of **1a** was achieved by the action of benzoic anhydride and perchloric acid to afford principally $\Delta^{4,5}$-enol benzoate **2a**. Enol acetylation afforded mainly the $\Delta^{3,4}$ isomer. Conversion of enol benzoate **2a** into lithium enolate **3a** by the procedure of House and Trost[1] followed by reaction with methyl iodide under a variety of conditions afforded in all cases an inseparable mixture of un-, mono-, di-, and trimethylated ketones. The steric situation here presumably slows methylation to such a degree that intermolecular transenolization may effectively compete with it. In marked contrast to these results addition of a solution of Simmons–Smith reagent to **3a** afforded high (65–75%) yields of a 3:1 mixture of *cis* (**4a**) and *trans* (**5a**) angularly methylated ketones without formation of any higher alkylated ketones.

In an exactly analogous manner **1b** was enol benzoylated, the enol benzoate was treated with methyllithium, and **3b** was allowed to react with an excess of Simmons–Smith reagent to afford in good yield a 7:3 mixture of **4b** and **5b**.

The actual processes involved in this methylation of **3a** and **3b** are not clear since quenching of the reaction mixture with deuterated acids afforded deuterium-free **4** and **5**. Two of the three hydrogens of the introduced methyl group are derived from the Simmons–Smith reagent since use of methylene iodide-d_2 [5] in alkylation of **3b** afforded **4b**-d_2 and **5b**-d_2 of the expected isotopic purity.

This synthetic procedure could prove of use in those cases where one wishes to introduce an alkyl group[6,7] by a process that is fast relative to any possible transenolization.[8]

Stoichiometric production of the enolate ion as above would seem to be a prerequisite of application of this synthetic method.

Experimental Section

Infrared spectra were determined in chloroform on a Model IR-5 Beckman infrared recording spectrophotometer. Ultraviolet adsorption spectra were determined in 95% ethanol on a Model 8 Cary recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates A-60 or A-60A recording spectrometer in deuteriochloroform, using tetramethylsilane (τ 10 ppm) as an internal reference. Melting points were determined on a calibrated Fisher-Johns melting point apparatus. The microanalyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

1-Benzoyloxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (2a).—A solution of 67.8 g (0.300 mol) of benzoic anhydride, 0.5 ml of 65% perchloric acid, 150 ml of methylene chloride and 30.0 g (0.143 mol) of **1a**[9] was stirred at room temperature under nitrogen for 3 hr. The solution was diluted with methylene chloride, washed successively with saturated sodium bicarbonate solution and water, and dried over magnesium sulfate. After removal of the solvent *in vacuo* the resulting brown oil was chromatographed on alumina to afford ultimately 30.6% (68% yield) of **2a**, an oil. An analytical sample was prepared by evaporative distillation at 140° (0.1 mm): infrared 5.80 μ (enol benzoate C=O); nmr τ 1.8–2.0 (2 H, multiplet, *o*-benzoyloxy aryl H), 2.3–3.0 (7 H, multiplet, aryl H), 7.0–7.5 (2 H, multiplet, benzylic CH_2), 8.25 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 318 (parent, 2%), 303 (7%), 105 (100%).

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.79; H, 6.90.

***cis*- (4a) and *trans*-4a,10a-Dimethyl-3,4,4a,9,10,10a-hexahydrol(2H)phenanthrone (5a).**—Simmons–Smith reagent[2] was prepared by refluxing for 55 min a mixture of 396 g (1.48 mol) of methylene iodide, 96 g (1.48 mol) of zinc–copper couple, 400 ml of ether, and a large crystal of iodine. While this reagent was cooling to 0°, in another flask 200 ml of 1.3 *M* ethereal methyllithium was added to a solution of 200 ml of anhydrous dimethoxyethane (DME) containing a few crystals of triphenylmethane. To the bright red methyllithium solution was added dropwise a solution of 23.0 g (0.0724 mol) of enol benzoate **2a** in 100 ml anhydrous dimethoxyethane. The Simmons–Smith reagent was filtered under a nitrogen atmosphere through a dry sintered-glass funnel, and the yellow filtrate was added slowly to the pink enolate solution. The initial reaction appeared to subside after addition of 20% of the reagent. After stirring for 30 min at room temperature, the reaction was quenched by pouring it into saturated aqueous ammonium chloride, and the ether layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield 20.0 g of a dark yellow oil. Chromatography of this on silica gel afforded 10.5 g (64% yield) of a 7:3 (by nmr) mixture of **4a** and **5a**. Crystallization from hexane of the early fractions afforded 5.86 g of **4a**: mp 67–68°; infrared 5.88 μ; nmr τ 2.6–2.9 (4 H, multiplet, aryl H), 6.9–7.3 (2 H, multiplet, benzylic $-CH_2-$), 8.75 (3 H, singlet, angular CH_3), 8.90 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 288 (parent, 77%), 213 (45%), 143 (100%).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.96; H, 8.75.

Crystallization of the last fraction eluted from hexane yielded 1.81 g (11%) of pure **5a**: mp 79–80°; infrared 5.88 μ (saturated

(1) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965), and earlier papers.

(2) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(3) E. Wenkert and D. A. Berges [*ibid.*, **89**, 2507 (1967)] have reported a similar reaction between enol ethers and iodomethylzinc iodide followed by hydrolysis of the alkoxycyclopropane.

(4) Details of the stereochemical assignment of ketones **4** and **5** will be reported later in a full paper.

(5) E. P. Blanchard and H. E. Simmons, *J. Amer. Chem. Soc.*, **86**, 1337 (1964).

(6) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3353 (1966).

(7) J. Furukawa, N. Kawabata, and J. Nishimura, *ibid.*, 3495 (1968).

(8) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).

(9) G. Stork and A. Burgstahler, *J. Amer. Chem. Soc.*, **73**, 3544 (1951).

C=O); nmr τ 2.6–2.9 (4 H, multiplet, aryl H), 6.9–7.3 (2 H, multiplet, benzylic $-CH_2-$), 8.92 (3 H singlet, angular CH_3), 8.93 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 228 (parent, 65%), 213 (73%), 131 (100%).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.07; H, 8.75.

1-Benzoyloxy-7-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (2b).—Following a procedure similar to that for the preparation of **2a**, 5.98 g (0.025 mol) of **1b**[3] was converted into 4.81 g (66%) of **2b**: mp 84–86°; infrared 5.78 μ (enol benzoate C=O); nmr τ 1.8–2.0 (2 H, multiplet, orthobenzoloxy aryl H), 2.4–3.5 (7 H, multiplet, aryl H), 6.24 (3 H, singlet, OCH_3), 8.54 (3 H, singlet, angular CH_3); ultraviolet λ_{max} 285 mμ (log ϵ 3.46), 275 (3.54), 228 (4.36); mass spectrum (*m/e*) 348 (parent 0.5%), 333 (6%), 105 (100%).

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.33; H, 7.04.

***cis*- (4b) and *trans*-4a,10a-Dimethyl-7-methoxy-3,4,4a,9,10,10a-hexahydro-1(2H)-phenanthrone (5b).**—Following a procedure similar to that for the preparation of **4a** and **5a**, 1.00 g (2.87 mmol) of **2b** was converted into 0.533 g (72%) of a 70:30 mixture of **4b** and **5b**. Crystallization of the mixture from hexane at room temperature yielded 114 mg (16%) of pure **5b**: mp 128–129.5; infrared 5.87 μ (saturated C=O); nmr τ 2.6–2.9 (1 H, multiplet, aryl H), 3.0–3.4 (2 H, multiplet, aryl H), 6.21 (3 H, singlet, OCH_3), 8.92 (3 H, singlet, angular CH_3), 8.93 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 258 (parent 47%), 243 (100%).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.35; H, 8.32.

Upon cooling the hexane solutions to 0° **4b** slowly crystallized. After several crops there was obtained 292 mg (40%) of **4b**: mp 50.5–53.5° (after one recrystallization from hexane); infrared 5.88 μ (s, saturated C=O); nmr τ 2.7–2.9 (1 H, multiplet, aryl H), 3.1–3.5 (2 H, multiplet, aryl H), 6.24 (3 H, singlet, $-OCH_3$), 8.77 (3 H, singlet, angular CH_3), 8.90 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 258, 243 (100%).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.14; H, 8.75.

Registry No.—**2a**, 18968-34-8; **2b**, 18936-36-2; **4a**, 18936-37-3; **4b**, 18936-38-4; **5a**, 18936-39-5; **5b**, 18936-40-8.

The Epoxidation of 3,3,6,6-Tetramethyl-1,4-cyclohexadiene[1]

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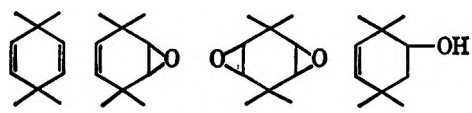
In 1965, we reported the synthesis and some reactions of 3,3,6,6-tetramethyl-1,4-cyclohexadiene (**1**).[2] Our interest in this system and the reports of the unusual reactivity of the structurally similar norbornadiene toward epoxidation[3] stimulated us to investigate the oxidation of **1** with peracetic acid. The recent publication of Berchtold's work on 1,4-cyclohexadiene[4] prompted us to report our findings.

The starting material, **1**, as obtained by the pyrolysis of the diacetate of 2,2,5,5-tetramethylcyclohexane-1,3-diol was contaminated with about 20% *p*-xylene.[2] To obviate the necessity of separating this contaminant from **1** it was determined that *p*-xylene did not react with peracetic acid under the conditions of our experiments. The epoxidation of **1** with peracetic acid in the presence of sodium carbonate[5] resulted in the formation of 2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptane (**2**) in 30% yield and *cis*-2,2,6,6-tetramethyl-4,8-dioxatricyclo[5.1.0.0^{3,5}]octane (**3**) in 11% yield. A gas chromatogram of the crude reaction mixture indicated that these were the only volatile products present and thus **1** upon epoxidation does not yield any products resulting from a skeletal rearrangement. The low yields of the two products were the result of their isolation by preparative gas chromatography rather than the presence of unidentified reaction products.



1 **2** **3** **4**

Monoepoxide **2** was characterized by its elemental analysis, its spectral properties, and its conversion by reduction with lithium aluminum hydride into 3,3,6,6-tetramethylcyclohexen-4-ol (**4**).

In order to place the structural assignment of **2** on firm ground, but with the somewhat unusual lithium aluminum hydride reduction of *exo*-2,3-epoxynorborn-5-ene[3b] in mind, we reduced **2** with lithium aluminum hydride. As in the epoxidation reaction above there was no evidence of a sketetal rearrangement and **4** was obtained in 71% yield. This material was identified by its elemental analysis, its spectral properties, and its conversion into a 3,5-dinitrobenzoate.

Bisepoxide **3** was characterized by its elemental analysis and its infrared and nmr spectra. The *cis* stereochemistry was assigned on the basis of the nmr spectrum and the examination of a molecular model of monoepoxide **2**. The nmr spectrum of **3** (CCl_4) had a singlet at δ 1.08 (6 H), a singlet at 1.22 (6 H), and a singlet at 2.56 (4 H). This spectrum is consistent with a system with four equivalent ring junction protons and a nonequivalent pair of two equivalent methyl groups, that is, the *cis*-bisepoxide. The *trans*-bisepoxide would be expected to have an nmr spectrum that would indicate the equivalence of the 12 methyl protons and the equivalence of the four ring junction protons.

The selective epoxidation of **2** to form **3** can be understood by examination of a molecular model of **2**. The combination of the epoxide ring (with forces carbon atoms 3, 4, 5, and 6 into a plane[6]) and the carbon–carbon double bond (which forces carbon atoms 1, 2, 3, and 6 into a plane) requires that the ring assume a boat conformation. There are two boat conformations possible. In one, **5**, the "flagpole" and "bowsprit" methyl groups are *trans* to the oxide ring and, in the other, **6**, they are *cis* to the oxide ring. Inspection of models of the two conformers shows that in **6** there are two hydrogen–methyl eclipsings and two methyl–

(1) Taken from the M.S. Thesis of J. T. S., Middlebury College, 1967.

(2) F. W. Grant, R. W. Gleason, and C. H. Bushweller, *J. Org. Chem.* **30**, 290 (1965).

(3) (a) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963); (b) J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, *Tetrahedron Lett.*, No. 23, 1789 (1965).

(4) T. W. Craig, G. R. Harvey and G. A. Berchtold, *J. Org. Chem.*, **32**, 3743 (1967). The authors are indebted to Professor Berchtold for a copy of their manuscript and for the nmr spectra of the *cis*- and *trans*-bisepoxide of 1,4-cyclohexadiene and to Dr. Craig for a copy of his thesis.

(5) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

(6) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

5 6

oxygen eclipsings that are not present in **5**. It would appear then that **5** would be more stable than **6** by at least 2.6 kcal (the difference in energy between *gauche* butane and that conformer which has two methyl–hydrogen elipsings and one hydrogen–hydrogen eclipsing) and thus would comprise approximately 99% of the mixture of **5** and **6**.[7] Thus the preferred conformation of **2** favors the formation of the *cis*-bisepoxide since in this conformation approach of the epoxidizing species to the carbon–carbon double bond on the side of the molecule *trans* to the epoxide ring is seriously hindered by the "flagpole" and "bowsprit" methyl groups. The preferential formation of the *cis*-bisepoxide should therefore be expected.

Experimental Section[8]

Epoxidation of 3,3,6,6-Tetramethyl-1,4-cyclohexadiene (1).—Following the procedure of Korach[5] 7.85 g of 34% peracetic acid (0.035 mol) which had been saturated with sodium acetate was added dropwise with rapid stirring to a suspension of 5.8 g of sodium carbonate in a solution of 6.0 g (0.035 mol) of **1** and 66.0 g of methylene chloride. The temperature of the reaction mixture was maintained at 23–25° during the course of the addition (0.5 hr) and for a period of 2 hr after the addition was completed during which time the reaction mixture was stirred rapidly. The reaction mixture was cooled to 0° and maintained at that temperature while it was neutralized with 25% sodium hydroxide. The reaction mixture was filtered and the organic layer separated. The aqueous layer was extracted with three 15-ml portions of methylene chloride and the extracts were combined with the original organic layer. After drying ($MgSO_4$) the methylene chloride was separated by distillation and the residue was fractionated using vpc at 133°. In this fashion 1.59 g (30%) of **2** was isolated. It had bp 176–177°; $n^{28}D$ 1.4493; ir (CCl_4) 3080 (=CH), 1650 (C=C), 1250 and 860 (epoxy);[9] nmr ($CDCl_3$) δ 5.07 (m, 2, -CH=CH-), 2.91 (2, m, epoxy hydrogens), 1.05 (s, 6, 2-CH_3) and 1.1 (s, 6, 2-CH_3).[10]

Anal. Calcd for $C_{10}H_{16}O$: C, 78.84; H, 10.64. Found: C, 78.66; H, 10.62.

Also isolated was 0.60 g (11%) of bisepoxide **3**: mp 83–84°; ir (KBr) 1260, 835 and 820 (epoxy).[9] See discussion for nmr data.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.60. Found: C, 71.22; H, 9.52.

3,3,6,6-Tetramethylcyclohexen-4-ol (4).—A solution of 1.0 g (6.6 mmol) of **2** in 25 ml of anhydrous tetrahydrofuran (THF) was added dropwise with stirring to a suspension of 0.25 g (6.6 mmol) of lithium aluminum hydride in 60 ml of anhydrous THF. After the addition was complete (0.5 hr) the reaction mixture was refluxed for 12 hr. Excess lithium aluminum hydride was destroyed and lithium and aluminum salts were precipitated using the method of Micovic[11] and the supernatent liquid was decanted. The granular inorganic residue was washed with two 10-ml portions of THF and the combined THF solution and washings were dried ($MgSO_4$). The THF was distilled through a semimicro column and the residue was purified by vpc at 133° yielding 0.72 g (71%) of **4**: mp 46–47°; ir (CCl_4) 3700 and 3500 (-OH), 1670 (C=C) and 1040 (CO); nmr ($CDCl_3$) δ 5.22 (s, 2, -HC=CH-), 3.68 (m, 1, J_{AX} = 7 Hz, J_{BX} = 9 Hz, -CHOH), 1.54 (d, 1, J = 9 Hz, -HCH-), 1.55 (d, 1, J = 7 Hz, -HCH-),[12] 1.06 (s, 3, -CH_3), 1.01 (s, 6, 2-CH_3), and 0.92 (s, 3, -CH_3).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.85; H, 11.78. Found: C, 77.63; H, 11.87.

A 3,5-dinitrobenzoate prepared according to the procedure of Brewster and Ciotti[13] and recrystallized from ethanol–water had mp 103–104°.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 58.61; H, 5.79; N, 8.04. Found: 58.94; H, 6.10; N, 8.05.

Registry No.—**1**, 2223-54-3; **2**, 19165-53-8; **3**, 19165-54-9; **4**, 19165-55-0.

(7) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 9.

(8) All melting points and boiling points are uncorrected. The infrared spectra were determined with a Perkin-Elmer Model 137 spectrophotometer. The nmr spectra were determined on a Varian A-60 spectrometer and the data are in parts per million using tetramethylsilane as an internal standard at 0.00 ppm. Gas chromatographic analyses and collections were performed using a 7 ft × 0.25 in. glass column packed with 30% DC 550 on base-washed 60/80 Chromosorb P. The microanalyses were performed by C. F. Geiger, Ontario, Calif.

(9) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

(10) The olefinic protons and the ring junction protons give rise to what appears to be two triplets centered at the above chemical shifts. A computer analysis of this system obtained through the courtesy of A. H. Turner at the University of Rochester showed $J_{14} = J_{23} = 1.1$ and $J_{15} = J_{24} = 1.2$ Hz.

(11) V. M. Micovic and M. LJ. Mihailovic, *ibid.*, **18**, 1190 (1953).

(12) The coupling constant for the two methylene protons is apparently nearly zero.

(13) J. H. Brewster and C. J. Ciotti, *J. Amer. Chem. Soc.*, **77**, 6214 (1955).

Clemmensen Reduction of 2,2,4,4,6,6-Hexamethyl-1,3,5-cyclohexanetrione. A Reinvestigation

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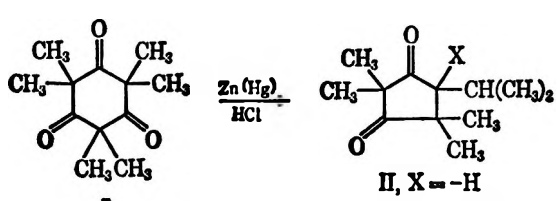
In the course of an investigation on the electrochemical reduction of 1,3-diketones,[1] we had occasion to repeat the recently described[2] Clemmensen reduction of 2,2,4,4,6,6-hexamethyl-1,3,5-cyclohexanetrione (I). Because our results differ from those previously reported in a manner having some mechanistic significance, we wish to report them at this time.

Reduction of I by amalgamated zinc in a two-phase toluene–hydrochloric acid system was reported to give the rearranged diketone II as the sole major product.[2] In our hands repetition of this reduction as originally described led to a crude reaction mixture, glpc analysis of which showed the presence of not one, but *two* major products, present in approximately equal amounts. Samples of the two products were readily isolated from the mixture by preparative glpc. The physical and spectroscopic properties of one of the products agreed with those described[2] for diketone II. The second product was a white crystalline solid to which we have assigned structure III.[3] The infrared spectrum of III



I II, X = -H III, X = -OH

(1) T. J. Curphey and R. L. McCartney, submitted for publication.

(2) M. L. Kaplan, *J. Org. Chem.*, **32**, 2346 (1967).

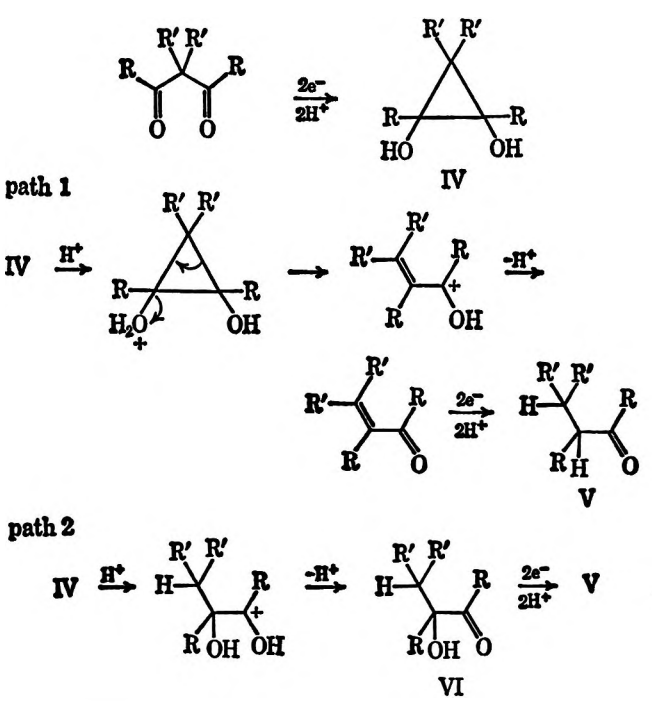
(3) The failure of the original investigator to detect III as a reduction product might have been due to its rather long retention time on glpc (see Experimental Section), to losses in the distillative work-up employed, or perhaps to overreduction (*vide infra*).

was similar to that of II but showed an additional sharp band at 3480 cm^{-1} attributed to -OH stretch. The 100-MHz nmr spectrum of III in benzene solution showed a singlet at δ 3.03 for the -OH group, a septet (after time-averaging for 31 scans) at δ 1.67 (J = 7 Hz) for the methine hydrogen, four singlets at δ 1.14, 1.12, 1.01, and 0.94 for the methyl groups attached to the ring, and two doublets (J = 7 Hz) at δ 0.93 and 0.73 for the two nonequivalent isopropyl methyls. Elemental analysis agreed with the assignment of structure III to this product.

The genetic relationship between II and III was explored by repeating the reduction with periodic glpc examination of aliquots of the reaction mixture. Table I shows the results of this experiment. As expected from the data shown in Table I, a reduction terminated after 22 hr gave a mixture from which II and III were isolated in yields (based on starting material taken) of 24 and 26%, respectively. Likewise, prolongation of the reduction period to 70 hr gave a 49% yield of II. The implication of these experiments, that III is the precursor of II, was further strengthened by subjecting III to the conditions of the Clemmensen reduction, whereupon II was isolated in 41% yield.

The mechanism of the abnormal Clemmensen reduction of certain 1,3-diketones has been the object of much recent investigation and discussion, principally by two groups of workers.[4-6] Both groups accepted the suggestion of Staschewski[4] that the first step in the reaction of such ketones is the formation of cyclopropanediol IV by an intramolecular pinacol reduction, but they initially differed on the subsequent fate of IV. On the one hand, Davis and coworkers[5a,c] adopted Staschewski's original suggestion that IV undergoes an acid-catalyzed rearrangement (Scheme I, path 1) to an unsaturated ketone,[7] the latter then being further reduced to the rearranged ketone V. Such a scheme was advanced by Kaplan[2] to rationalize the formation of II from I. On the other hand, Wenkert and Kariv[6] suggested (Scheme I, path 2) that protolysis of IV leads not to an unsaturated ketone, but to ketol VI, which is then further reduced to V. Clearly our isolation of ketol III from the reduction of I supports the Wenkert mechanism for such reductions. The fact that apparently in no case has an unsaturated ketone been detected as an intermediate in the abnormal Clemmensen reduction of a 1,3-diketone and that, where a careful search has been made, ketol intermediates were isolated,[5b,6] often as major products, strongly suggests that there is currently no basis for invoking the intermediacy, however mechanistically plausible, of unsaturated ketones in such reductions. Recent work by Davis[5b] has apparently led him to the same conclusion.

SCHEME I



Experimental Section[8]

Clemmensen Reduction of 2,2,4,4,6,6-Hexamethyl-1,3,5-cyclohexanetrione.—A mixture of 12 g of amalgamated zinc,[2] 8 ml of water, 18 ml of concentrated hydrochloric acid, 10 ml of toluene and 2.1 g (0.01 mol) of triketone was refluxed with magnetic stirring. At periodic intervals 8-ml portions of hydrochloric acid (at 5, 8, 22, 30, 32, 44, and 55 hr) and 4-g portions of amalgamated zinc (at 24, 30, 45, and 60 hr) were added. During the course of the reaction aliquots of the toluene layer were withdrawn, worked up, and analyzed on a 3 ft × 0.25 in. column of 20% XF-1150 on acid-washed silanized Chromosorb W operated at 165° and a helium flow rate of 80 ml/min. Under these conditions the retention time of I was 11 min, of II 6 min, and of III 15 min.[3] The results of these analyses are presented in Table I.

TABLE I
PRODUCT COMPOSITION DURING THE CLEMMENSEN REDUCTION OF I

Time, hr	Composition, %[a]		
	I	II	III
4	89	3	8
9	78	8	14
22	35	30	35
29	19	48	33
48	4	80	16
69	1	88	11

[a] Expressed as per cent of the total peak area for I + II + III. No correction for detector sensitivity was applied.

After 70 hr the total reaction mixture was worked up, the organic extract concentrated at the water pump, and the residue distilled under high vacuum. The distillate was recrystallized from pentane at −78° to give 0.96 g (49%) of **2,2,4,4-tetramethyl-5-isopropyl-1,3-cyclopentanedione** (II), mp 29.5–30.4° (lit.[2] mp 30°). The ir and nmr spectra of this material were as previously described[2] with the exception that on our ir instrument

(4) D. Staschewski, *Angew. Chem.*, **71**, 726 (1959).

(5) (a) N. J. Cusack and B. R. Davis, *Chem. Ind.* (London), 1426 (1964); (b) K. M. Baker and B. R. Davis, *ibid.*, 768 (1966); (c) N. J. Cusack and B. R. Davis, *J. Org. Chem.*, **30**, 2062 (1965).

(6) E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965).

(7) This rearrangement was postulated to involve the intermediacy of cyclopropyl cations, but recent work on the chemistry of cyclopropanols [see C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968)] favors revision to the concerted ring opening as depicted.

(8) Melting points were taken using Anschütz thermometers fully immersed in a stirred oil bath. Infrared spectra were measured on dilute solutions in carbon tetrachloride using a Beckman IR-5A spectrophotometer. The nmr spectra were measured with Varian Associates Models HA-100 and A-60 spectrometers on solutions containing internal tetramethylsilane reference. A Varian C-1024 time-averaging computer was employed in conjunction with the 100-MHz spectrometer. Gas–liquid partition chromatography (glpc) was performed on a Wilkens Aerograph Model A-90-P3. All reaction mixtures were worked up by extracting the aqueous phase with ether, washing the combined organic phases with saturated sodium bicarbonate and sodium chloride solutions, and drying the extract over magnesium sulfate.

the carbonyl bands fell at 1720 (s) and 1760 cm^{-1} (w) instead of at 1745 and 1780 cm^{-1}. When the reaction was terminated after refluxing for only 22 hr and the total organic extract (after concentration at the water pump) chromatographed on a 20 ft × $\frac{3}{8}$ in. column of 30% SE-30 at 260° and a flow rate of 80 ml/min, there was obtained 0.47 g (24%) of II and 0.54 g (26%) of III. The sample of **2,2,4,4-tetramethyl-5-hydroxy-5-isopropyl-1,3-cyclopentanedione (III)** thus obtained had mp 37.6–38.0°, absorbed in the ir at 1720 (s), 1760 (w), and 3480 cm^{-1} (m), and in the nmr (see text for analysis) at δ 3.03 (singlet, 1 H), 1.67 (septet, J = 7 Hz, 1 H), and 0.7–1.2 (multiplet, 18 H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.01; H, 9.68.

Clemmensen Reduction of III.—A 0.230-g sample of III was subjected to the reduction procedure described above for a reaction time of 43 hr. Glpc analysis of the mixture at this time showed approximately 7% unreacted III and 62% II. Separation and purification by preparative glpc gave 0.078 g of II (41% yield), mp 29.4–30.2°, identical in all respects (ir, nmr, and mixture melting point) with the material prepared directly from I.

Registry No.—I, 778-18-7; III, 19165-42-5.

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A New Spirocyclohexenedione System

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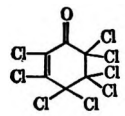
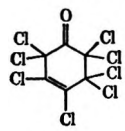
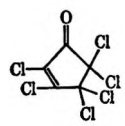
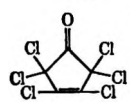
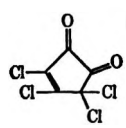
Received July 1, 1968

In the course of an investigation on photodecomposition products of pentachlorophenol,[1] a new spirocyclohexenedione compound (**1**) was found to form from pyrocatechol by the action of chlorine.

According to Zincke and Küster,[2] pyrocatechol reacts with chlorine in acetic acid to produce tetrachloropyrocatechol. However, it was found that further introduction of chlorine at higher temperature produced new light yellow crystals having the composition $C_{12}Cl_8O_4 \cdot H_2O$ (hydrate) in an 80% yield. Chemical and spectral evidence showed that this was spiro-[2′,3′,4,5,6,6′,6′,7-octachloro-1,3-benzodioxole-2,1′-[2]-cyclohexene]-4′,5′-dione hydrate (**1**). Mass spectrum of hydrate **1** had a molecular peak at m/e 488 (M^+, 8Cl, as an anhydrous form). Ultraviolet and infrared spectra showed the presence of an α,β-unsaturated ketone group (see Table I) and a phenoxyl nucleus. Dehydration of **1** yielded a yellow colored anhydrous substance, $C_{12}Cl_8O_4$ (**2**), showing spectral bands of an unsaturated 1,2-diketone.[3] The anhydrous substance lost its color in air owing presumably to the conversion of the 1,2-diketone system by the hydration into the ketone system. The infrared spectra of **1** and **2** agreed with this view. When **1** was dissolved in 75% acetic acid and the solution was poured into water, a colorless dihydrate (**3**) was precipitated. The infrared spectrum showed no carbonyl absorption and the ultraviolet spectrum at λ_{max} 234 mμ was compatible with a monoene structure.

TABLE I

PRINCIPAL BANDS IN ULTRAVIOLET AND INFRARED SPECTRA OF DERIVATIVES

Compd	λ_{max}, mμ (ϵ)	Solvent	ν_{max}, cm^{-1}
1	261 (17,000)	$CHCl_3$	1,730[a]
 [d]	267–268 (10,500)	C_6H_{12}	1,745[b]
 [d]	235–237 (9,000)	C_6H_{12}	1,779[b]
 [e]	259 (10,000)	95% C_2H_5OH	1,739[c]
 [e]	223 (10,000)	95% C_2H_5OH	1,776[c]
 [f]	226 (12,300) 283 (7,840)	C_6H_{14}	1,795 1,748[b]

[a] KBr disk. [b] CCl_4 solution. [c] $CHCl_3$ solution. [d] L. Denivelle and R. Fort, *C. R. Acad. Sci., Paris*, **242**, 2359 (1956). [e] See ref 7. [f] R. M. Scribner, *J. Org. Chem.*, **30**, 3657 (1965).

Reaction of **1** with *o*-phenylenediamine to form dihydrophenazine **4** confirmed the potential 1,2-diketone system. Acetylation of **1** gave a colorless spiro acetyl ketal (**5**). On reduction, **1** afforded a phenol derivative which gave a triacetate. The reductive acetylation of **1** afforded the same compound. These compounds were identical with a quinol[4] and the acetate[4] derived from 3,4,6-trichloro-5-(2,3,4,5-tetrachloro-6-hydroxyphenoxy)-1,2-benzoquinone, respectively.[1,5] Chlorination of this benzoquinone gave **1** in good yield. Alkaline hydrolysis of **1** yielded a monobasic acid (**6**) which was proved to be a product of the benzylic acid rearrangement (Scheme I). In infrared spectrum, the carbonyl band of **6** was similar to that of 1-hydroxy-2,3,4,4,5,5-hexachloro-2-cyclohexene-1-carboxylic acid.[2]

Hexachloro-3-cyclohexene-1,2-dione (**8**),[2] the anhydrous chlorination product of pyrocatechol, gave, on the benzylic acid rearrangement, 1-hydroxy-2,3,4,4,5,5-hexachloro-2-cyclohexene-1-carboxylic acid which on decarboxylation gave rise to hexachlorocyclopentenone. The Raman spectra[6] as well as physical[7] and chemical[8] properties of this cyclopentenone furnished its assigned structure. The yellow cyclohexenedione (**8**) gave, however, readily a colorless monohydrate (**9**), the

(1) M. Kuwahara, N. Kato, and K. Munakata, *Agr. Biol. Chem.* (Tokyo), **29**, 880 (1965); **30**, 232, 239 (1966).

(2) T. Zincke and F. Küster, *Ber.*, **21**, 2719 (1888); W. Eller and V. Lorenz, *ibid.*, **58**, 494 (1925).

(3) N. B. Haynes, D. Redmore, and C. J. Timmons, *J. Chem. Soc.*, 2420 (1963).

(4) C. L. Jackson and G. L. Kelley, *Amer. Chem. J.*, **47**, 197 (1912).

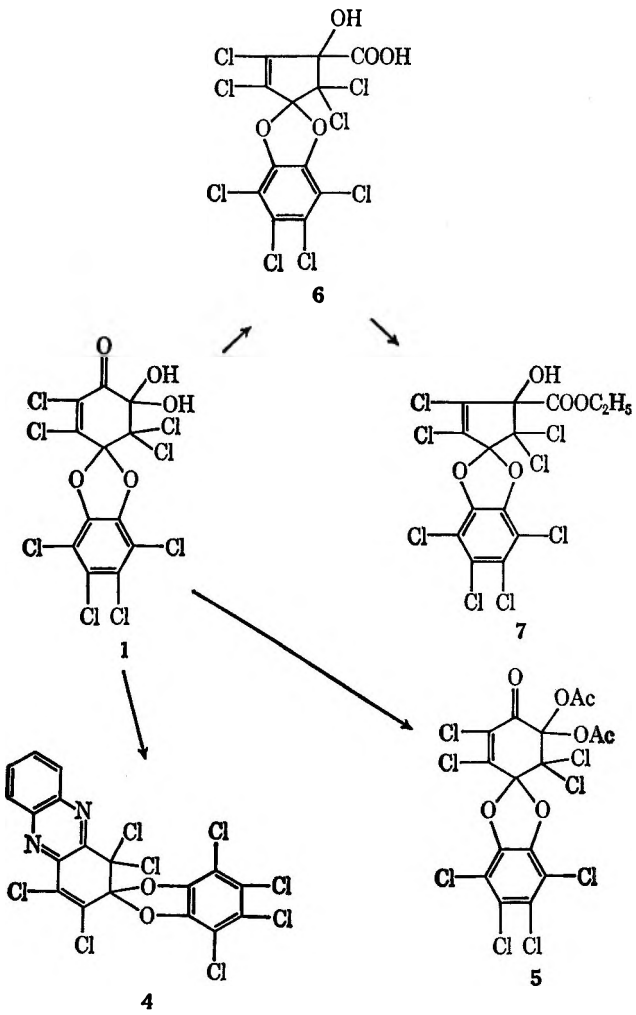
(5) C. L. Jackson and P. W. Carleton, *ibid.*, **39**, 493 (1908).

(6) H. V. Brederode, H. Gerding, and H. J. Prins, *Rec. Trav. Chim. Pays-Bas*, **65**, 174 (1946).

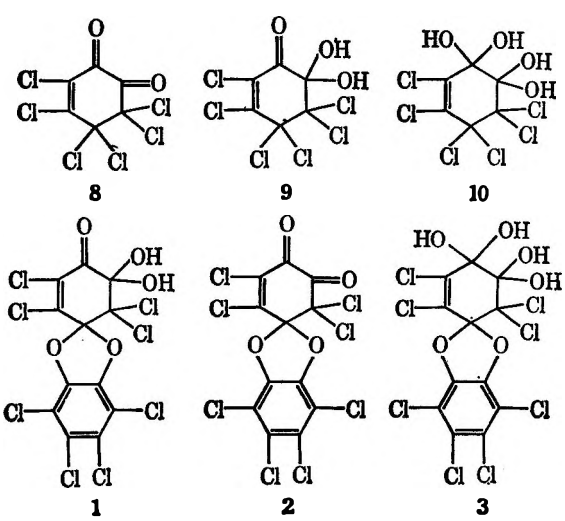
(7) E. T. McBee, D. K. Smith, and H. E. Ungnade, *J. Amer. Chem. Soc.*, **77**, 559 (1955).

(8) J. S. Newcomer and E. T. McBee, *ibid.*, **71**, 946 (1949).

SCHEME I



position of the hydration being untouched. The ultraviolet spectral data satisfied the structures **9** and **8** in accord with the nature of **1** and **2**, respectively.



In a freshly prepared ethanol solution, the ultraviolet spectra of **9** and **1** exhibited each absorption maximum at λ_{max} 262 and 253 mμ characteristic of an α,β-unsaturated ketone (see Table I). These absorption intensities decreased rapidly on standing and new absorption maxima appeared at λ_{max} 222 mμ (ε 9300) and 234 (17,900), respectively. These phenomena might be accounted for by the reversible addition[9] of ethanol forming the hemiketal or the ketal. These data would suggest the conversion of the conjugated ketone systems of **9** and **1** into the monoene systems of **10** and **3** which would appear compatible with shorter wavelength shifts of the absorption maxima by 40 and 19 mμ, respectively. Similar conversion was observed on other 1,2-diketones such as dimeric 3-methoxyl-1,2-benzoquinone[10] and 5-cyclooctene-2,3-dione.[11]

Experimental Section

All melting points were determined on a Yanagimoto melting point apparatus. Infrared spectra were recorded with a Hitachi Model EPI-2 spectrophotometer and ultraviolet spectra with a Hitachi Model EPS-2 spectrophotometer.

Spiro[2′,3′,4,5,6,6′,6′,7-octachloro-1,3-benzodioxole-2,1′-[2]-cyclohexene]-4′,5′-dione Hydrate (1). A.—Chlorine was passed slowly through a solution of pyrocatechol (200 g) in 97% acetic acid (1 l.). The temperature of the mixture was maintained between 20 and 30°. During the reaction, tetrachloropyrocatechol precipitated and the mixture became semisolid. Further introduction of chlorine at 60–70° converted the semisolid mixture into a red solution and then its color turned yellow. The solvent was removed under reduced pressure and the residue (460 g) was recrystallized from chloroform to afford light yellow needles (**1**): mp 209–210°; $\lambda_{max}^{CHCl_3}$ 261, 293, 300 mμ (ε 17,000, 3820, 3160); λ_{max}^{EtOH} 234, 295, 302 mμ (ε 17,900, 2520, 2820); ν_{max}^{KBr} 3350 (OH), 1730 (C=O), 1590 cm^{-1} (C=C); mass spectrum *m/e* (anhydrous form) 488 (M^+, 8Cl), 460 ($M^+ - CO$), 453 ($M^+ - Cl$), 432 ($M^+ - 2CO$), 425 ($M^+ - Cl - CO$), 397 ($M^+ - Cl - 2CO$).

Anal. Calcd for $C_{12}Cl_8O_4 \cdot H_2O$: C, 28.27; H, 0.40; Cl, 55.65. Found: C, 28.22; H, 0.71; Cl, 55.58.

Anhydrous Product.—On drying over phosphorus pentoxide for 5 hr at 120° (0.1 mm), **1** lost 1 mol of water and gave the anhydrous form (**2**): mp 207–210°; ν_{max}^{KBr} 1770, 1720, 1580 cm^{-1}.

Anal. Calcd for $C_{12}Cl_8O_4$: C, 29.30; Cl, 57.67. Found: C, 29.31; Cl, 57.61.

Dihydrate.—Monohydrate **1** was dissolved in 75% aqueous acetic acid and water was added. Precipitated colorless crystals (**3**) were collected, mp 112–114°, solidified and remelted at 207–209°: λ_{max}^{EtOH} 234, 293, 302 mμ (ε 18,500, 2840, 2920); ν_{max}^{KBr} 3350, 1635 cm^{-1}. This compound was converted into **1** in the air or by recrystallization from chloroform or ethanol.

Anal. Calcd for $C_{12}H_4Cl_8O_6$: C, 27.31; H, 0.76; Cl, 53.74. Found: C, 28.05; H, 1.10; Cl, 54.16.

The elemental analysis was not satisfactory presumably because **3** lost water easily in the air to give **1**.

B.—An excess of the chlorine was passed through a solution of 3,4,6-trichloro-5-(2,3,4,5-tetrachloro-6-hydroxyphenoxy)-1,2-benzoquinone[1,6] (3 g) in acetic acid (50 ml) at below 20°. When the solvent was removed under reduced pressure and the resulting crystals were recrystallized from chloroform, there were obtained light yellow needles (1 g), mp 208–209°, identical with spirocyclohexenedione **1** by mixture melting point and infrared spectrum.

Spiro[1,1,3,4,4′,5′,6′,7′-octachloro-1,2-dihydrophenazine-2,2′-[1,3]benzodioxole] (4).—A solution of *o*-phenylenediamine (3 g) in methanol (50 ml) was added with stirring to a solution of **1** (15 g) in a mixture of methanol (80 ml), glacial acetic acid (20 ml) and chloroform (50 ml). When the vigorous exothermic reaction subsided, the mixture was kept at 20° with stirring and allowed to stand in an ice box for 1 day. The yellow solid was collected by filtration, washed with methanol and after drying weighted 14 g. An analytical sample was prepared by crystallization from chloroform as light yellow needles (**4**), mp >300°.

Anal. Calcd for $C_{18}H_4Cl_8N_2O_2$: C, 38.34; H, 0.71; N, 4.97; Cl, 50.30. Found: C, 38.27; H, 0.84; N, 4.97; Cl, 49.97.

Spiro[2′,3′,4,5,6,6′,6′,7-octachloro-5′,5′-diacetoxy-1,3-benzodioxole-2,1′-[2]cyclohexen]-4′-one (5).—Spirocyclohexenedione **1** (10 g) was acetylated with acetic anhydride (100 ml) and sulfuric acid (0.5 ml) by a usual method to give acetate **5**, yield 10 g.

(9) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

(10) E. Adler, R. Magnusson, B. Berggren, and H. Yhomelius, *Acta Chem. Scand.*, **14**, 515 (1960).

(11) L. Horner and H. Merz, *Ann. Chem.*, **570**, 89 (1950).

Recrystallization from ethanol gave colorless plates: mp 207–208°; $\lambda_{max}^{CHCl_3}$ 257, 292, 301 mμ (ε 16,900, 3130, 3050); ν_{max}^{KBr} 1780 (C=O), 1769 (C=O), 1736 (C=O), 1592 cm^{-1} (C=C); mass spectrum *m/e* 590 (M^+, 8Cl), 488 [$M^+ - (CH_3CO)_2O$], 460 [$M^+ - CO - (CH_3CO)_2O$].

Anal. Calcd for $C_{16}H_6Cl_8O_7$: C, 32.36; H, 1.02; Cl, 47.75. Found: C, 32.37; H, 1.15; Cl, 47.76.

2,3′,4′-Trihydroxy-2′,3,4,5,5′,6,6′-heptachlorodiphenyl Ether.—Zinc dust (10 g) was added with stirring to a solution of **1** (10 g) in acetic acid (100 ml). The mixture was heated for 1 hr and poured into water after removal of the catalyst. The resulting crystals were collected and recrystallized from benzene to give colorless prisms, mp 180° (lit.[4] mp 181–182°), yield 7 g.

2,3′,4′-Triacetoxy-2′,3,4,5,5′,6,6′-heptachlorodiphenyl Ether. A.—Spirocyclohexenedione **1** (10 g) was dissolved in acetic anhydride (100 ml). The mixture was treated with zinc dust until the solution became colorless. After a few drops of sulfuric acid was added, the mixture was heated for 30 min on a water bath. The mixture was poured into water to give colorless prisms (6 g), mp 147–148° (lit.[4] mp 144°).

Anal. Calcd for $C_{18}H_9Cl_7O_7$: C, 36.92; H, 1.55; Cl, 42.39. Found: C, 36.97; H, 1.52; Cl, 42.35.

B.—Acetylation of 2,3′,4′-trihydroxy-2′,3,4,5,5′,6,6′-heptachlorodiphenyl ether (3 g) with acetic anhydride and sulfuric acid gave the colorless triacetate (2 g), mp 147–148°.

Spiro[2′,3′,4,5,5′,5′,6,7-octachloro-4′-hydroxy-1,3-benzodioxole-2,1′-[2]cyclopentene]-4′-carboxylic Acid (6).—Spirocyclohexenedione **1** (10 g) was heated on a water bath with 10% aqueous sodium hydroxide (10 ml) and dioxane (50 ml) for 2 hr. The mixture was poured into water and the resulting crystals were collected by filtration to yield 9 g of the crude material. Recrystallization of this compound from chloroform gave colorless prisms (**6**): mp 188° dec; ν_{max}^{KBr} 3370, 2900 (OH), 1741 (C=O), 1636 cm^{-1} (C=C). Its molecular weight by a potentiometric titration with 0.1 *N* sodium hydroxide was 500.0 (theoretical 527.8) and it was a monobasic acid, pK_a' 3.55 in 10% ethanol solution. The pK_a' value was assumed to be the pH of half-neutralization.

Anal. Calcd for $C_{12}H_2Cl_8O_5 \cdot H_2O$: C, 27.31; H, 0.76; Cl, 53.74. Found: C, 27.54; H, 1.31; Cl, 53.62.

Spiro[2′,3′,4,5,5′,5′,6,7-octachloro-4′-hydroxy-1,3-benzodioxole-2,1′-[2]cyclopentene]-4′-carboxylic Acid Ethyl Ester (7). A.—Esterification of **6** (5 g) with ethanol and sulfuric acid gave 2 g of its ester (**7**): mp 176–177°; ν_{max}^{KBr} 3350 (OH), 1740 (C=O), 1638 cm^{-1} (C=C).

B.—To the solution of **1** (5 g) in ethanol (40 ml) was added hydrochloric acid (5 ml). The mixture was heated on a water bath for 2 hr and poured into water. The resulting crystals were collected, dried and recrystallized from ethanol to give colorless prisms, mp 176–177°, yield 2.5 g. This compound was identified as ethyl ester **7** of **6** by mixture melting point and infrared spectrum.

Anal. Calcd for $C_{14}H_6Cl_8O_5$: C, 31.26; H, 1.12; Cl, 52.73. Found: C, 31.07; H, 1.31; Cl, 52.59.

Hexachloro-3-cyclohexene-1,2-dione hydrate (**9**) was prepared by the method indicated by Zincke and Küster.[2] Chlorine was passed through a solution of pyrocatechol (20 g) in acetic acid (400 ml) under cooling. The reaction mixture was poured into water. The resulting precipitate was collected by filtration and recrystallized from ethanol to obtain colorless prisms (**9**, 39 g): mp 90–92° (lit.[2] mp 93–94°); $\lambda_{max}^{CHCl_3}$ 269 mμ (ε 8500); ν_{max}^{KBr} 1723 cm^{-1}.

Anhydrous Form (**8**).—The acetic acid was removed from the above reaction mixture *in vacuo* and the red residue was distilled to give a yellow liquid (**8**): bp 114–116° (0.35 mm) [lit.[2] bp 170° (18 mm)]; $\lambda_{max}^{CHCl_3}$ 269 mμ (ε 8830); ν_{max} 1778, 1720 cm^{-1}.

1-Hydroxy-2,3,4,4,5,5-hexachloro-2-cyclohexene-1-carboxylic acid was produced by the method reported by Prins.[6] A solution of **8** (12.7 g) in acetic acid (25 ml) was added with stirring to a 0.15-mol solution (40 ml) of sodium carbonate. The acid was set free by adding a mixture of acetic acid (25 ml) and hydrochloric acid (12 ml). The mixture was poured into water and the precipitate was filtered to afford colorless plates (8 g): mp 112–113° (lit.[2] mp 111°); ν_{max}^{KBr} 1730 cm^{-1} (C=O).

Registry No.—**1**, 19254-91-2; **2**, 19254-92-3; **3**, 19294-05-4; **4**, 19294-06-5; **5**, 19294-07-6; **6**, 19254-90-1; **7**, 19254-93-4; **8**, 19254-94-5; **9**, 19254-95-6.

The Thermolysis of Bromodifluoroacetic Anhydride

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The thermal decomposition of fluorinated carboxylic acid anhydrides has been of interest for several years.[1,2]

Kirshenbaum, *et al.*,[2] in a detailed study of the action of heat on the silver salts of perfluorocarboxylic acids, reports qualitative data on the thermolysis of perfluorobutyric anhydride. The reactions were carried out at autogenous pressures at 400–435° for 3 hr. The anhydride in the presence of Ag_2O gave the coupled product, C_6F_{14}. When, however, the thermolysis was attempted using a perfluoroanhydride *without* Ag_2O very little coupled product was realized.

In our studies, we have found that the thermolysis of bromodifluoroacetic anhydride proceeds almost quantitatively in the absence of an added catalyst (*i.e.*, Ag_2O), as represented by eq 1.

$$2BrCF_2\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CF_2Br \longrightarrow BrCF_2\overset{O}{\overset{\|}{C}}Br + 2CO_2 + CO + BrCF_2Br + CF_2{=}CF_2 \quad (1)$$

The coupled products in Kirshenbaum's work were stable, isolable compounds but, in the case of bromodifluoroacetic anhydride, the coupled product, $BrCF_2CF_2Br$, is unstable at high temperatures (*i.e.*, 300°). An independent experiment has confirmed the presence of Br_2 + polyperfluoroethylene and perhaps $CF_2{=}CF_2$, from the thermolysis of $BrCF_2CF_2Br$ under the same experimental conditions used in the thermolysis of

$$BrCF_2\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CF_2Br$$

Experimental Section

A. Apparatus.—The thermolysis system consisted of an airtight, heated vertical Vycor tube loosely packed with glass wool. The reactant entered the system through an addition funnel and was flushed down with anhydrous nitrogen. The products from the thermolysis were trapped in cold traps at −70°.

B. Procedure.—In a typical run, the Vycor tube and glass wool was heated to 150° for 2 hr under a stream of nitrogen. The temperature was then increased to 300° and bromodifluoroacetic anhydride (100 g, 0.30 mol) was allowed to enter slowly into the reaction zone.

The material condensing in the traps was then distilled through a 6-in. Vigreux column. Based on eq 1, a 76% yield (25 g) of $BrCF_2Br$, bp 23° (lit.[3] bp 20–25°), and 92% yield (33 g) of $BrCF_2C(=O)Br$, bp 71°, was isolated. Infrared spectroscopy (CCl_4) shows two absorptions in the carbonyl region at 5.55 (strong) and 5.68 μ (weak) for $BrCF_2C(=O)Br$. These bands are in accord with the spectra of known acid halides.[4] ^{19}F nmr shows a single at 59.1 ppm (relative to $CFCl_3$) and mass spectrometry gives a fragmentation pattern consistent with

(1) R. N. Haszeldine, British Patent 747,893 (1956).

(2) A. D. Kirshenbaum, A. G. Streng and M. Hauptschein, *J. Amer. Chem. Soc.*, **75**, 3141 (1953).

(3) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1958, p 48.

(4) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 45.

$BrCF_2C(=O)Br$, with the molecular ion at 236 ($C_2Br_2F_2O$) and the most abundant m/e at 129 $(CF_2Br)^+$. The properties of the ethyl ester of $BrCF_2C(=O)Br$ were identical with a sample of authentic $BrCF_2C(=O)CH_2CH_3$ prepared from the corresponding acid and ethanol.[5]

Dibromodifluoromethane was identified mass spectrally with a molecular ion (CF_2Br_2) at 208 and the most intense m/e at 191 $(CFBr_2)^+$.

Carbon dioxide and carbon monoxide were identified mass spectrally when the decomposition was performed in such a way as to intercept the effluent gases from the thermolysis by an AEI mass spectrometer.

Registry No.—Bromodifluoroacetic anhydride, 7601-98-1.

Acknowledgments.—The author wishes to thank Mr. R. Gohlke for interpreting the mass spectral data and Dr. Y. Kim for his timely suggestions.

(5) G. A. Grindahl, W. X. Bajzer, and O. R. Pierce, *J. Org. Chem.*, **32**, 603 (1967).

O *vs.* C Alkylation of Ethyl Acetoacetate

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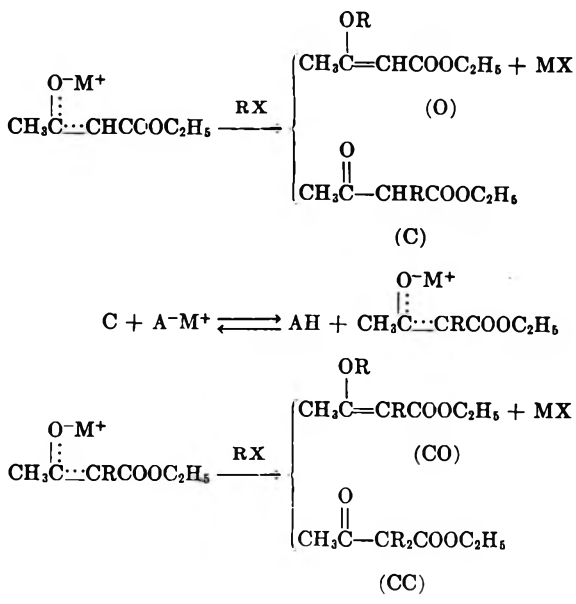
Following a number of isolated instances of O alkylation of ethyl acetoacetate,[1] several reports of the fairly general applicability of this reaction have appeared by now.[2-4] These studies have revealed that the O/C-alkylation ratio is remarkably dependent on the structure of the alkyl group, the solvent, the temperature and the cation; however, a more detailed investigation of these effects was hampered by the fact that the over-all yields are often rather poor. A recent communication concerning this reaction in hexamethylphosphoramide[5] (HMPA) prompts us to report our own results obtained with this solvent. We have found that the use of HMPA allows not only better yields, but also the highest O/C ratios yet observed. This reaction is therefore useful for studies of ambident anion behavior as well as for synthetic purposes. The alkylation of ethyl acetoacetate is described in Scheme I.

In most cases, the reaction was carried out at about 100°; the anion was generated by the addition of ethyl acetoacetate to an ethoxide salt followed by the careful removal of ethanol, and the dissolution of the remaining solid in HMPA. The alkylating agent was in each case injected slowly under the surface of the solution so as to minimize evaporation losses. The products could be readily separated from the starting material, the solvent

SCHEME I



and added water by means of extractions with *n*-pentane. The analysis of the four products could be carried out completely by means of either vpc or nmr, as detailed in the Experimental Section. The two methods agreed closely in each instance. Table I shows some of the results of the alkylation of the potassium salt of ethyl acetoacetate in HMPA. The reason for the improved yields is not known; however, alkylation and reduction of DMSO by alkylating agents are known reactions.[6] Of equal interest is the fact that the O/C ratios are a great deal higher in HMPA. This ratio increases along the series acetone < acetonitrile < DMSO ≈ dimethylformamide (DMF) ≈ dimethylacetamide ≈ N-methylpyrrolidone < HMPA (data in part from ref 3). A similar sequence (tetrahydrofuran (THF) < ethylene glycol dimethyl ether (glyme) < DMSO ≈ DMF) has been observed[7] in several alkylation reactions of sodium β-naphthoxide. It has been pointed out that the dielectric constants (in parentheses) of these solvents increase roughly in the same order: THF (7) ≈ glyme (7) < DMSO (45) ≈ DMF (37), and acetone (21) < acetonitrile (39) ≈ dimethylacetamide (37). However, the dielectric constant of HMPA is only equal to 30.[8] It is furthermore observed[3,4] that a rise in temperature causes an increase in O/C ratio although the dielectric constant rapidly declines with increasing temperature; we therefore prefer to think of these trends as a correlation with solvent basicity. Such basicity can be defined and measured in a number of ways. One of these is the downfield shift in parts per million of the proton signal of chloroform in infinite dilution in the solvent of interest, as compared to that in cyclohexane. This measure is used here because most of the appropriate data are available: THF, 0.80; acetone, 0.94; DMF, 1.30; DMSO, 1.34; HMPA, 2.03. To the limited extent then that data involving aprotic solvents are available, the O/C ratio appears to correlate

(1) (a) G. D. Lander, *J. Chem. Soc.*, 729 (1900); (b) J. L. Simonsen and R. Storey, *ibid.*, 2106 (1909); (c) C. D. Hurd and K. Wilkinson, *J. Amer. Chem. Soc.*, **70**, 739 (1948); (d) S. J. Rhoads, R. W. Hasbrouck, C. Pryde, and R. W. Holder, *Tetrahedron Lett.*, 669 (1963); (e) K. R. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964).

(2) S. T. Yoffe, K. V. Vatsuro, E. E. Kugutcheva, and M. I. Kabachnik, *Tetrahedron Lett.*, 593 (1965).

(3) G. Brieger and W. M. Pelletier, *ibid.*, 3555 (1965).

(4) W. J. le Noble and J. E. Puerta, *ibid.*, 1087 (1966).

(5) A. L. Kurz, I. P. Beletskaya, A. Macias, and O. A. Reutov, *ibid.*, 3679 (1968).

(6) For a recent review of the properties of DMSO, see D. Martin, A. Weise, and H. J. Niclas, *Angew. Chem. Intern. Ed. Engl.*, **6**, 318 (1967).

(7) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Amer. Chem. Soc.*, **85**, 1148 (1963).

(8) For an up-to-date review of the properties of HMPA, see H. Normant, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1046 (1967).

TABLE I
COMPARISON OF YIELDS AND PRODUCT RATIOS IN HMPA AND DMSO

Alkyl halide	Yield[a,c]	Mole ratio of the products: O	C	CC	CO
Isopropyl chloride	78 (52)	81 (62)	19 (38)	0 (0)	0 (0)
n-Propyl chloride	89 (73)	61 (47)	23 (25)	8 (28)	8 (0)
Ethyl bromide	94 (73)	46 (26)	34 (68)	16 (6)	4 (0)
Methyl iodide[b]	83 (74)	14 (4)	58 (79)	28 (17)	0 (0)
Allyl chloride	88 (80)	17 (0)	45 (100)	38 (0)	0 (0)
Benzyl chloride	93 (60)	13 (5)	51 (45)	36 (50)	0 (0)

[a] Percentage of the alkylating agent accounted for by the products. [b] The sodium salt was used in this case; the potassium salt in all others. [c] The data in parentheses are taken from our earlier study with DMSO.[4]

better with basicity than with the dielectric constant. This question has been discussed by Delpuech[9] in another connection.

It is of interest to compare our results with earlier studies of medium effects on ambident anion behavior.[7,10,11] These studies show that the use of more highly basic aprotic solvents will tend to solvate the counterion and hence leave the oxygen atom of the anion exposed to approach by the alkylating agent; less basic solvents will lead to extensive ion pairing or even clustering, and in such cases C alkylation becomes the alternative mode of alkylation. The effect of heterogeneity[10] in certain cases may well have a similar basis; one may visualize the oxygen atom of phenoxide ion as protected by several counterions in the solid phase, but perhaps by only one ion in benzene *solution*, and thus account for C alkylation in the former case and O alkylation in the latter. In protic solvents, on the other hand, dissociation may be complete, but now the oxygen atom of the anion is shielded by several solvent molecules, and a lowered O/C ratio again results; this has been shown[11] by the correlation of O/C ratios with H bonding ability. These effects can be summarized by the statement: *the freer the anion, the larger the O/C ratio.*

In HMPA the O atom of the ambident anion may well be more accessible than in any other known medium. This is supported by the data shown in Table II. The O/C ratio does not change as the cation is varied in size from Na^+ to NBu_4^+, nor does a reagent such as tetraglyme have any effect; the smallest cation, Li^+, depresses the ratio somewhat. Reutov[5] found such a depression with both lithium and sodium with the use of diethyl sulfate at 20°. We also find, as he did, that the reaction with the lithium salt is much slower. In contrast, small cations tend to depress the O/C ratio to a considerable degree in DMSO,[3,4] and such cation effects have also been noted in the alkylations of other ambident anions.[12,13] Furthermore, although it is observed that the O/C ratio in DMSO tends to increase with increasing temperature,[3,4] as would be expected if further dissociation of ion pairs occurs as the temperature is increased, our studies show no such temperature dependence in HMPA. With isopropyl chloride and the potassium salt, the O/C ratio was 81/19 at 50, 90 and 130°. It is, of course, not necessary that the entire salt sample be completely dissociated in HMPA, as long as the ion association–dissociation equilibria are rapid.

$$M^+(HMPA) + A^- \rightleftharpoons \text{ion pairs} \rightleftharpoons \text{higher aggregates}$$
$$\downarrow \qquad\qquad \downarrow \qquad\qquad \downarrow$$
high O/C ratio — lower O/C ratio — low O/C ratio

The low sensitivity of the O/C ratio to either cation or temperature changes suggests that the alkylation in HMPA proceeds largely through the free anion. It is of interest to point out in this connection that conductance measurements have recently shown several types of ion pairs to be completely unassociated[14] in dilute HMPA solution. It therefore seems possible that the O/C ratio is reaching a maximum in HMPA, and that we are in fact observing the limiting value;[15] any protic or less basic medium would lower the ratio through selective deactivation of the oxygen site by either one or more counterions, or by one or more solvent molecules.

Not a great deal is known as yet about the influence of the alkyl group on the O/C ratio. It is commonly assumed that the ratio is increased as the SN1 character of the alkylating agent increases,[16] since such a correlation allows a ready interpretation of the effect of silver ion on the course of many alkylation reactions. In the case of ethyl acetoacetate, the facts that diazomethane[17]

TABLE II
O/C RATIO WITH ALLYL CHLORIDE AT 95° IN HMPA WITH VARIOUS CATIONS

Cation	O/C	Reactions time, min
Li^+	12/88	210
Na^+	17/83	5
K^+	17/83	3
$N\text{-}(n\text{-}Bu)_4^+$	17/83	3
K^+ (tetraglyme)[a]	16/84	3

[a] Highly effective in separating ion pairs [see T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **89**, 2764 (1967)], and thus in promoting O alkylation [see H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968)].

(9) J. J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).
(10) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).
(11) N. Kornblum, P. J. Berrigan, and W. J. le Noble, *ibid.*, **85**, 1141 (1963).
(12) R. Gompper, *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964).
(13) (a) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958); (b) I. Forsblad, *Arkiv Kemi*, **14**, 403 (1960); (c) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **84**, 43 (1962).
(14) (a) A. Cserhegyi, J. Chaudhuri, E. Franta, J. Jagur-Grodzinski, and M. Szwarc, *ibid.*, **89**, 7129 (1967); (b) H. F. Ebel and R. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **4**, 878 (1965).
(15) For another interesting example of this phenomenon, see S. G. Smith and D. V. Milligan, *J. Amer. Chem. Soc.*, **90**, 2393 (1968).
(16) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955).
(17) F. G. Arndt in "Organic Analysis," Vol. I, Interscience Publishers, New York, N. Y., 1953, pp 197–241.

TABLE III

EFFECTS OF STERIC AND ELECTRONIC FACTORS ON THE O/C RATIO IN HMPA

No.	Chloride[a,c]	Yield, %	Product ratio, % O	C	CC	CO
1	$CH_3CH_2CH_2-$	89	61	23	4	4
2	$(CH_3)_2CH-$	78	81	19	0	0
3	$CH_3CH_2(CH_3)CH-$	75	86	14	0	0
4	$(CH_3)_3CCH_2-$	13[b]	100	0	0	0
5	$C_6H_5CH_2-$	93	13	51	36	0
6	$(C_6H_5)_2CH-$	93	39	61	0	0
7	$2,6\text{-}Me_2C_6H_3CH_2-$	93	19	81	0	0
8	$4\text{-}MeOC_6H_4CH_2-$	88	11	57	32	0
9	$4\text{-}MeC_6H_4CH_2-$	97	13	54	33	0
10	$4\text{-}ClC_6H_4CH_2-$	95	11	48	41	0
11	$4\text{-}CF_3C_6H_4CH_2-$	97	9	50	41	0

[a] The temperature was approximately 100°; in each case potassium was used. [b] This reaction was stopped at low conversion because of the onset of side reactions (ester ether interchange reactions; see Experimental Section). [c] Registry no.: 3 (C derivative) 1540-31-4; 3 (O derivative), 1540-22-3; 4 (O derivative), 19289-27-1; 6 (C derivative), 19289-28-2; 6 (O derivative), 19289-29-3; 7 (C derivative), 19289-30-6; 7 (O derivative), 19289-31-7.

and chloromethyl methyl ether[1b] give ample amounts of the enol ethers have been considered to substantiate that view. However, 2-nitropropane is O alkylated by 3-bromocyclohexene but C alkylated by tropylium bromide;[18] ethyl acetoacetate and tropylium bromide in unbuffered aqueous solution give the C-tropyl derivative.[19] Additional examples are quoted in the preliminary report.[4] In that report it was demonstrated that, in the reaction of a series of common halides with ethyl acetoacetate anion, the O/C ratio in DMSO was highest for those alkylating agents having the lowest SN2 reactivity, and that SN1 reactivity did not appear to correlate with it. Similar results are apparent from an inspection of Table I.[20]

SN2 reactivity is usually associated with steric effects, whereas SN1 reactivity is governed primarily by electronic factors. Our data in HMPA (Table III) show that steric effects are more important in this reaction. Within each series the effect of crowding near the halogen-bonded carbon atom is an increase in the O/C ratio; thus, neopentyl chloride leads to exclusive O alkylation. This effect has also been observed in the alkylation of cyclic β-keto esters by α-halo esters,[21] and in the alkylation of enolates (Table II, footnote *a*). On the other hand, variation of the *para* substituent in benzyl chloride from methoxy to trifluoromethyl has no significant effect. The steric factor cannot be considered exclusively responsible, however. Certainly the steric requirements of allyl and *n*-propyl chloride are not very different, to mention an obvious example.

The effect is probably related to the fact that acetyl oxygen can be easily approached from almost any direction, but the α-carbon atom can of course only be approached in a direction perpendicular to the plane containing its three bonds. Alkylating agents that are rather highly branched near the site of the leaving group would therefore prefer the oxygen atom more than those that are not so crowded.

The leaving group effect[3,4,22] also appears to fit the SN2 reactivity correlation, but this cannot be explained by the same steric argument. Perhaps the most reasonable explanation of this observation is due to Pearson and Songstad,[23] who attribute it to symbiosis, the tendency of either hard or soft ligands to flock together at the site of displacement.

Experimental Section

Alkylations.—A typical example follows. About 0.1 mol of the alkali metal is dissolved in ethanol under nitrogen in a three-necked flask fitted with a gas inlet, a reflux condenser capped with a drying tube, a thermometer well and a magnetic stirrer. An equivalent amount of ethyl acetoacetate is added and the alcohol is removed by flash evaporation. The residue is vacuum dried for several hours, and dissolved with stirring in 200 ml of HMPA; meanwhile the mixture is heated to 95–125°. The nitrogen inlet is replaced by a serum cap. The equivalent amount of alkyl halide is introduced below the surface of the solution by means of a syringe fitted with a long needle. The syringe also permits the withdrawal of small samples, which can be titrated to monitor the remaining base. When the reaction is over, the mixture is cooled, poured into 500 ml of cold water, neutralized if necessary and extracted with several 100-ml portions of pentane which are combined, washed with a little water to remove traces of ethyl acetoacetate and HMPA, briefly dried over anhydrous magnesium sulfate and flash evaporated. The crude product can be analyzed by either nmr or vpc techniques. Nmr analysis depends on the facts that the O derivative has a vinyl proton signal at τ 4.8–5.15 and that the acetyl methyl protons of the O, C, and CC derivatives are invariably well separated (τ 7.6–7.7, 7.8–7.95 and 7.8–8.15, respectively). For vpc analysis in the aliphatic series, a 1.75-m column charged with 20% Apiezon L absorbed on 20/80 Chromosorb W was used at 130–155°. For the aromatic compounds, a 5-ft column charged with 3% OV-17 absorbed on 100/120 Airopak 30 was used at 175–195°. The retention times for ethyl acetoacetate and the O, C, CC, and CO derivatives would typically be in the ratio 1:2:3:5:8. Analytical data and physical properties of the products are shown in Table IV. Since Reutov[5] has reported that the presence of an equivalent of alcohol may affect the product ratio, we point out that we treated the sodium salt with benzene in order to remove any trace of alcohol by means of azeotropic distillation; this did not affect the product distribution. *Anal.* Calcd for $C_6H_9O_3Na$: Na, 15.1. Found: Na, 15.5.

The experiment involving the NBu_4^+ salt was carried out by

(18) M. Bersohn, *J. Amer. Chem. Soc.*, **83**, 2136 (1961).

(19) M. E. Vol'pin, I. S. Akhrem, and D. N. Kursanov, *J. Gen. Chem., USSR* **30**, 1207 (1960); see also K. Conrow, *J. Amer. Chem. Soc.*, **81**, 5461 (1959).

(20) (a) The reaction of allyl chloride is of interest in that no O derivative was obtained in DMSO at all. The reaction in HMPA with the bromide has been examined by Normant and Cuvigny,[20b] who apparently did not find any of the enol ether in that case either. (b) H. Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, 1881 (1965)

(21) A. Chatterjee, D. Banerjee, and S. Banerjee, *Tetrahedron Lett.*, 3851 (1965).

(22) (a) R. Chong and P. S. Clezy, *ibid.*, 741 (1966); (b) G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, 51 (1966).

(23) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

TABLE IV

ANALYTICAL DATA[a] AND PHYSICAL PROPERTIES[b] OF THE ALKYLATION PRODUCTS[c]

Alkyl group	C derivative			O derivative			CC derivative		
	n^{25}D or mp, °C	C, %	H, %	n^{25}D or mp, °C	C, %	H, %	n^{25}D or mp, °C	C, %	H, %
CH_3	1.4195[d]			1.4480			1.4165		
	(1.4194)[d-f]			(1.4479)[f]			(1.4162)[e,f]		
C_2H_5[g]	1.4212			30.0			1.4299		
	(1.4225)[d-f]			(30.2)[e,f]			(1.4305)[d-f]		
n-C_3H_7[g]	1.4271			1.4498	62.97[f]	9.28[f]	1.4356		
	(1.4255)[d-f]			(1.4496)[f]	(62.76)	(9.36)	(1.4369)[f]		
i-C_3H_7	1.4250[d]			1.4496	62.85[f]	9.13[f]			
	(1.4252)[d,f,h]			(1.4496)[f,h]	(62.76)	(9.36)			
sec-C_4H_9	1.4290	64.20	9.68	1.4486	64.33	9.69			
		(64.49)	(9.74)		(64.49)	(9.74)			
neo-C_5H_{11}[i]				1.4456	65.70	9.95			
					(65.97)	(10.07)			
CH_2=$CHCH_2$	1.4362			1.4582[j]			1.4547		
	(1.4365)[k]						(1.4572)[l]		
$C_6H_5CH_2$	1.4989			1.5225	70.93	7.39[f]	1.5427		
	(1.4988)[f,m]			(1.5222)[f]	(70.88)	(7.32)	(1.5430)[m]		
$(C_6H_5)_2CH$	85.5	76.91	6.73	1.5621	76.76	6.48			
		(77.00)	(6.80)		(77.00)	(6.80)			
2,6-$(CH_3)_2C_6H_3CH_2$	1.5060	72.17	7.95	68	72.77	8.25			
		(72.55)	(8.12)		(72.55)	(8.12)			
4-$CH_3OC_6H_4CH_2$	1.5062[d]	66.94	7.13	1.5391[d]		7.08	1.5340[d,n]		
	(1.5077)[o]	(67.20)	(7.20)			(7.20)			
4-$CH_3C_6H_4CH_2$	1.5020	72.08	7.88	1.5241	71.48	7.49	49	77.74	7.52
		(71.77)	(7.74)		(71.77)	(7.74)		(78.08)	(7.74)
4-$ClC_6H_4CH_2$[p]	1.5119	61.50	5.94	1.5372	61.28	5.87	92.5	63.28	5.36
		(61.30)	(5.94)		(61.30)	(5.94)		(63.34)	(5.32)
4-$CF_3C_6H_4CH_2$[q]	1.4590	57.93	5.23				65	58.97	4.68
		(58.33)	(5.25)					(59.19)	(4.52)

[a] Theoretical values are shown in parentheses. [b] Literature values are shown in parentheses. [c] The small amounts of CO derivatives obtained with C_2H_5 and *n*-C_3H_7 were identified by means of nmr only. [d] At 20°. [e] C. M. French, *Trans. Faraday Soc.*, **48**, 216 (1952). [f] Reference 4. [g] D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960). [h] Reference 2. [i] When the reaction is continued beyond 13% conversion, side reactions set in giving rise to products with ethyl ether and neopentyl ester linkages. Eventually all four cross-products are obtained. They were isolated by vpc and identified by nmr (*Anal.* Calcd for neopentyl β-ethoxycrotonate: C, 65.97; H, 10.07. Found: C, 65.70; H, 9.87. *Anal.* Calcd for neopentyl β-neopentoxycrotonate: C, 69.38; H, 10.81. Found: C, 68.97; H, 10.38.) [j] W. M. Lauer and E. I. Kilburn, *J. Amer. Chem. Soc.*, **59**, 2586 (1937). [k] M. S. Schechter, N. Green, and F. B. LaForge, *ibid.*, **71**, 3165 (1949). [l] At 17.4°: J. W. Bruhl, *J. Prakt. Chem.*, **50**, 132, 137 (1894). [m] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961). [n] This value may not be that of the pure compound since the product was not obtained in analytically pure form. Treatment with aqueous base gave rise to di-*p*-methoxybenzylacetic acid [mp 105° (*Anal.* Calcd: H, 6.67; neut equiv, 300. Found. H, 6.73; neut equiv, 289)] for which the C analysis was also outside the normally acceptable limits. [o] At 17.2°: V. V. Feofilaktov, *Bull. Acad. Sci. USSR, Classe Sci. Chim.*, 521 (1941); *cf. Chem. Abstr.*, **37**, 23482 (1943). [p] Further data: O derivative, Cl, 13.61 (calcd 13.92); C derivative, Cl, 14.47 (calcd 13.92); CC derivative, Cl, 18.74 (calcd 18.69). [q] The O derivative decomposed on standing and could not be analyzed other than by nmr. Most of the substituted benzyl derivatives required tlc for final purification.

the addition of 1 equiv of tetra-*n*-butylammonium chloride and the precipitation of the potassium chloride before injecting the alkylating agent. The experiment involving tetraglyme was carried out by the addition of 1 equiv of tetraglyme purified by distillation from calcium hydride.

Materials.—The solvent can be readily recovered from the alkylation mixtures in about 80% yield as follows. The water is removed by flask evaporation for about 8 hr at 35–40°; the remaining liquid is dried overnight over magnesium sulfate and finally vacuum distilled from calcium hydride at 76–80° (1 mm), $n^{25}D$ 1.4570 (lit.[24] 1.4570). *p*-Trifluoromethylbenzoyl chloride was converted into the ethyl ester by the procedure of Hass and Bender.[25] The product was reduced to the benzyl alcohol[25] by the method of Nystrom and Brown.[26] The alcohol was then converted[27] into the chloride.[28] *p*-Methoxybenzyl chloride[29] was prepared similarly. 2,6-Dimethylbenzyl chloride was prepared from the corresponding benzoic acid as reported by Raaen and Eastham.[30] The physical constants of these compounds agreed in all cases closely with those reported by the authors quoted.

Registry No.—Ethyl acetoacetate, 141-97-9.

Acknowledgment.—This work was supported in part by the National Science Foundation.

(24) Q. A. Trementozzi and G. M. Kosolapoff, British Patent 657,294 (1952); *cf. Chem. Abstr.*, **47**, 4898e (1953).
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(26) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197 (1947).
(27) A. Streitwieser and W. C. Langworthy, *ibid.*, **85**, 1757 (1963).
(28) L. H. Sarett and T. Y. Shen, U. S. Patent 3,196,162 (1965); *cf. Chem. Abstr.*, **63**, 16308*f* (1965).
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Reduction of Ferrocene Methiodides. Synthesis of the Dimethylferrocenes

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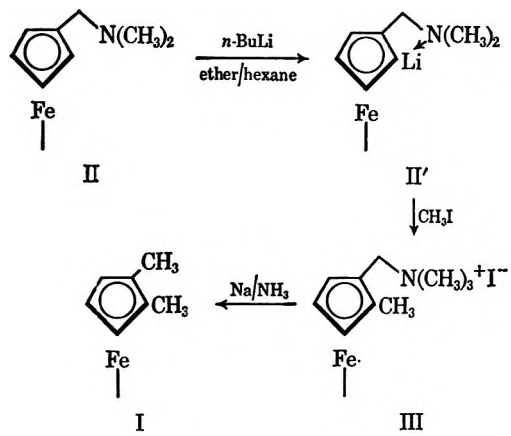
We have recently described a method which is suitable for the preparation of alkylferrocenes.[2] Utilizing this method, as well as another reduction procedure, we have succeeded in an unequivocal synthesis of 1,2-dimethylferrocene (I). This method constitutes the first direct preparation of 1,2-dimethylferrocene. Syntheses of this compound from 1,2-disubstituted precursors have been reported recently.[3]

Dimethylaminomethylferrocene (II) was lithiated with *n*-butyllithium yielding the 2-lithio intermediate II′.[4] Treatment of this intermediate with a large excess of methyl iodide and reprecipitation of the crude product from methanol/ether yielded 2-methyl-N,N,N,-N-trimethylferrocenylmethylammonium iodide (III). The crude methiodide was taken directly to the reduction step as described for methylferrocene.[2] Work-up and chromatography on neutral alumina brought a 78% yield of 1,2-dimethylferrocene. Scheme I outlines this procedure.

SCHEME I



The purity of the 1,2-dimethylferrocene was monitored by vapor phase chromatography (vpc) on a 6-ft Apiezon L (15%) on Chromosorb P column. Repeated chromatograms demonstrated conclusively that material of from 98 to 99% purity could be obtained by this method. The major impurities were methylferrocene (identical retention time as that of an authentic sample) and an unidentified material which had a longer retention time than I. Methylferrocene was probably formed by reduction of the methiodide of unmethylated amine.

Attempts to improve the purity of I by column chromatography on alumina or by recrystallization proved discouraging. However, several fractional reprecipitations of the crude methiodide from methanol/ether gave methiodide which decomposed between 178 and 179° to a black powder. An nmr spectrum of methiodide III in $CDCl_3$ exhibited a two-proton singlet at 4.78 ppm assigned to the methylene protons, a one-proton signal at 4.55 ppm assigned to the ring proton adjacent to the trimethylaminomethyl substituent, a seven-proton signal at 4.23 ppm assigned to the remaining ring protons, and a nine- and a three-proton signal at 3.23 and 2.17 ppm, respectively, assigned to the nitrogen and ring methyl groups. This purified methiodide (III) upon reduction and work-up yielded 1,2-dimethylferrocene of purity greater than 99% by vpc. 1,2-Dimethylferrocene has the following properties: parent peak at *m/e* 214; bp 67–68° (0.5 mm); mp 33–35°. An nmr spectrum in $CDCl_3$ showed six protons at 1.91 ppm and eight protons at 3.98 ppm. An infrared (ir) spectrum exhibited bands at 9.04 and 9.98 μ.[5]

A somewhat different route was also found to produce 1,2-dimethylferrocene. Lithiation of dimethylaminomethylferrocene and treatment with methyl iodide was effected essentially as recorded above. The methiodide thus formed was isolated and purified. Reduction of this purified methiodide by an overnight treatment with lithium aluminum hydride in tetrahydrofuran (THF) gave I in 56% yield.

(1) (a) To whom inquiries should be sent at Southern Illinois University. (b) Duke University.
(2) D. W. Slocum and W. Jones, *J. Organomet. Chem.*, **15**, 262 (1968).
(3) (a) K. Schlögl and M. Fried, *Monatsh. Chem.*, **95**, 558 (1964); (b) H. Falk, G. Haller, and K. Schögl, *ibid.*, **98**, 592 (1967).
(4) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).
(5) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953; M. Rosenblum, *Chem. Ind.* (London), 953 (1958); P. L. Pauson, *Quart. Rev.* (London), 391 (1955).

The sodium in ammonia reduction technique was also utilized for the preparation of 1,1′-dimethylferrocene. The dimethiodide of 1,1′-bis(dimethylaminomethyl)ferrocene[6] was subjected to sodium/ammonia for 15 min. The ammonia was allowed to evaporate; the crude oil after extraction was taken up in petroleum ether and chromatographed on alumina. 1,1′-Dimethylferrocene, identical in all respects with previously reported preparations,[7] was isolated in 66% yield.

In an attempt to prepare 1,3-dimethylferrocene, dimethylaminomethylation of methylferrocene was effected according to Nesmeyanov, *et al.*;[8] the resulting oil was converted into crude methiodide and reduced with sodium/ammonia in 84% yield to what had been tentatively reported as 1,3-dimethylferrocene.[8] Spectral examination revealed, however, that the reduction product, as well as the original amine, was a mixture of all three possible isomers. Others, in the instance of the amine mixture, have reported similar observations.[9]

Experimental Section[10]

Preparation of 1,2-Dimethylferrocene (I).—Dimethylaminomethylferrocene (II, 17.0 g, 0.07 mol) was placed in a 500-ml three-neck flask equipped with a nitrogen inlet and an addition funnel. *n*-Butyllithium (95 ml of a 15 *M* solution in hexane) was added over a 15-min period. The reaction was stirred for a 2.25-hr period after which time 25 g (0.17 mol) of methyl iodide was added. Soon after the addition of the methyl iodide crystallization occurred. The crude crystals were filtered and washed with ether. The solid was dissolved in chloroform, the remainder being removed by filtration. The solution was partially evaporated and petroleum ether was added to precipitate the methiodide. The solid was filtered and dried to give 20.0 g (72% yield) of 2-methyldimethylaminomethylferrocenemethiodide (III). This material was dissolved in methanol and ether was slowly added causing reprecipitation of about half of the material. The product was filtered and dried: mp 178–179° dec. *Anal.* Calcd for $C_{15}H_{22}NIFe$: C, 45.14; H, 5.57; N, 3.51; I, 31.80; Fe, 13.99. Found: C, 44.96; H, 5.46; N, 3.70; I, 32.02; Fe, 13.82.

The methiodide (III, 2.83 g, 7.5 mmol) was placed in a flask equipped with a stirrer and covered with about 200 ml of ammonia. Sodium beads (1.81 g, 79 g-atoms) were added after being cleaned with ethanol. The reaction mixture was stirred for 10 min before quenching with ammonium chloride. The evaporated mixture was partitioned between petroleum ether and water. The organic portion was chromatographed on alumina I with petroleum ether as eluent yielding 1,2-dimethylferrocene (I): mp 33–35°; 1.31 g, 89% yield (99.1% pure by vpc analysis). Anal. Calcd for $C_{12}H_{14}Fe$: C, 67.29; H, 6.54; Fe, 26.17. Found: C, 67.27; H, 6.43; Fe, 25.94. Principal ir absorptions were noted at 3.29, 3.48, 5.6–6.3 (broad), 6.80, 7.10, 7.23, 7.90, 8.30, 9.03, 9.64, 9.97, and 12.40 (broad) μ. An nmr spectrum exhibited singlets at 3.98 ppm (eight protons) and 1.91 ppm (six protons) assigned to the ring and methyl protons, respectively. A mass spectrum was run on a Consolidated Electrodynamics 21–104 (70-eV ionizing voltage, 250° inlet temperature) with the observation of significant peaks at *m/e* 214 (parent peak), 148, 121, 91, and 56.

Vapor phase chromatography of dimethylferrocene on a 15% Apiezon L on Chromosorb P, 0.25 in. × 6 ft column at 210° with a 60–100-cc He/min flow rate gave the following retention times: 8.5 min, methylferrocene, and 10 min, dimethylferrocene. On a diisodecyl phthalate on 45–60 W A/W DMCS 700 0.25 × 4 ft column at 190° with a 30-cc He/min flow rate the following retention times were recorded: 10.5 min, methylferrocene, and 14 min, 1,2-dimethylferrocene. All chromatograms were run on an F & M Laboratory chromatograph model 700.

As noted in the discussion above, 1,2-dimethylferrocene of somewhat lower purity could be obtained by taking the crude methiodide directly to the reduction step.

1,2-Dimethylferrocene was also prepared by reducing the above-produced methiodide (III, 4.0 g, 10.0 mmol) with lithium aluminum hydride (2.5 g, 0.066 mol) in 60 ml of tetrahydrofuran with overnight refluxing. A work-up procedure similar to that recorded above was employed. 1,2-Dimethylferrocene (1.2 g, 56% yield) was again isolated, this material being identical with the previously produced product as shown by the identity of their respective ir spectra.

Preparation of 1,1′-Dimethylferrocene.—The dimethiodide[11] of 1,1′-bis(dimethylaminomethyl)ferrocene (2.9 g, 4.9 mmol) was placed in a flask equipped with a stirrer and covered with ammonia. Excess (about 10:1) sodium was added, and the blue solution was stirred for 5 min before quenching with ammonium chloride. Water was added and the mixture was extracted with ether. Chromatography of the organic portion on alumina (activity I) gave, as the main band, 1,1′-dimethylferrocene (0.7 g, 66% yield), which was identified by its ir spectrum.[12]

Registry No.—I, 12126-15-7; III, 12111-93-2.

Acknowledgment.—We would like to thank Professors P. L. Pauson and W. E. Watts for communicating to us results before they were published. We would also like to thank Professor Gilbert Mains for the mass spectrum of dimethylferrocene. The work performed at Duke University was supported by the National Science Foundation and that at Southern Illinois University by the Petroleum Research Fund.

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(7) (a) E. A. Hill and J. H. Richards, *J. Amer. Chem. Soc.*, **83**, 4216 (1961); (b) L. T. Reynolds and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **9**, 86 (1959); (c) A. N. Nesmeyanov, E. G. Perevalova, Z. A. Beinoravichute, and I. L. Malygina, *Dokl. Akad. Nauk SSSR*, **121**, 117 (1958).

(8) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shiloutzeva, and Yu A. Ustynyuk, *ibid.*, **124**, 331 (1959).

(9) (a) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shiloutseva, and A. A. Ponomarenka, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 171 (1967); (b) P. L. Pauson, M. A. Sandhu, W. E. Watts, R. C. Haley, and G. R. Knox, *J. Chem. Soc., C*, 1851 (1967).

(10) Elemental analyses were performed by Alfred Bernhardt, West Germany. Melting points were determined on a Hoover melting point apparatus and were corrected. The nmr spectra were run on a Varian A-56/60 spectrometer using tetramethylsilane as an internal standard. All ir spectra were determined as Nujol mulls or smears on a Perkin-Elmer Model 137 Infracord spectrometer.

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(12) L. T. Reynolds and G. Wilkinson, *J. Inorg. Nucl. Chem.* 9, **86** (1959).

Formation of 2-Ferrocenylbenzofuran and Some Acetylenic Derivatives of Ruthenocene[1,2]

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Several recent publications have described a variety of excellent routes for the formation of ferrocenylacetylenes.[3–5] During the course of our studies on metallocenylacetylenes, it was of interest to determine if these same methods could be employed for the

(1) Part XVI of a series "Organometallic π-Complexes." Part XV: M. D. Rausch and A. Siegel, *J. Org. Chem.*, **33**, 4545 (1968).

(2) Taken from the Ph.D. thesis of A. Siegel, University of Massachusetts, 1967.

(3) K. Schlögl and W. Streyer, *Monatsh.*, **96**, 1520 (1965).

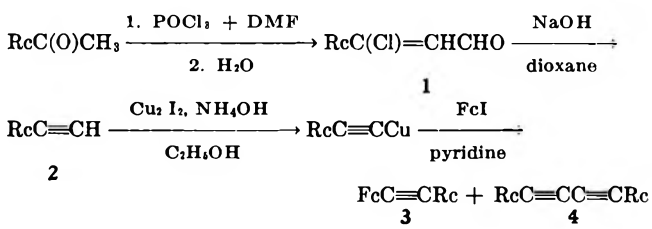
(4) M. D. Rausch, A. Siegel, and L. P. Klemann, *J. Org. Chem.*, **31**, 2703 (1966).

(5) M. Rosenblum, N. Brawn, J. Papenmeier, and M. Applebaum, *J. Organometal. Chem.*, **6**, 173 (1966).

synthesis of analogous acetylenic ruthenocenes. After completion of our program in this area,[2] Hofer and Schlögl independently reported certain similar results.[6]

Treatment of acetylruthenocene with a solution of phosphorus oxychloride and dimethylformamide according to the method of Arnold and Žemlička[7] afforded β-formyl-α-chlorovinylruthenocene (1) in 89% yield. When a dioxane solution of 1 at reflux was caused to react with aqueous sodium hydroxide according to the general procedure of Bodendorf and Kloss,[8] ethynylruthenocene (2) was obtained in 83% yield. A subsequent reaction between the copper(I) salt of 2 and iodoferrocene in refluxing pyridine solution afforded the mixed metallocenylacetylene, ferrocenylruthenocenylacetylene (3), together with a small amount of the oxidative coupling product, diruthenocenylbutadiyne (4).[9] These reactions are illustrated in Scheme I.

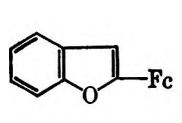
SCHEME I



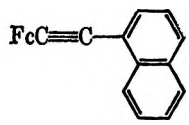
The two reaction products 3 and 4 exhibit very similar solubility properties and virtually identical R_f values on thin layer chromatography (tlc). All attempts to obtain an analytically pure sample of 3 by means of preparative tlc or fractional sublimation were unsuccessful. The nmr spectrum of 3 exhibits resonances characteristic of both monosubstituted ferrocenyl and ruthenocenyl substituents, and is in accordance with the assigned structure. The mass spectrum of the reaction product between ruthenocenylethynylcopper(I) and iodoferrocene is especially informative, since it exhibits a principal parent molecular ion peak at *m/e* 440, assignable to 3, and a minor molecular ion peak at *m/e* 510, assignable to the coupling product 4. Additional peaks in the mass spectrum are likewise assignable to fragmentation products derived from 3 and 4.

Stephens and Castro[9a,10] observed that, in reactions between cuprous acetylides and aryl iodides in which the latter bears an *ortho* nucleophilic substituent, such as NH_2, COOH, OH, etc., arylacetylenes are not obtained, but rather cyclization occurs to produce the corresponding heterocycle. In our studies, we have found that a reaction between *o*-iodophenol and ferrocenylethynylcopper(I) produces 2-ferrocenylbenzofuran (5) in 85% yield. The absence of any acetylenic or hydroxylic absorption bands in the ir spectrum of 5, and the marked downfield shifts of the 2,5 and the 3,4 protons in the nmr spectrum of 5 compared with corresponding proton resonances for ferrocenyl acetylenes clearly exclude any uncyclized structure.

(6) O. Hofer and K. Schlögl, *ibid.*, **13**, 443 (1968).
(7) Z. Arnold and J. Žemlička, *Proc. Chem. Soc.*, 227 (1958).
(8) K. Bodendorf and P. Kloss, *Angew. Chem. Intern. Ed. Engl.*, **2**, 98 (1963).
(9) The formation of oxidative coupling products in this type of reaction has been noted earlier: (a) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966); (b) M. D. Rausch, A. Siegel, and L. P. Klemann, *ibid.*, **34**, 468 (1969).
(10) C. E. Castro and R. D. Stephens, *ibid.*, **28**, 3313 (1963).



5



6

A reaction between ferrocenylethynylcopper(I) and 1-iodonaphthalene proceeded normally to produce the expected acetylene, ferrocenyl-1-naphthylacetylene (6), in 83% yield.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Mr. Charles Meade of the University of Massachusetts Microanalytical Laboratory.

β-Formyl-α-chlorovinylruthenocene (1).—Acetylruthenocene[11] (600 mg, 2.20 mmol) was added in small portions to a preformed solution of the Vilsmeier complex (from 3.0 ml of phosphorus oxychloride and 30 ml of dimethylformamide) at 0°. The orange-red solution was stirred for 15 min at 0° and 2 hr at 25° and then poured into 75 ml of cold, saturated sodium acetate solution. After stirring for 1 hr, the yellow precipitate which had formed was filtered, washed repeatedly with water, and was dried, resulting in 675 mg of yellow crystals, mp 109.5–110.5°. The product was recrystallized from heptane to produce 620 mg (89% yield) of 1 as bright yellow crystals, mp 114–115°.

Anal. Calcd for $C_{13}H_{11}ClORu$: C, 48.83; H, 3.47. Found: C, 48.68; H, 3.43.

The nmr spectrum ($CDCl_3$) showed τ 0.00 (d, 1, J = 7 Hz, CHO), 3.62 (d, 1, J = 7 Hz, =CH), 4.90 (t, 2, 2,5 protons), 5.20 (t, 2, 3,4 protons), and 5.35 ppm (s, 5, π-C_5H_5). The ir spectrum (CCl_4) showed 1668 (C=O) and 1601 cm^{-1} (C=C).

Ethynylruthenocene (2).—β-Formyl-α-chlorovinylruthenocene (150 mg, 0.47 mmol) was dissolved in 25 ml of dioxane and heated to reflux under nitrogen. With stirring, 15 ml of hot 5 *N* sodium hydroxide solution was added in one portion. The reaction mixture was stirred *vigorously* at reflux for an additional 30 min and then allowed to cool to room temperature. The resulting mixture was concentrated *in vacuo* overnight and extracted repeatedly with ethyl ether until the extracts were colorless, and the combined extracts were washed with water and dried over magnesium sulfate. After evaporation of the solvent, a tlc experiment on the resulting residue (pentane as eluent) indicated a band of relatively high R_f as well as several bands of appreciably lower R_f. The residue was subsequently chromatographed on alumina using pentane as the eluent to give 100 mg (83% yield) of 2 as pale yellow crystals. After one recrystallization from pentane, 2 had mp 73–74°.

Anal. Calcd for $C_{12}H_{10}Ru$: C, 56.45; H, 3.95. Found: C, 56.19; H, 3.75.

The nmr spectrum ($CDCl_3$) showed τ 5.13 (t, 2, 2,5 protons), 5.38 (s, 5, π-C_5H_5), 5.43 (t, 2, 3,4 protons), and 7.33 ppm (s, 1, acetylenic proton). The ir spectrum (CCl_4) showed 2110 cm^{-1} (C≡C).

Ferrocenylruthenocenylacetylene (3).—Iodoferrocene (47 mg, 0.15 mmol) and ruthenocenylethynylcopper (I) (48 mg, 0.15 mmol, prepared by the method of Stephens and Castro[10]) were heated at reflux in 25 ml of pyridine (dried over potassium hydroxide and refluxed over barium oxide before use) for 8 hr under nitrogen. The reaction mixture was allowed to cool to room temperature, diluted with *ca.* 25 ml of water, and filtered. The residue was dissolved in a minimum volume of chloroform and chromatographed on an alumina column. Elution with 1:1 hexane–benzene produced 40 mg (60% crude yield) of 3, contaminated with diruthenocenylbutadiyne (4), as an orange powder, mp 259.5–261° (N_2). The product was subsequently vacuum sublimed at 180° (1 mm); the melting point did not change.

Anal. Calcd for $C_{22}H_{18}FeRu$: C, 60.15; H, 4.13. Found: C, 59.31; H, 3.97.

(11) M. D. Rausch, E. O. Fischer, and H. Grubert, *J. Amer. Chem. Soc.*, **82**, 76 (1960).

The nmr spectrum ($CDCl_3$) showed τ 5.13 (t, 2, 2,5 protons of ruthenocenyl group), 5.40 (s, 5, π-C_5H_5 of ruthenocenyl group), 5.43 (t, 2, 3,4 protons of ruthenocenyl group), 5.52 (t, 2, 2,5 protons of ferrocenyl group), 5.80 (s, 5, π-C_5H_5 of ferrocenyl group), and 5.82 ppm (t, 2, 3,4 protons of ferrocenyl group).

2-Ferrocenylbenzofuran (5).—*o*-Iodophenol (3.3 g, 15 mmol) and ferrocenylethynylcopper (I)[4] (4.1 g, 15 mmol) were heated to reflux in 100 ml of dried pyridine for 8 hr under nitrogen. After work-up in the usual manner, followed by chromatography of the product on alumina using hexane as the eluent, 3.6 g (80% yield) of a pale orange solid, mp 128–130°, was isolated. After recrystallization from hexane, pink needles of **5**, mp 130–131°, were obtained.

Anal. Calcd for $C_{18}H_{14}FeO$: C, 71.55; H, 4.67. Found: C, 71.21; H, 4.64.

The nmr spectrum ($CDCl_3$) showed τ 2.57 (m, 4, aryl protons), 3.25 (s, 1, H-3 on furan ring), 5.16 (t, 2, 2,5 protons on ferrocenyl group), 5.57 (t, 2, 3,4 protons on ferrocenyl group), and 5.80 ppm (s, 5, π-C_5H_5).

Ferrocenyl-1-naphthylacetylene (6).—1-Iodonaphthylene (Eastman, 3.80 g, 15 mmol) and ferrocenylethynylcopper (I)[4] (4.1 g, 15 mmol) were heated to reflux in 100 ml of dried pyridine under nitrogen for 8 hr. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with methylene chloride. The latter was washed with water, 5% hydrochloric acid, 5% sodium hydroxide solution, and water and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* followed by recrystallization of the residue from hexane afforded 2.8 g (83% yield) of **6**, mp 162–162.5°. An analytical sample was prepared by sublimation at 180° (1 mm).

Anal. Calcd for $C_{22}H_{16}Fe$: C, 78.59; H, 4.80. Found: C, 78.41; H, 4.75.

The nmr spectrum ($CDCl_3$) showed τ 2.35 (m, 7, naphthyl protons), 5.50 (t, 2, 2,5 protons), 5.78 (s, 5, π-C_5H_5), and 5.80 ppm (t, 2, 3,4 protons). The ir spectrum (KBr) showed 2200 cm^{-1} (C≡C).

Registry No.—**1**, 12337-23-4; **2**, 12337-22-3; **3**, 12337-26-7; **5**, 12337-24-5; **6**, 12337-25-6.

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Nuclear Magnetic Resonance Spectroscopy. Low-Temperature Studies of Diallylmagnesium[1]

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Allylic organoalkali metal compounds have been observed to exhibit reversible changes in nmr spectra (*e.g.*, AA'BB'C → AB_4 for allyllithium) over the temperature range from −100 to +110°.[3] In contrast, allymagnesium bromide is reported to display a simple AB_4 spectrum at −80°[4] and diallylmagnesium to behave similarly from −60 to +37° in tetrahydrofuran.[3a]

It has now been found that magnesium halide free diallylmagnesium (from diallylmercury) in tetrahydrofuran shows the same AB_4 type of nmr spectrum as was reported for allylmagnesium bromide[4] over the temperature range from +37 to −120 ± 5°.[5]

Observation of reversible changes in pmr spectra with temperature for allyllithium[3a] and pentadienyllithium[3c] has led to suggestions that these substances are ionic and that exchange of the magnetic environments of the hydrogens on the terminal carbons is rapid at high temperatures, either as the result of rotation about the C···C bonds of the allylic anion or through transient covalent bond formation with the metal cation to give the simple organometallic compounds with a C—C single bond available for rapid rotation. However, the picture of simple discrete ions, or even ion pairs that are solvent separated, is clouded by evidence that allyllithium is rather highly aggregated ($n_{app} > 1.4$ at 0.8 M)[3a] even in tetrahydrofuran solution.[6]

The general pattern of the chemical shifts in allyl- and γ-methylallyl Grignard reagents,[4,7] and the corresponding R_2Mg compounds, is in best agreement with the suggestion[4,7] that in these substances there is a rapid intramolecular (or intermolecular)[8] allylic exchange of magnesium between the terminal atoms ($XMgCH_2CH{=}CH_2 \rightleftharpoons CH_2{=}CHCH_2MgX$; X = Br or alkenyl). However, the chemical-shift argument loses some of its force because the proton chemical shifts of allyllithium where ionic character seems quite important[3] are rather similar to those for diallylmagnesium (see Table I) and allylmagnesium bromide. Nonetheless, it is difficult to conceive of diallylmagnesium as an ion pair of two allyl anions and a dipositive magnesium cation. Furthermore, it seems unlikely that a γ-methylallyl anion–magnesium bromide ion pair would have just the chemical shifts for the α and γ protons which correspond to expectations for the covalent structure. That there may be substantial differences in structure between the allyllithium and allylmagnesium compounds is corroborated to some degree by the infrared double-bond stretching absorption of diallylmagnesium which is intermediate between

TABLE I
AVERAGE PROTON CHEMICAL SHIFTS OF ALLYL–X COMPOUNDS

X	H (β), ppm	H (α and γ), ppm
Li	6.38[a]	2.17[a]
-MgBr	6.38[b]	2.50[b]
C_3H_5Mg-	6.30[c]	2.45

[a] Reference 3. [b] Reference 4. [c] In tetrahydrofuran, not sufficiently soluble in ether to give satisfactory spectra.

(1) Supported in part by the National Science Foundation.

(2) On sabbatical leave from Brooklyn College of the City University of New York, 1967–1968.

(3) (a) P. West, J. I. Purmort and S. V. McKinley, *J. Amer. Chem. Soc.*, **90**, 797 (1968); (b) V. R. Sandel, S. V. McKinley, and H. H. Freedman, *ibid.*, **90**, 495 (1968); (c) R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 205 (1967).

(4) G. M. Whitesides, J. E. Nordlander, and J. D. Roberts, *Discussions Faraday Soc.*, **34**, 185 (1962); *J. Amer. Chem. Soc.*, **84**, 2010 (1962).

(5) Addition of N,N,N',N'-tetramethylethylenediamine to a dimethyl ether solution of diallylmagnesium permitted going to −135 ± 5°, but there was no change in the nmr pattern. Viscosity broadening of the N-methyl group signals led to overlap with the B_4 doublet (terminal carbon protons) below −130°. Perdeuteriotetrahydrofuran solutions of diallylmagnesium exhibited similar behavior. Crystallization of diallylmagnesium occurred at temperatures from −75 to −105° for solutions ranging from 2.65 to 1.33 M.

(6) P. West and R. Waack, *J. Amer. Chem. Soc.*, **89**, 4395 (1967).

(7) J. E. Nordlander, W. G. Young, and J. D. Roberts, *ibid.*, **83**, 494 (1961).

(8) Recent evidence for intermolecular exchange of alkyl groups in dialkylmagnesium compounds suggests that intermolecular exchange may be quite important; see H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

TABLE II

DOUBLE-BOND STRETCHING ABSORPTION OF ALLYL-X COMPOUNDS

X	ν, cm⁻¹ Ether	Tetrahydrofuran	
HgC_3H_5			1620[a]
MgC_3H_5	1577[b,c]	1568[b,c]	
MgBr[d]	1588	1570	
MgCl[d]	1580	1565	
Li[e]	1540[f]	*f*	1542[g]
Na[h]			1535[g]

[a] Perkin-Elmer 237, 0.1-mm NaCl cells in CCl_4 solution. [b] Beckman IR-7, 0.1-mm IRTRAN-2 cells. [c] G. Wilke and P. Heimbach [*Angew. Chem. Intern. Ed. Engl.*, 5, 151 (1966)] cite an unpublished value of 1575 cm^{-1}. [d] C. Prevost and B. Grosse, *C. R. Acad. Sci., Paris*, **252**, 1023 (1961). [e] D. Seyferth and M. Weiner, *J. Org. Chem.*, **26**, 4797 (1961). [f] Reported as 1525–1540 cm^{-1} in ref 3a. [g] Nujol mull. [h] E. J. Lanpher, *J. Amer. Chem. Soc.*, 79, 5578 (9957).

the values for covalent diallylmercury and ionic allyllithium (see Table II). In any case, it should be clear that rotation around all of the C—C and C=C bonds of the species which comprise diallylmagnesium is extremely facile.

Experimental Section

Diallylmercury, bp 59–60.5° (0.75 mm), was prepared in 61% yield from allylmagnesium bromide (75–90%)[9] following literature directions.[10]

Diallylmagnesium.—Equivalent quantities of triply sublimed magnesium (0.0106 mol) and diallylmercury (0.010 mol) were stirred in 25 ml of dry ether in a nitrogen atmosphere at room temperature. A white precipitate of insoluble diallylmagnesium and metallic mercury began to form at once. After 2 hr, the reaction appeared to be complete and the colorless supernatant showed the presence of diallylmagnesium from its infrared spectrum but was too dilute to give satisfactory proton nmr spectra.

Diallylmercury (0.01 mol) reacted with magnesium (0.0106 g atom) in dry tetrahydrofuran (10.0 ml) to give a solution of diallylmagnesium. The reaction was not complete after 3.0 hr, therefore an excess of magnesium was added and the mixture was stirred overnight. Several samples of the resulting solution were placed in thick-walled nmr tubes, diluted with freshly distilled dry tetrahydrofuran and sealed. Concentrations ranged from 0.28 to 1.00 *M* and the chemical shifts were concentration invariant over this range.

Registry No.—Diallylmagnesium, 6928-75-2.

(9) O. Grummitt, E. P. Budewitz, and C. C. Chudd in "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, pp 749–750.

(10) A. E. Borisov, I. S. Saveljeva, and S. R. Serdyuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **5**, 924 (1965). An English translation appears in *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 896 (1965)

Reductions with Organosilicon Hydrides. II. Preparation of Aldehydes from Acyl Chlorides[1a]

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In the preceding paper,[1a] the palladium-catalyzed cleavages of carbon–halogen bonds of halocarbons by organosilicon hydrides were reported. In this Note the analogous reaction with acyl chlorides performed *via* a simple procedure that may prove useful for the preparation of aldehydes is described (eq 1).

$$R_3SiH + RCOCl \xrightarrow{Pd} R_3SiCl + RCHO \quad (1)$$

Jenkins and Post[2] have reported the uncatalyzed reaction of aroyl halides with tribenzylsilane in refluxing ether, and with triethylsilane when catalyzed by $AlCl_3$, to give the corresponding halosilane and the aldehyde, the latter in 30–50% yields. However, a later study by Eaborn and Baines[3] showed that in the uncatalyzed reactions the transformations actually took place not at ether reflux, but at a much higher temperature, probably during distillation. However, the yields of aldehyde obtained by the latter workers were always less than 15%, and this was attributed to decomposition of the aldehyde in the reaction mixture at the temperatures required for the reaction (≫100°). Very high yields of the halosilanes were obtained, thus indicating that substantial amounts of the aldehyde had formed initially.

We have found that a palladium catalyst apparently drastically alters the course of the reaction, since in many cases the reaction proceeds at room temperature. The results of the palladium-catalyzed reactions of triethylsilane with various acyl chlorides are given in Table I. The aldehydes were isolated as their 2,4-dinitrophenylhydrazone derivatives (2,4-DNPH), after the catalyst was filtered. The yields for the unbranched aliphatic acyl chlorides are in the range 50–70%, which is higher than that reported for the corresponding reductions by $Li(t\text{-}BuO)_3AlH$[4] and comparable or slightly less than that obtained with the

TABLE I

10% PALLADIUM-CHARCOAL-CATALYZED REACTIONS OF TRIETHYLSILANE WITH ACYL CHLORIDES

Acyl halide	Procedure[a]	Yield of 2,4-DNPH, % Crude	Recrystallized
CH_3COCl	A	Reacts[b]	
CH_3CH_2COCl	C	0	
n-C_3H_7COCl	A	65	59
$(CH_3)_2CHCOCl$	E	0	
$CH_3CH_2CH(CH_3)COCl$	D	0	
$(CH_3)_2CHCOBr$	A	71	65
$(CH_3)_3CCOCl$	E	9	5
n-$C_7H_{15}COCl$	B		46
C_6H_5COCl	C	70	60
o-$CH_3C_6H_4COCl$	D	28	15
o-$CH_3OC_6H_4COCl$	C	42	38
o-$CH_3OC_6H_4COCl$	E	35	30
p-$CH_3OC_6H_4COCl$	A	43	39
m-$C_6H_4(COCl)_2$[c]	E	75[d]	
$CH_3CHCHCOCl$	C	33	18
$PhCHCHCOCl$	D		9

[a] See Experimental Section. [b] The reaction was so violent that all of the acetaldehyde distilled. [c] An excess of Et_3SiH (15 mmol) was used for the amount of isophthaloyl chloride (5 mmol) used. [d] Isolated as the bisphenylhydrazone derivative.

(1) (a) For the preceding paper, see J. D. Citron, J. E. Lyons, and L. H Sommer, *J. Org. Chem.*, **34**, 638 (1969). (b) To whom correspondence should be addressed: Elastomer Chemicals Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del. 19898.

(2) J. W. Jenkins and H. W. Post, *ibid.*, **15**, 556 (1950).

(3) C. E. Baines, Ph.D. Dissertation, University of Leicester, 1957. The author is indebted to Professor C. Eaborn for supplying a copy of this dissertation.

(4) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **80**, 5377 (1958).

Rosenmund reaction.[5] While the low reactivity of pivaloyl chloride, $(CH_3)_3CCOCl$, isobutyryl chloride, and α-methylbutyryl chloride could be explained on steric grounds, the complete inertness of propionyl chloride was unexpected. A subtle change in steric requirements may cause a specific poisoning effect, but other factors such as traces of foreign catalyst poisons cannot be ruled out. Use of acyl bromides as illustrated by isobutyryl bromide may permit isolation of α-branched aldehydes.

The aroyl chlorides gave yields in the 40–70% range, which is slightly lower than either the lithium alkoxyaluminum hydride[4] or Rosenmund reductions.[5] However, it should be emphasized that the reactions are extremely easy and convenient to perform, a factor which may compensate for lower yields, especially when only small amounts of aldehyde are needed. Some care is necessary to ensure that groups which react catalytically with organosilicon hydrides such as α-halo[6] and polyhalo[1a] are not present.

TABLE II

10% PALLADIUM–CHARCOAL-CATALYZED REACTIONS OF OCTANOYL CHLORIDE WITH ORGANOSILICON HYDRIDES

Silane	Procedure[a]	—Yield of 2,4-DNPH, %— Crude	Recrystallized
$MeCl_2SiH$	C	0	
Me_2ClSiH	B	0	
Et_3SiH	B		46
Me_2PhSiH	E	0	
$MePh_2SiH$[b]	E	40	21[c]
Ph_2SiH_2	E	0	
$MePhClSiH$	E	24	16

[a] See Experimental Section. [b] n-C_3H_7COCl was used. [c] The melting point, 94–103.5°, indicated that this derivative was very impure.

Attempts were made to improve the yields by varying the silane (Table II), the molar ratio of the reactants (Table III), and the temperature (Table IV). It is quite apparent from Table II that Et_3SiH is the most effective reducing agent. Relatively small changes in the steric and/or electronic properties of the silane

TABLE III

10% PALLADIUM–CHARCOAL-CATALYZED REACTIONS OF TRIETHYLSILANE WITH OCTANOYL CHLORIDE[a]

Molar ratio of Et_3SiH/n-$C_7H_{15}COCl$	Yield, % recrystallized 2,4-DNPH[b]
3.0:1.0	43
1.25:1.0	55
1.0:1.0	46
1.0:1.25	55
1.0:3.0	56

[a] Using procedure B. [b] Based upon deficient constituent of the reaction.

cause large, and as yet unexplained, differences in reactivity at the catalyst surface. Table III illustrates that varying the molar ratio of the reactants has little effect upon the yield of aldehyde. A small excess of either Et_3SiH or octanoyl chloride gives a slightly higher yield.

(5) E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, Chapter 7, 362 (1948).

(6) N. F. Orlov, R. A. Bogatkin, Z. I. Sergeeva, and M. G. Voronkov, *Zh. Obshch. Khim.*, **33**, 1934 (1963); N. F. Orlov and L. N. Slezar, *ibid.*, **36**, 1078 (1966).

TABLE IV

LOW TEMPERATURE 10% PALLADIUM–CHARCOAL-CATALYZED REACTIONS OF TRIETHYLSILANE WITH ACYL CHLORIDES

Acyl chloride	—Yield of 2,4 DNPH, %— Crude	Recrystallized
n-C_3H_7COCl	80	74
n-$C_7H_{15}COCl$	83	75
C_6H_5COCl	46	45
o-$CH_3OC_3H_4COCl$	4	2
p-$CH_3OC_6H_4COCl$[a]	23	7

[a] Reacted at +10–15° for 2 hr.

Use of low temperatures (~−70°) at the start of the reaction appreciably increased the yield of the unbranched aliphatic aldehydes by 19–29%. However, the yields from aroyl chlorides which reacted at low temperature were decreased. This may be due to lower inherent reactivity. However, difficulty was experienced at low temperatures with these acid chlorides because they solidified. Even when p-methoxybenzoyl chloride was allowed to react at +10–15°, a lower yield was obtained.

Isolation of the aldehyde by distillation at atmospheric pressure of the filtered reaction mixture confirmed the observation[3] that little or no aldehyde could survive in this medium at higher temperatures. However, as indicated in eq 2 and 3, good yields of Et_3SiCl were obtained. In order to circumvent the decomposition, a reaction mixture was washed with water until neutral,

$$Et_3SiH + PhCOCl \xrightarrow[2.\ \text{atm distillation}]{1.\ 10\%\ \text{Pd–C}} Et_3SiCl + PhCHO \quad (2)$$

66% 31%

$$Et_3SiH + n\text{-}C_3H_7COCl \xrightarrow[2.\ \text{atm distillation}]{1.\ 10\%\ \text{Pd–C}} Et_3SiCl + n\text{-}C_3H_7CHO \quad (3)$$

88% <3%

thus hydrolyzing the chlorosilane and any residual acyl chloride. Upon vacuum distillation a yield of octanal comparable with the 55% yield of 2,4-DNPH was obtained (eq 4). Thus removal of the possible hydrogen chloride sources in the reaction mixture allows isolation of the free aldehyde.

$$Et_3SiH + n\text{-}C_7H_{15}COCl \xrightarrow[2.\ H_2O\ \text{wash}\quad 3.\ \text{vacuum distillation}]{1.\ 10\%\ \text{Pd–C}} n\text{-}C_7H_{15}CHO \quad (4)$$

51%

Experimental Section

All of the acyl chlorides were the best commerical grades and were distilled just before use. The organochlorosilanes were obtained from the Dow Corning Corp. and redistilled. Triethylsilane, dimethylphenylsilane, and methyldiphenylsilane were prepared by $LiAlH_4$ reduction of the corresponding chlorosilanes. The catalyst (10% Pd–C) was used as purchased from Matheson Coleman and Bell. All reactions were performed in a nitrogen atmosphere.

Preparation of 2,4-Dinitrophenylhydrazone Derivatives.—To 45–55 mg of 10% Pd–C was added 10 mmol of the freshly distilled acyl chlorides. The organosilicon hydride (10 mmol) was then added, and the reaction was allowed to proceed (cooling in a water bath if the temperature exceeded ~80°). In the various procedures referred to in Tables I, II, and III, the following times of reaction were used: A, 5 min; B, 15 min; C, 16–24 hr; D, 5 min (on steam bath); E, 16–24 hr (on steam bath). After the appropriate period had elapsed, 5 ml of pentane (benzene in the case of aroyl chlorides) was added, and the mixture

was filtered into either an H_3PO_4–EtOH or HCl–EtOH solution of 10 mmol of 2,4-dinitrophenylhydrazine. The derivative was filtered, dried, weighed, and recrystallized from an appropriate solvent. Yields are given in Tables I, II, and III.

Reaction of Et_3SiH with Benzoyl Chloride.—Into a 25-ml erlenmeyer flask containing 100 mg of 10% Pd–C and 6.0 ml (50 mmol) of PhCOCl was added 8.0 ml (50 mmol) of Et_3SiH. The mixture heated to 60° and some gas was evolved. After standing overnight (18 hr), the mixture was filtered and then distilled at atmospheric pressure on a $\frac{3}{8} \times 24$ in. spinning-band column. The first fraction was pure Et_3SiCl, and a total of 5.0 g (66%) of the chlorosilane, bp 142.5–147°, was isolated. The mixture was then distilled at reduced pressure to give 1.6 g (31%) of PhCHO, bp 60.5–65° (16 mm).

Reaction of Et_3SiH with Butyryl Chloride.—The procedure is similar to the preceding reaction except that the reaction mixture was filtered after 15 min. Upon distillation the first fractions, bp 89–135°, were mixtures of n-C_3H_7COCl (0.6 g), Et_3SiH (1.0 g), and n-C_3H_7CHO (0.1 g) [all estimated by infrared (ir) spectrum]. The next fractions were 5.4 g (88%, correcting for recovered Et_3SiH) of Et_3SiCl, bp 143–147°. No other material except a trace of butyric acid distilled up to a pot temperature of 205°.

Reaction of Et_3SiH with Octanoyl Chloride.—Into a 25-ml erlenmeyer flask were placed 100 mg of 10% Pd–C, 4.25 ml (25 mmol) of octanoyl chloride, and 4.8 ml (30 mmol) of Et_3SiH. After some bubbling, the temperature of the flask rose to ~100° (2 min), and it was cooled in a water bath. After 1 hr, the reaction mixture was filtered into a separatory funnel containing 20 ml of ether, 20 ml of water, and 0.21 g of $NaHCO_3$. The contents were shaken, and then the ether layer was washed with water several times over the course of 2 hr until neutral. The organic layer was dried over anhy Na_2SO_4 and then distilled under vacuum. The first fraction isolated was n-octanal, 1.63 g (51%), bp 31° (0.6 mm), $n^{23.5}D$ 1.4234.

Low Temperature Reactions.—Into a flask containing 50 mg 10% Pd–C was added 10 mmol of acid chloride. While stirring (magnetic) the mixture was cooled to ~−70° with a Dry Ice–acetone bath. Ten millimoles of Et_3SiH (in the case of aroyl chlorides the Et_3SiH was added first, owing to solidification of the acid chloride) was then added and the system was stirred for 1 hr. At the end of this time, the mixture was allowed to warm slowly (1 hr) to +10° in the acetone bath. It was allowed to stir for 15 min at room temperature and then worked up with 2,4-DNPH as above. The results are given in Table IV.

Registry No.—Triethylsilane, 617-86-7; benzoyl chloride, 98-88-4; butyryl chloride, 141-75-3; octanoyl chloride, 111-64-8.

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Activation of Manganese Dioxide by Azeotropic Removal of Water

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Manganese dioxide, once known as a relatively selective oxidant of allylic alcohols, is now viewed as a less discriminate, condition-dependent oxidizing agent. Numerous functionalities can be oxidized by various types of manganese dioxide used over a wide range of time, temperature, and solvent polarity.[1] Whereas oxidations with manganese dioxide are generally simple to perform, the reproducible preparation of the activated reagent is often difficult and time consuming. The preparation and properties of manganese dioxide activated by an expeditious and reproducible procedure are reported herein.

Precipitated manganese dioxide was prepared from solutions of manganous sulfate, sodium hydroxide, and potassium permanganate according to a modified Attenburrow procedure.[2] Following the filtration and washing steps, the wet filter cake, containing about 40–60% water, was stored in a closed bottle. Portions of the wet material were activated conveniently, as needed, by the simple expedient of azeotropic distillation of the excess water with benzene, thereby circumventing the lengthy drying and grinding procedures usually employed for activation of precipitated manganese dioxide. With adequate rates of stirring (to break up lumps) and heating, the azeotropic activation is complete in about 1 hr, leaving a dense, brownish black, rapidly sedimenting precipitate having the appearance of irregular agglomerates under the microscope. In the presence of substrate, however, the agglomerates are quickly dispersed in benzene to a blackish brown suspension of fine, slowly sedimenting particles. Reagent activated by the azeotropic method can be used directly or stored under benzene; the benzene may be replaced with another solvent by successive decantations and washings; or the reagent may be collected by filtration for storage and/or use in other solvents. Both wet filter cake and the activated reagent under benzene have been stored unchanged for more than 1 year.

Inspection of the data in Table I shows that the reagent prepared by the azeotropic method is a typical activated manganese dioxide. No effort was made to optimize yields and conditions, or to evaluate activity and substrate specificity in comparison with activated manganese dioxide prepared *via* standard procedures.[3]

Azeotropic procedures have been employed by Pratt[2,4] as a useful device for following the rates of manganese dioxide oxidations in which the by-product water is distilled into a Dean–Stark trap. The reagent used for these studies, however, had already been activated in the conventional way in a prior step.[5]

The structure of activated manganese dioxide remains an enigma.[3,6,7] Gritter, *et al.*,[3] have noted an important role for cationic impurities, and Evans[6] and Henbest[8] have pointed to the critical role for water of hydration. In the present procedure, the azeotroping serves to remove occluded (not firmly bound) water and, presumably, water adsorbed to oxidatively active

(1) For leading references, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," 1st ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 637.

(2) E. F. Pratt and S. P. Suskind, *J. Org. Chem.*, **28**, 638 (1963).

(3) Some differences in activity for various preparations of activated manganese dioxide have been demonstrated in the study of R. J. Gritter, G. D. Dupre, and T. J. Wallace, *Nature*, **202**, 179 (1964).

(4) E. F. Pratt and J. F. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1961); E. F. Pratt and T. P. McGovern, *ibid.*, **29**, 1540 (1964).

(5) The activation procedures employed in the studies of Pratt[2,4] included a combination of some of the following steps prior to azeotroping: drying at 125° for various periods of time, grinding to pass a 60-mesh screen, redrying at 125°, equilibration with atmospheric moisture, and storing at −20° in closed containers.

(6) R. M. Evans, *Quart. Rev.* (London), **13**, 61 (1959), and references cited therein.

(7) W. F. Pickering, *Rev. Pure Appl. Chem.*, **16**, 185 (1966), and references cited therein.

(8) H. B. Henbest, E. R. H. Jones, and T. C. Owen, *J. Chem. Soc.*, 4909 (1957); and H. B. Henbest and A. Thomas, *ibid.*, 3032 (1957).

TABLE I

CHARACTERIZATION OF AZEOTROPICALLY ACTIVATED MANGANESE DIOXIDE[a]

Starting material	Product	Yield, %	Time, hr
$C_6H_5CH_2OH$	C_6H_5CHO	70[b]	1.0
$C_6H_5CHOHCH_3$	$C_6H_5COCH_3$	70[b]	0.5
$C_6H_5CH=CHCH_2OH$	$C_6H_5CH=CHCHO$	70[b]	1.0
$C_6H_5CHOHCOC_6H_5$	$C_6H_5COCOC_6H_5$	50	16
$C_6H_5CHOHCHOHC_6H_5$ (*meso*)	C_6H_5CHO	60[b]	1.0
$(C_6H_5)_2COHCOH(C_6H_5)_2$	$(C_6H_5)_2CO$	65[b]	16
$C_6H_5CHOHCH_2NH_2$	C_6H_5CHO	55[b]	3.0
$C_6H_5CHOHCOOC_2H_5$	$C_6H_5COCOOC_2H_5$	65[b]	1.0
$(C_6H_5)_2COHCOOH$	$(C_6H_5)_2CO$	45[b]	16
Hydroquinone	Quinone	65	1.0
Geraniol	Citral	80[c,d]	2.0
$C_6H_5CH_2CH_2OH$	Recovered starting material	80[c]	0.5

[a] Oxidations were performed with 1.0 g of substrate and 10.5 g (25 g of wet) of manganese dioxide in 125 ml of benzene at room temperature with stirring, except as noted. See Experimental Section for details. [b] As the 2,4-dinitrophenylhydrazone. [c] By gas chromatography. [d] Geraniol (2 g) as substrate.

adsorption sites on the surface. The azeotropically activated material contains 7% water as compared to an excess moisture content of 4–8% reported for material prepared by the Attenburrow procedure.[6] Continued azeotroping, past the point of complete activation, does not remove the firmly bound water of hydration, and so there is no danger of deactivating the activated hydrate by this azeotropic procedure.

On the assumption that the activation of precipitated manganese dioxide involves, as the critical step, the liberation of active sites on the surface by desorption of adsorbed water, it was reasoned that activation might also be effected by azeotroping at a lower temperature and, perhaps, even by the simple expedient of extractive dehydration by means of solvents having an avidity for water. The results of preliminary experiments indicate that some degree of azeotropic activation can indeed be achieved using ethyl ether, carbon tetrachloride, chloroform, and propionitrile. These are qualitative results, only, and no data was sought regarding the relative oxidizing power of the reagents prepared in this way *vs.* that using the benzene procedure. The results of extractive activation by ethyl ether or acetonitrile, summarized in Table II, indicate that significant activation can also be achieved with appropriate dehydrating solvents.

TABLE II

EXTRACTIVE ACTIVATION *vs.* THE BENZENE AZEOTROPIC PROCEDURE[a]

Method of activation	Oxidizing power[b]
A. Standard benzene azeotrope	1.5 mequiv of [O] per g of reagent[c]
B. 25 g of wet MnO_2 extracted with ten 200-ml portions of ethyl ether	0.47 mequiv of [O] per g of reagent
C. 25 g of wet MnO_2 extracted with five 200-ml portions of acetonitrile	0.87 mequiv of [O] per g of reagent

[a] Manganese dioxide (25 g of wet) was activated by azeotropic distillation with benzene or by repetitive extractions with ethyl ether or acetonitrile. Oxidations were performed with 3.0 g of benzyl alcohol for 1 hr. See Experimental Section for details. [b] Oxidizing power was calculated from the amount of benzaldehyde-2,4-dinitrophenylhydrazone which could be prepared after the 1-hr oxidation, based on 10.5 g of activated reagent. [c] This value compares favorably with the value of 1.25–1.35 mequiv of [O] per g of MnO_2 reported by Henbest, *et al.*,[8] for oxidation of allylic alcohols.

The foregoing results not only demonstrate an efficient azeotropic procedure for activating precipitated manganese dioxide, but point to the possibility that useful procedures may be devised for production of manganese dioxides of intermediate degrees of activity for application to substrates requiring greater selectivity than heretofore available by conventional methods for preparation of the active reagent.

The observation that some degree of activation may be achieved simply by washing the wet precipitate with an appropriate dry solvent is consistent with the early hypothesis[9] that the initial step in the manganese dioxide oxidation is adsorption of substrate. An ensuing publication will present evidence that the rate-determining step in the manganese dioxide oxidation of benzylic alcohols is C–H bond cleavage.

Experimental Section

Preparation of Activated Manganese Dioxide.—Active manganese dioxide was prepared by a modified Attenburrow procedure.[2] After the final water wash the filter cake was left on the funnel with suction for about 24 hr. Surface cracks were closed with a flat spatula to facilitate washing and water removal. The hydsated filter cake was cut into chunks and stored in closed bottles. Activation of small quantities was effected as required by the following procedure. Into a 250-ml flask fitted with a Dean–Stark trap, condenser, and magnetic stirrer were added 150 ml of benzene and 25 g of the hydrated precipitated manganese dioxide (large chunks were crumbled on Glassine paper prior to addition). Water (14.5 ml) was removed by vigorous azeotropic distillation with stirring over about 1 hr, or until separation of water was complete. Reagent activated in this way was brownish black and dense, as contrasted to the blackish brown and finely dispersed appearance after addition of substrates for oxidation. Wet filter cake has been stored for more than 2 years without change. Activated reagent has been stored in stoppered flasks under benzene for 1 year without loss of activity. In a second run, the wet filter cake was pressed on the funnel until the water content, determined by azeotroping, was about 40%. This material, upon azeotropic activation, had the same oxidizing power on a dry-weight basis as the material used in Table II.

Oxidations, Table I.—Substrates were added at room temperature under nitrogen to stirred mixtures of 10.5 g (from 25 g of wet) of activated manganese dioxide (above) in 125 ml of benzene. The flasks were stoppered and the mixtures stirred for the designated times. The reaction mixtures were filtered through Celite and the filter cakes were washed with three portions of fresh solvent. Benzene was removed from the combined filtrates and washings under reduced pressure. Products of oxidation were identified directly or as the 2,4-dinitrophenylhydrazones.

(9) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

Activations, Table II.—In preliminary experiments, 2.5-g samples of wet manganese dioxide were azeotropically activated using ethyl ether, carbon tetrachloride, chloroform, or propionitrile. After a suitable azeotroping period, as judged by the appearance of the manganese dioxide, excess benzyl alcohol was added, with stirring for about 0.5 hr. Following filtration and solvent removal, benzaldehyde was detected by conversion to the 2,4-dinitrophenylhydrazone. In each case a substantial amount of the derivative formed, indicating some degree of activation. The wet catalyst, unactivated, gave no detectable benzaldehyde under these conditions.

The extractive activations with ethyl ether and acetonitrile were performed as follows. Wet manganese dioxide (25-g samples) was stirred vigorously with ten 200-ml portions or five 200-ml portions of ether or acetonitrile, respectively. Stirring was continued for about 5 min for each portion of fresh solvent. Spent solvent was decanted prior to addition of fresh solvent. To the activated materials, in benzene solvent, were then added 3-g samples of benzyl alcohol. After 1 hr, the yield of benzaldehyde, as the 2,4-dinitrophenylhydrazone, was determined. Oxidizing power was determined in comparison with benzene-azeotroped material, on the basis of 10.5 g of active material in each case.

Registry No.—Manganese dioxide, 1313-13-9.

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Catalytic Decomposition and Chemical Reduction of Diaryliodonium Salts. Reactions Involving Ligand Transfer[1]

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Copper(I) salts have been shown to be extremely efficient catalysts for the decomposition of diaryliodonium salts.[2] A study of the reaction of iodonium salts with metal salts more strongly reducing than copper(I), *i.e.*, titanium(III) and chromium(II), has been initiated, and the copper-catalyzed reaction has been further investigated.

Titanium(III) chloride was found to be an efficient catalyst for the decomposition of diphenyliodonium chloride (Table I). The reaction in water proceeds to completion with 0.06 equiv of titanium(III) chloride, yielding only iodobenzene and chlorobenzene without consuming titanium(III). The same reaction in methanol, however, went only 39% to completion, with complete consumption of catalyst (Table I). The main products were iodobenzene and benzene, along with small quantities of chlorobenzene and biphenyl.

Polarographic studies[3] of iodonium salts had previously revealed that diphenyliodonium cations may accept one electron ($E_{1/2} = -0.2$ V *vs.* sce) forming diphenyliodine, which is unstable and rapidly decomposes to iodobenzene and phenyl free radicals. Further, the reactions of diphenyliodonium salts have been intensively studied, and on the basis of several factors (product distribution, steric effects, dehydrogenation of solvent, effect of oxygen, polymerization of styrene) an initial step of electron transfer from carbanion to iodonium ion has been proposed.[4a,5] In the light of these earlier conclusions and in light of the above results with titanium(III) chloride, a mechanism to explain this catalysis is now proposed.

The reaction is formulated as initiated by an electron transfer from a titanium(III) species[6] to yield unstable diphenyliodine and a titanium(IV) species.[6] In turn, diphenyliodine decomposes to iodobenzene and a phenyl free radical,[3] whose fate is determined by the solvent and other reactants. In water the phenyl radicals react exclusively with a titanium(IV) species, forming chlorobenzene and regenerating titanium(III) by a ligand-radical transfer process.[7] In methanol, however, the predominant path is hydrogen abstraction from solvent; regeneration of titanium(III) is therefore much less efficient. The reaction in water, in the presence of acrylonitrile, yielded polyacrylonitrile. Polymerization did not take place under identical conditions in the absence of iodonium salt. This observation is in accord with the postulated existence of phenyl free radical intermediates. Product distribution studies of the titanium(III)-catalyzed decomposition of unsymmetrical 4-methoxydiphenyliodonium chloride in water showed the ratio of cleavages of C_6H_5–I/$CH_3OC_6H_4$–I to be 1.4. This insensitivity of carbon–iodine bond cleavage to polar substituents on the phenyl ring has been taken to indicate nonpolar bond fission.[4,8] The yield of chlorobenzene, from reactions run in methanol, was independent of acid and chloride ion concentrations but did depend on the Ti(IV)/Ti(III) ratio (Table I). Addition of $TiCl_4$ to methanol results in the formation of $TiCl_2(OMe)_2$.[9] The resulting increased concentration of titanium(IV)-bound chloride, which can undergo ligand-radical transfer to a phenyl radical, is reflected in significantly increased yields of chlorobenzene. As expected, anisole was not detected since methoxide does not readily undergo ligand-radical transfer.[7a] To the knowledge of the authors ligand-radical transfer processes involving titanium salts have not previously been described.

Chromium(II) chloride, a more powerful reducing agent than titanium(III), yielded mainly iodobenzene

(1) This paper is largely based on part II of a dissertation submitted by P. Bodlaender in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), 1967.

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(3) H. E. Bachofner, F. M. Beringer, and L. Meites, *J. Amer. Chem. Soc.*, **80**, 4269, 4274 (1958).

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(5) (a) F. M. Beringer and P. S. Forgione, *Tetrahedron*, **19**, 739 (1963); (b) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3417 (1963).

(6) Information about the stability constants of titanium chloride complexes is extremely limited. Indications are that titanium(III) chloride, in aqueous solutions under the conditions of the reactions here studied, exists mainly as $TiCl^{2+}$, a partially hydrolyzed species. The situation for titanium(IV) chloride is even less clear but the participation of $Ti(OH)_2Cl_2$ or $TiOCl_2$ seems to be a possibility: L. G. Sillen and A. E. Martell, Special Publication No. 17, The Chemical Society, Burlington House, London, 1966; F. R. Duke and P. R. Quinney, *J. Amer. Chem. Soc.*, **76**, 3800 (1954); A. G. Stromberg and A. I. Kartushenskaya, *Zh. Fiz. Khim.*, **35**, 1058 (1961); B. I. Nabivanets, *Zh. Neorg. Khim.*, **7**, 412, 417 (1962).

(7) (a) J. K. Kochi, *Tetrahedron*, **18**, 483 (1962); (b) J. K. Kochi and R. V. Submaranian, *J. Amer. Chem. Soc.*, **87**, 1508, 4855 (1965); (c) A. H. Lewin, A. H. Dinwoodie, and T. Cohen, *J. Org. Chem.*, **32**, 3844 (1964).

(8) M. C. Caserio, D. L. Glusker, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 336 (1959).

(9) R. Feld and P. L. Cowe, "The Organic Chemistry of Titanium," Butterworth and Co. Ltd., London, 1965, pp 1, 20, L54.

TABLE I

PRODUCTS OF REACTIONS OF DIPHENYLIODONIUM CHLORIDE WITH TITANOUS CHLORIDE[a]

Solvent	$[TiCl_3]/[-I^+-]$	Additive	Reaction,[b] %	Product yield, %[c,d] PhCl	PhH	Ph_2
Water	0.10		100	100		
Water (1 *N* HCl)	0.06		100	100		
Methanol	1.0		97[e]	10	86	4
Methanol	0.30		85[f]	8	88	4
Methanol	0.21		70	3	83	4
Methanol	0.06		39[g]	2	82	6
Methanol	1.0	HCl[h]	89[i]	0	87	3
Methanol	1.0	LiCl[j]	100	6	88	6
Methanol	1.0	$TiCl_4$[k]	93	27	69	4
Methanol	1.0	(O_2)[l]	100	20	76	4
Methanol	0.09	(O_2)[m]	60[n]	46	48	6
Water	0.10	CH_2=CHCN[o]	47	Polyacrylonitrile (63%)[p]		

[a] Reactions were run in an inert atmosphere and deaerated solvents at 65° for 24 hr. [b] Determined from PhI analysis and also by the recovery of iodonium salt as the iodide. When both procedures were used on the same run, they agreed to within 2%. $TlCl_3$ does not react with PhI under the conditions of the reaction. [c] Determined by vpc. [d] Normalized to 100%. Total recovery was 100% except where noted. [e] Total recovery was 90%. [f] Total recovery was 96%. [g] Total recovery was 85%. [h] 1.0 mol of HCl/mol of $Ph_2I^+Cl^-$. [i] Total recovery was 91%. [j] 0.6 mol of LiCl/mol of $Ph_2I^+Cl^-$. [k] 0.16 mol of $TiCl_4$/mol of $Ph_2I^+Cl^-$. [l] Solvent was not degassed, and the reaction was left open to the atmosphere. [m] $TiCl_3$ was exposed to atmosphere before using. [n] Yield is based on the weight of starting acrylonitrile. [o] 1.0 mol of CH_2=CHCN/mol of $Ph_2I^+Cl^-$. Reaction was run at 80° for 8 hr. In the absence of iodonium salt, polymerization was not observed. [p] Total recovery was 93%.

and benzene with smaller quantities of chlorobenzene and biphenyl from reactions with diphenyliodonium chloride in water (Table II). Chromium(II) is irreversibly oxidized during the course of the reaction. Stoichiometry requiring a 2:1 ratio of metal salt to diphenyliodonium chloride is indicated by the results summarized in Table II. A proposed mechanism is based on established iodonium salt chemistry and on the currently accepted explanation of the reduction of alkyl halides by chromium(II) salts.[10] As with titanium(III), a one-electron transfer from a low-valent metal complex to the iodonium cation results in the initial formation of diphenyliodine, which decomposes rapidly to iodobenzene and phenyl free radicals. The phenyl radical may be captured by a second chromium(II) ion to furnish an organometallic intermediate, which on protonation yields benzene and the chromium(III) ion; alternatively, the radicals may dimerize to form biphenyl. The use of less than the stoichiometrically required amount of reducing agent caused a significant increase in the yield of biphenyl. This observation seems to rule out a coupling reaction involving a diphenylchromium intermediate[11] and indicates that capture of phenyl radicals by chromium(II) and the dimerization reaction are competitive reactions, with the former being favored. Further, material balance of iodobenzene indicates no loss of iodobenzene, thus excluding a coupling involving iodobenzene.

TABLE II

PRODUCTS OF REDUCTION OF DIPHENYLIODONIUM CHLORIDE WITH CHROMOUS CHLORIDE IN WATER[a]

$[CrCl_2]/[-I^+]$	Additive	Reaction,[b] %	Product yield, %[c] PhCl	PhH	Ph_2
1.0		61[d]	11	50	39
2.0		85	9	84	7
2.0	LiCl[e]	82[f]	14	76	10
2.0	$CrCl_3$[g]	85	14	74	12
2.0[h]	(O_2)	83	29	63	8
2.0[i]		96	44	51	5

[a] Reactions were run for 1 hr at 95°, in an inert atmosphere and deaerated solvents. [b] Determined from PhI analysis and also by the recovery of iodonium salt as the iodide. When both procedures were used on the same run, they agreed to within 5%. [c] Determined by vpc. Normalized to 100%. Total recovery was 96–100% except where noted. [d] Total recovery was 92%. [e] 1.0 mol of LiCl/mol of $Ph_2I^+Cl^-$. [f] Total recovery was 80%. [g] 0.32 mol of $CrCl_3$/mol of $Ph_2I^+Cl^-$. [h] The concentration of chromium(II) was determined for the fresh uncontaminated solution which was then briefly exposed to the atmosphere. [i] Chromium(II) chloride solution showed signs of decomposition.[j] [j] J. J. Lingane and R. L. Pecsok, *Anal. Chem.*, **20**, 425 (1948).

Reactions previously postulated[3,4a,8] for the copper-catalyzed decomposition of diaryliodonium salts were analogous to those for the well-established copper-catalyzed reactions of aryldiazonium salts in the Sandmeyer and Meerwein reactions.[14] The suggested mechanistic path involved an electron transfer from copper(I) to the iodonium cation, with subsequent homolytic cleavage of the aryl–iodine bonds, followed by ligand-radical transfer from copper(II) to the aryl radical, with regeneration of copper(I). Evidence for

The yields of chlorobenzene were independent of the concentration of LiCl and $CrCl_3$ but did increase if solutions containing chromium(II) were briefly exposed to air prior to the reaction or if solutions were used which showed signs of decomposition. In the latter two cases the solutions were at a higher pH.[12] This behavior was also observed in the titanium(III) system. Whether a pH-dependent ligand-radical transfer process is operating, possibly involving oxygenated complexes of chromium[13] or titanium, is not clear at this time. The observation by Kochi and Davis[10b] that benzyl chloride is regenerated during the reaction with chromium(II) chloride may be relevant.

(10) (a) D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Amer. Chem. Soc.*, **88**, 3017 (1966); (b) J. K. Kochi and D. D. Davis, *ibid.*, **86**, 5264 (1964); (c) J. K. Kochi and D. Buchanan, *ibid.*, **87**, 853 (1965); (d) C. E. Castro, *ibid.*, **83**, 8262 (1961).

(11) M. Tsutsui and H. Zeiss, *ibid.*, **81**, 1367 (1959).

(12) See Table II, footnote *j*.

(13) M. Ardon and G. Stein, *J. Chem. Soc.*, 2095 (1956).

(14) (a) N. A. Cowdry and D. S. Davies, *Quart. Rev.* (London), **6**, 358 (1952); (b) J. K. Kochi, *J. Amer. Chem. Soc.*, **79**, 2942 (1957); (c) S. C. Dickerman, K. Weiss, A. K. Ingberman, *ibid.* **80**, 1904 (1958); (d) G. N. Schrauzer, *Ber.*, **94**, 1891 (1961).

TABLE III

PRODUCTS OF COPPER-CATALYZED DECOMPOSITION OF DIPHENYLIODONIUM CHLORIDE[a]

Solvent	$[CuCl^-]/[-I^+-]$	Cupric salts	% yield[b,c]	
			PhCl	PhOH
Water	0.031		95	5
Water (0.25 *N* HCl)	0.031		100	
Methanol	0.020		100	
Acetone	0.027		100	
Water	0.028	$CuSO_4$[d]	89	11
Water	0.030	$Cu(NO_3)_2$[e]	89	11
Water[f]		$Cu(NO_3)_2$[g]	86	14
Water[h]	0.030		96	4

[a] Reactions were run at 60–65° for 1 hr in an inert atmosphere and deaerated solvents. Reactions went 100% to completion as determined from analyses for iodobenzene and for unreacted iodonium salt. [b] Determined by vpc; neither PhH nor Ph_2 could be found in any of the runs. Concentrations corresponding to 1% yields would have been detected. [c] Normalized to 100%. Total recovery was 98–100% except where noted. [d] 1.1 mol/mol of $Ph_2I^+Cl^-$. [e] 3.2 mol/mol of $Ph_2I^+Cl^-$. [f] Reaction time was 4 hr. [g] 3.1 mol/mol of $Ph_2I^+Cl^-$. [h] Solvent was not deaerated.

the proposed mechanism was derived largely from kinetic studies,[15] polarographic data,[3] and product analysis of the copper-catalyzed decomposition of unsymmetrically substituted iodonium salts.[4a,8] A recently suggested mechanism involves heterolytic carbon–iodine bond cleavages.[16] However, this mechanism seems to be precluded by the insensitivity of the carbon–iodine bond cleavage to the polar nature of the substituents in unsymmetrical iodonium salts.[4,8]

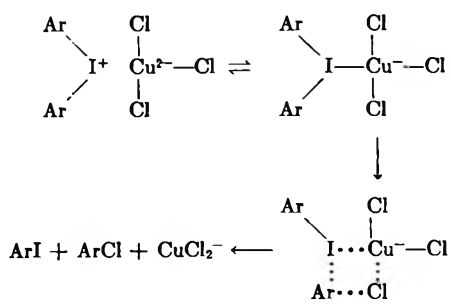
We have reinvestigated the copper(I) chloride catalyzed decomposition of 4-nitro- and 4-methoxydiphenyliodonium chloride and found the cleavage ratio C_6H_5–I/RC_6H_5–I to be 1.5 in both cases. This is in close agreement with previously reported data[4a,8] and with the ratio determined for the titanium(II) catalyzed reaction. However, copper-catalyzed reactions of diphenyliodonium chloride in water, methanol and acetone did not yield any benzene or biphenyl, the expected products from reactions involving phenyl free radical intermediates (Table III). Moreover, neither arylated products nor polymers were detected when reactions were carried out in the presence of α,β-unsaturated substrates of types used in Meerwein arylations (acrylonitrile was most intensively studied).[17] The absence of free-radical intermediates have been substantiated only for cases involving ligand transfer of chlorine, iodine and water. These results are in strong contrast to those obtained from the copper-catalyzed reactions of diazonium salts[14] and with those reactions of iodonium salts[4a,5] which proceed *via* electron transfer. In each of these cases the existence of free radical intermediates has been clearly demonstrated.

The differences in products in the decomposition of diphenyliodonium chloride catalyzed with copper(I) and with titanium(III) point clearly to two different reaction paths. While a mechanism involving initial electron transfer to the iodonium ion best explains the products of the titanium(III)-catalyzed reaction, an alternative reaction path, which does not involve the intermediacy of phenyl free radicals, seems to operate in the copper(I)-catalyzed reaction. A previously reported observation[4a] that copper(I) catalyzes the reaction of cyanide ion with the diphenyliodonium ion, even at high cyanide concentrations, also seems to rule out an electron-transfer step as the oxidation potential of $Cu(CN)_2^-$ is highly negative ($E^\circ = -1.12$ V).[18] Further, the faster reactions of the diphenyliodonium ion with copper(I) complexes than with more strongly reducing complexes of other metals suggests a different mechanism for the copper(I)-catalyzed reaction. For example, at 65° under identical conditions the decomposition of diphenyliodonium chloride was complete in less than 0.5 hr in the presence of copper(I) chloride and in more than 8 hr in the presence of titanium(III) chloride; for the reaction to proceed to completion in 1 hr in the presence of chromium(II) chloride, a temperature over 90° was necessary.

A modification of the previously proposed mechanism is therefore put forward for the copper(I) chloride-catalyzed decomposition of diaryliodonium salts: complex formation between copper(I) and the iodonium cation possibly involving donation of the 5s electrons of iodine to the empty 4p or 4d orbitals of copper with back donation from the filled 3d orbitals of copper to the empty 5d or 4f orbitals of iodine; subsequent decomposition of the complex *via* a four-center concerted process in which there is no net change in the oxidation state of copper. (Analogous four-center processes have been proposed for reactions of aryl halides with copper(I) chloride.[19])

In Scheme I the initial copper(I) species may be $CuCl_2^-$ or $CuCl_3^{2-}$, these being the predominant species

SCHEME I



(15) F. M. Beringer, E. M. Gindler, M. Rapoport, and R. J. Taylor, *J. Amer. Chem. Soc.*, **81**, 352 (1956).

(16) O. A. Chaltykyan, "Copper-Catalyzed Reactions," Consultants Bureau, New York, N. Y., p 60.

(17) Meerwein and coworkers have reported the arylation of several α,β-unsaturated substrates using diphenyliodonium iodide under the conditions of the Meerwein reaction but experimental details were not given: H. Meerwein, E. Buchner, and K. van Emster, *J. Prakt. Chem.*, **152**, 237 (1939).

(18) W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice Hall, Inc., Englewood Cliffs, N. J., 1952.

(19) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev.* (London), **19**, 95 (1965).

present in aqueous solutions under the reaction conditions,[20] or solvated neutral species which might predominate in methanol and acetone.[19] In aqueous solutions a copper-bound water molecule may also undergo ligand transfer resulting in the formation of phenol.[7c] However, in acetone and methanol the only products are iodobenzene and chlorobenzene, thus indicating exclusive ligand transfer of chloride. In agreement with other workers,[7] chloride was found to undergo ligand transfer more effectively than water. Nitrate[7c,14b] and sulfate[7a] are not involved in ligand transfer reactions. High ratios of copper(II) sulfate or nitrate to copper(I) chloride increase yields of phenol, probably because competition for chloride ion results in more highly solvated copper(I) species in this system. While acid has no appreciable effect on the rate of hydrolysis,[8] increased chloride ion concentration completely eliminates phenol production (Table III).

In summary of this last point, while present data cannot give the exact structure of the proposed complex of the diphenyliodonium ion with a di- or trichlorocuprate(I) ion and thus the possibility exists of structures different from that suggested above, the experimental observations strongly indicate a concerted reaction mode without free aryl intermediates.

Experimental Section

Starting Materials. Reagents.—All reagents were Fisher Certified Reagents except as noted. Iodobenzene, bromobenzene and chlorobenzene were distilled. Acrylonitrile (Eastman) was distilled and stored in the dark. Diphenylamine sulfonate (0.005 *M*) was obtained from the G. Fredrich Smith Chemical Co., Ohio.

Solvents.—Solvents for recrystallizations and reactions were deionized water, methanol (Electrograde, Nitine Inc.) and acetone (Fisher Certified Reagent, distilled from potassium carbonate).

Iodonium Salts.—4-Nitro- and 4-methoxydiphenyliodonium chloride were prepared by known procedures.[21,22] Diphenyliodonium chloride was prepared by a variation worked out by Doptoglon, of a previously reported procedure.[22,23] Diphenyliodonium iodide[24] is easily prepared by adding potassium iodide to an aqueous solution of diphenyliodonium chloride.

Copper Solutions.—Copper(I) solution was prepared by dissolving cuprous chloride in a deaerated 1 *M* lithium chloride solution in water. The clear colorless solution, stored in the dark in a bottle stoppered with a rubber septum, was titrated periodically. Concentration of copper(I) (0.0720 *M*) was found to be invariant. Aliquots were removed *via* syringe while argon was being bubbled through the solution and were used for all copper(I)-catalyzed reactions in aqueous solvents. For reactions in nonaqueous solvents copper(I) solution were made up as needed in deaerated 1 *M* lithium chloride solutions of methanol or acetone. Copper(II) solutions were made up as needed by dissolving the cupric salt in a minimum of solvent. For reactions in which both copper species were used, the copper(I) and copper(II) solutions were mixed before their addition to the reaction mixture.

Titanous Chloride.—Commercially available 20% aqueous titanous chloride (Fisher) was used. Aliquots were removed as described above. Solutions were titrated for titanium(III) before use.

Chromous Chloride.—Solutions of 0.4 *M* chromous chloride in 0.4 *M* hydrochloric acid were prepared as previously reported[12] by reduction of an acidified potassium dichromate solution with excess 30% hydrogen peroxide, and the resulting chromic chloride was in turn reduced to chromous chloride with zinc amalgam (1% mercury). The solution was stored over zinc amalgam in a 2-l. three-necked flask fitted with a gas inlet for argon, a mercury seal and a stopcock fitted with a rubber septum through which aliquots were removed *via* syringe. Solutions showed signs of decomposition after 1 week due to gradual reduction of hydrogen ion by zinc; this finally raised the pH to such a value that hydrolytic precipitation of the chromous ion occurred.[12] Aliquots were titrated before use.

Analysis for Copper(I), Titanium(III), and Chromium(II) Species.—Copper(I), titanium(III) and chromium(II) were analyzed according to procedures described by Kolthoff and Dandell.[25] Solutions of these species were added to an excess of deaerated, acidified solution of ferric alum. The resulting ferrous species was titrated with standard potassium dichromate solution using diphenylamine sulfonate indicator. All determinations were repeated and agreed to within 3%.

Catalyzed Decomposition and Chemical Reduction of Diaryliodonium Salts.—A generalized procedure is described below. Product yields, reaction time and temperature, and ratios of moles of reagent to moles of $-I^+-$ are listed in Tables I–III.

Unless otherwise stated, all reactions were run in an inert atmosphere in a three-necked, 1-l. flask fitted with a condenser and an addition funnel. Argon, initially passed through a chromous chloride solution to remove oxygen, was dispersed through the solvent (200 ml), magnetically stirred at the temperature of the reaction, and was swept through the reaction system for 1.5 hr. Iodonium salt (30 mmol) was then added and argon was bubbled through for an additional 0.5 hr. Reactions were protected from the atmosphere by a mercury seal attached to the upper end of the condenser. Solutions of catalyst or reducing agent were admitted dropwise over a period of 10 min, the dropping funnel having been charged with reagent by means of a syringe through a rubber septum.

After the indicated time the reaction mixture was allowed to cool, acidified with hydrochloric acid (to prevent loss of possible phenols) and extracted five times with 40-ml portions of methylene chloride. When solvents were methanol or acetone, 1 l. of water was added before extraction. The methylene chloride solution was dried over magnesium sulfate, filtered and analyzed by vapor phase chromatography (vpc).

Gas Chromatographic Analysis.—Organic extracts in methylene chloride solutions were analyzed by vpc (Aerograph Model No. 152OA) on a 6 ft, 5% SE-30 column (on Chromosorb G A/W DMCS). The temperature was programmed: 2 min at 75°, then 4°/min to 250° with an initial helium flow rate of 50 ml/min. Bromobenzene was used as internal standard, and the thermal conductivities of all products were calibrated *vs.* bromobenzene. For product analysis of reactions of 4-nitro- and 4-methoxydiphenyliodonium chloride, biphenyl was used as the internal standard after preliminary investigations showed biphenyl not to be a product of these reactions. Thermal conductivities of all products were calibrated *vs.* biphenyl in these cases.

The yield of iodobenzene was used as a measure of the extent of reaction. This was occasionally checked by recovering unreacted iodonium salt, if any, as the iodide. These procedures agree to within 2% of each other. None of the reagents was found to react with iodobenzene or chlorobenzene under the conditions of the reaction.

Attempted Meerwein-Type Arylations.—Organic products from these reactions were extracted as previously described. In preliminary runs the methylene chloride solution was evaporated, the high-boiling residues were fractionally distilled at reduced pressure. Products were identified by vpc. In no case were products such as α-chlorohydrocinnamonitrile [bp 137–140° (15 mm)] arising from the arylation of acrylonitrile found.[26]

Deaerated substances were usually added to the reaction mixture prior to addition of catalyst. Alternative addition of a solution containing both substrate and catalyst made no difference in product distribution.

Reaction of Diphenyliodonium Chloride with Titanous Chloride in the Presence of Acrylonitrile.—Diphenyliodonium chloride

(20) G. Bodlaender and O. Strobeck, *Z. Inorg. Chem.*, **31**, 458 (1902); N. Szabo and Z. Szabo, *Z. Physik. Chem.*, **A166**, 228 (1933); R. Vesten, A. Somersalo, and B. Mueller, *Acta Chem. Scand.*, **7**, 745 (1953); T. Hurlen, *ibid.*, **16**, 279 (1962).

(21) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillian, G. Masullo, M. Mausner, and E. Sommer, *J. Amer. Chem. Soc.*, **81**, 342 (1959).

(22) F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *ibid.*, **75**, 2705 (1953).

(23) F. M. Beringer and D. D. Doptoglon, unpublished results.

(24) F. M. Beringer and E. M. Gindler, "Organic Compounds of Polyvalent Iodine;" Chilean Iodine Educational Bureau, Inc., New York, N. Y., 1956.

(25) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 1st ed, The Macmillian Co., New York, N. Y., 1947, p 596.

(26) C. G. Koelsch, *J. Amer. Chem. Soc.*, **65**, 57 (1943).

reacted with titanous chloride in the presence of acrylonitrile to yield a white solid which began to appear after 20 min of reaction. After 8 hr at 80° titanous chloride was completely consumed, and 47% of the iodonium salt had reacted. A control reaction under identical conditions, but without iodonium salt, showed no change after 8 hr. The solid was collected, washed and triturated in turn with water, methanol and ether, yielding 5.0 g (63% based on starting acrylonitrile) of polyacrylonitrile. The polymer was dissolved in a minimum of dimethylformamide at 80–90°, and the solution was filtered hot through Celite. Water was slowly added to the cooled solution until no more precipitation occurred. The collected solid was dried to yield 3.0 g of polyacrylonitrile, mp 250° dec (lit.[13] 250–310° dec).

Identification was made from solubility characteristics and infrared and nmr spectra. The polymer was found to be insoluble in water, alcohols, acetone, ethylacetate, ether, methylene chloride and pentane but was soluble in dimethylformamide.[3] An infrared spectrum (potassium bromide pellet) exhibited strong peaks at 2230 (-CN), 1450 (CH, CH_2) and 1050 cm^{-1} (C–C skeletal).[13] An nmr spectrum (on a Varian A-60 spectrometer) of a solution in deuterated dimethyl sulfoxide exhibited broad signals at τ 7.9 and 6.8 and a very weak signal at 2.7.

Registry No.—Diphenyliodonium chloride, 1483-72-3; titanous chloride, 7705-07-9; chromous chloride, 10049-05-5.

Deuterium Isotope Effect upon a Bimolecular Dehydrochlorination of *t*-Butyl Chloride in Acetonitrile

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We have extended our recent study of the secondary deuterium isotope effect upon the unimolecular dehydrochlorination of *t*-butyl chloride in acetonitrile[1] to a study of the deuterium isotope effect under conditions for bimolecular reaction in this solvent. It is known that bimolecular reactions of tertiary halides in dipolar aprotic solvents frequently show a small amount of substitution reaction accompanying dehydrohalogenation[2,3] and complications of this type have been avoided by use of chloride ion as the reagent to promote the bimolecular dehydrochlorination. Chloride ion in acetonitrile is quite efficient in this capacity[4] and, with this reagent, any substitution reaction will be symmetrical. The dehydrochlorination of *t*-butyl chloride is subject to marked reversal and, in the absence of reagents which remove hydrogen chloride, the reaction in aprotic solvents comes to an early equilibrium.[5] In the unimolecular dehydrochlorination,[1] added pyridine reacted with the hydrogen chloride to form pyridinium chloride[6] and prevent complications due to movement toward an equilibrium. In the presence of chloride ion, hydrogen chloride is effectively coordinated to give the hydrogen dichloride anion[7] and pyridine can be omitted.

A serious complication to the kinetic pattern is that the unimolecular reaction will be subject to a positive salt effect upon addition of tetraethylammonium chloride and the dehydrochlorination rate increase will consist of two components—one due to the superimposed bimolecular reaction and one due to a positive salt effect upon the underlying unimolecular reaction. In order to analyze the kinetics of the bimolecular reaction, we have attempted to arrive at the magnitude of salt effects upon the unimolecular reaction by assessing the rate increase upon addition of identical concentrations of tetraethylammonium perchlorate—a salt containing an anion which, relative to chloride ion, is ineffective in promoting bimolecular dehydrohalogenation in acetonitrile.[8] Perchlorate ion does not coordinate with hydrogen chloride and our studies of the effect of added tetraethylammonium perchlorate were carried out in the presence of pyridine (Table I).

Our kinetic results can be analyzed provided that we make the assumption that the salt effects upon the unimolecular reaction are identical (or, at least, very nearly so) for additions of either tetraethylammonium chloride or tetraethylammonium perchlorate (Table II).

The deuterium isotope effect (k_2^H/k_2^D) is 3.81 ± 0.21. The magnitude of this effect has important implications with respect to the mechanism of bimolecular, merged substitution and elimination which was given a detailed description several years ago,[4] and which recently appears to have gained wider,[9,10] but not universal,[11,12] acceptance. In assessing the extent of carbon–hydrogen bond breaking, and interpreting in terms of a mechanism in which carbon–chlorine heterolysis is running ahead of carbon–hydrogen heterolysis, we are on a scale of roughly 2.6:6 and not, as in most previous investigations, of roughly 1:6. With this in mind, the value of 3.8 is comparable with the values of between 2 and 3 observed for halide ion promoted elimination from tertiary α-halogenated ketones in acetonitrile.[13]

Under the same conditions of temperature and solvent, the deuterium isotope effect is significantly higher than the value of 2.62 ± 0.02 observed for E1 reaction.[1] This is consistent with a loose intermediate or transition state (approaching an ion triplet) and incorporating a moderate weakening of a carbon–hydrogen bond in the transition state of the rate-determining step.[13] If a transition state was involved which featured only SN2 character superimposed upon a E1-type process, then one might expect, related to the extent that the positive charge on the α carbon was reduced, an isotope effect for the bimolecular reaction diminished below that observed for the E1 reaction.

(1) D. N. Kevill and J. E. Dorsey, *Chem. Ind.* (London), 2174 (1967).
(2) D. N. Kevill, G. A. Coppens, and N. H. Cromwell, *J. Org. Chem.*, **28**, 567 (1963).
(3) D. Cook and A. J. Parker, *J. Chem. Soc., B*, 142 (1968).
(4) D. N. Kevill and N. H. Cromwell, *Proc. Chem. Soc.*, 252 (1961); *J. Amer. Chem. Soc.*, **83**, 3812, 3815 (1961).
(5) Y. Pocker, *J. Chem. Soc.*, 1292 (1960).
(6) E. Gelles, E. D. Hughes, and C. K. Ingold, *ibid.*, 2918 (1954).
(7) Y. Pocker, *ibid.*, 240 (1958).
(8) G. A. Coppens, D. N. Kevill, and N. H. Cromwell, *J. Org. Chem.*, **27**, 3299 (1962).
(9) G. M. Fraser and H. M. R. Hoffmann, *J. Chem. Soc., B*, 425 (1967).
(10) A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968).
(11) D. J. McLennan, *J. Chem. Soc., B*, 705 (1966).
(12) J. F. Bunnett and E. Bacciochi, *J. Org. Chem.*, **32**, 11 (1967).
(13) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Amer. Chem. Soc.*, **88**, 4489 (1966).

TABLE I

EFFECT OF TETRAETHYLAMMONIUM PERCHLORATE UPON THE FIRST-ORDER RATE COEFFICIENTS, k_1^1 (sec^{-1}), FOR PYRIDINIUM ION PRODUCTION FROM ~0.2 *M* *t*-BUTYL CHLORIDE OR ~0.2 *M* *t*-BUTYL CHLORIDE-d_9 IN ACETONITRILE AT 45.0°, IN THE PRESENCE OF 0.04 *M* PYRIDINE

(i) *t*-Butyl Chloride

$[NEt_4ClO_4]$	0.000	0.100	0.200	0.300	0.400	0.500
$10^5k_1^1$	2.66	3.52	4.30	5.09	5.73	6.39

(ii) *t*-Butyl Chloride-d_9

$[NEt_4ClO_4]$	0.000	0.100	0.125	0.200	0.251	0.300	0.375	0.400	0.500
$10^5k_1^1$	1.01	1.58	1.64	1.77	1.96	2.18	2.26	2.41	2.48

TABLE II

EFFECT OF NEt_4Cl UPON THE INITIAL SPECIFIC RATES, k_1^{11} (sec^{-1}), FOR ACID PRODUCTION FROM ~0.2 *M* *t*-BUTYL CHLORIDE OR ~0.24 *M* *t*-BUTYL CHLORIDE-d_9 IN ACETONITRILE AT 45.0°, AND APPLICATION OF CORRECTION FOR INITIAL SPECIFIC RATES, k_1^1 (sec^{-1}), ON REPLACEMENT OF NEt_4Cl WITH AN IDENTICAL CONCENTRATION OF NEt_4ClO_4

(i) *t*-Butyl Chloride

$[NEt_4Cl]$	0.0100	0.0200	0.0400	0.0800	0.100	0.150	0.200[c]
$10^5k_1^{11}$	3.16	3.78	4.94	7.67	9.23	12.60	15.33
$10^5k_1^1$ [a]	2.75	2.83	3.00	3.35	3.52	3.89	4.30
$10^5\Delta k_1$[b]	0.41	0.95	1.94	4.32	5.71	8.71	11.03

$[NEt_4Cl]$	0.200[d]	0.200[e]	0.200	0.300	0.400	0.400
$10^5k_1^{11}$	15.36	15.48	15.05	22.19	29.58	28.04
$10^5k_1^1$ [a]	4.30	4.30	4.30	5.09	5.73	5.73
$10^5\Delta k_1$[b]	11.06	11.18	10.75	17.10	23.85	22.31

$10^5\Delta k_1^H = 10^5k_2^H[NEt_4Cl] = (56.2 \pm 1.1)[NEt_4Cl]$

(ii) *t*-Butyl Chloride-d_9

$[NEt_4Cl]$	0.0964	0.1925	0.289	0.385	0.385[f]
$10^5k_1^{11}$	3.00	4.60	6.35	8.17	7.85
$10^5k_1^1$ [a]	1.54	1.86	2.10	2.30	2.30
$10^5\Delta k_1$[b]	1.46	2.74	4.25	5.87	5.55

$10^5\Delta k_1^D = 10^5k_2^D[NEt_4Cl] = (14.7 \pm 0.6)[NEt_4Cl]$

[a] Obtained by graphical interpolation within the data of Table I. [b] $\Delta k_1 = k_1^{11} - k_1^1$. [c] [*t*-BuCl]; 0.100 *M*. [d] [*t*-BuCl]; 0.300 *M*. [e] [*t*-BuCl]; 0.400 *M*. [f] [*t*-BuCl-d_9]; 0.120 *M*.

TABLE III

(A) [*t*-C_4D_9Cl], 0.2405 *M*; [C_5H_5N], 0.200 *M*; 2.00-ml aliquots; titers in milliliters of 0.00579 *N* methanolic NaOMe

Time, hr	0.00	136.87	183.47	256.20	329.62	401.17	526.38	598.98	618.57
Titer	0.00	0.46	0.57	0.76	0.96	1.15	1.61	1.84	1.89
10^5k_1, sec^{-1}		1.127	1.042	0.996	0.979	0.965	1.033	1.039	1.033

Mean value for k_1 is $(1.027 \pm 0.016) \times 10^{-5}$ sec^{-1}

(B) [*t*-C_4D_9Cl], 0.1548 *M*; [C_5H_5N], 0.0400 *M*; [NEt_4ClO_4], 0.300 *M*; 2.00-ml aliquots; titers in milliliters of 0.00579 *N* methanolic NaOMe

Time, hr	0.00	66.30	114.30	168.73	219.66	264.54	309.01	359.56
Titer	0.15	0.42	0.62	0.84	1.05	1.25	1.45	1.71
10^5k_1, sec^{-1}		2.13	2.15	2.14	2.15	2.19	2.22	2.29

Mean value for k_1 is $(2.18 \pm 0.021) \times 10^{-5}$ sec^{-1}

(C) [*t*-C_4H_9Cl], 0.200 *M*; [NEt_4Cl], 0.100 *M*; 5.00-ml aliquots; titers in milliliters of 0.01158 *N* methanolic NaOMe

Time, hr	0.00	13.53	23.35	36.18	49.53	61.33	70.57	159.63
Titer	0.02	0.41	0.69	1.05	1.41	1.74	2.06	4.55
10^5k_1, sec^{-1}		9.25	9.26	9.21	9.10	9.09	9.27	9.35

Mean value for k_1 is $(9.23 \pm 0.11) \times 10^{-5}$ sec^{-1}

Experimental Section

Materials.—Tetraethylammonium chloride and tetraethylammonium perchlorate (Eastman) were recrystallized from acetone and dried under vacuum, at 70°, for 12 hr. Acetonitrile (Mallinckrodt "Nanograde") was purified[14] by placing 800 ml in a round-bottomed flask, together with 10 g of anhydrous Na_2CO_3 and 15 g of $KMnO_4$. The acetonitrile was distilled at 5–10 ml/min. The distillate was made slightly acidic with concentrated H_2SO_4 and decanted from precipitated ammonium sulfate. The acetonitrile was then distilled through a fractionating column at 10 ml/hr with a reflux ratio of 20:1. A small forecut was discarded. Pyridine was purified by the method of Burgess and Kraus,[15] dried with CaH_2, and fractionated. The *t*-butyl chloride (Eastman) was fractionally distilled and the *t*-butyl chloride-d_9 (Merck Sharp and Dohme of Canada product of 99% minimum isotopic purity on atom % D basis) was used as received.

(14) J. F. O'Donnell, J. T. Ayres, and C. K. Mann, *Anal. Chem.*, **37**, 1161 (1965).

(15) D. S. Burgess and C. A. Kraus, *J. Amer. Chem. Soc.*, **70**, 706 (1948).

Kinetic Methods.—All runs were carried out in stoppered volumetric flasks. Stock solutions of reactants were maintained at 45.0° and used to prepare reaction mixtures for kinetic runs. For runs with *t*-butyl chloride, 5.00-ml aliquots were removed from 50 ml of reaction mixture. For runs with *t*-butyl chloride-d_9, 2.00-ml aliquots were removed from 25 ml of the reaction mixture. The extent of dehydrochlorination was determined by addition of the aliquots to 20 ml of acetone, previously rendered neutral to resorcinol blue (Lacmoid) indicator, followed by titration against a standard solution of sodium methylate in methanol. In the three illustrative runs in Table III, the first-order rate coefficients are the integrated first-order rate coefficients with respect to the *t*-butyl chloride or *t*-butyl chloride-d_9. The errors quoted along with the mean values are standard errors of the mean.

Registry No.—*t*-Butyl chloride, 507-20-0; *t*-butyl chloride-d_9, 918-20-7; NEt_4Cl, 56-34-8; NEt_4ClO_4, 2567-83-1; acetonitrile, 75-05-8.

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Acid-Catalyzed Reactions of α- and β-Styryl Azides[1]

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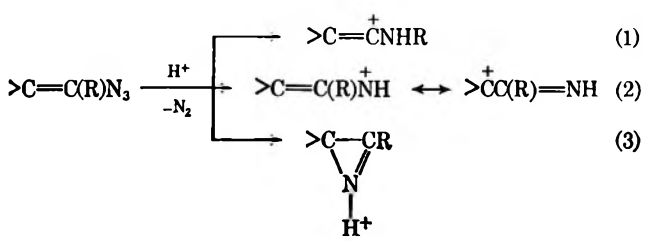
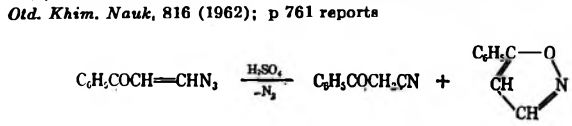
Rearrangement during acid degradation of certain alkyl azides is concerted with the evolution of nitrogen.[2] Both rearrangement[3] by path 1 and azirine ring closure by path 3 may be concerted with nitrogen evolution from a vinyl azide and an unrearranged hybrid cation may be available by path 2. If formed, it should afford certain products derived from an unrearranged carbonium ion and others from a nitrenium ion[4a] as well as rearrange to a new carbonium ion or cyclize to an azirinium ion.



(1) Financial assistance from NASA Grant No. NGR 14-012-004.

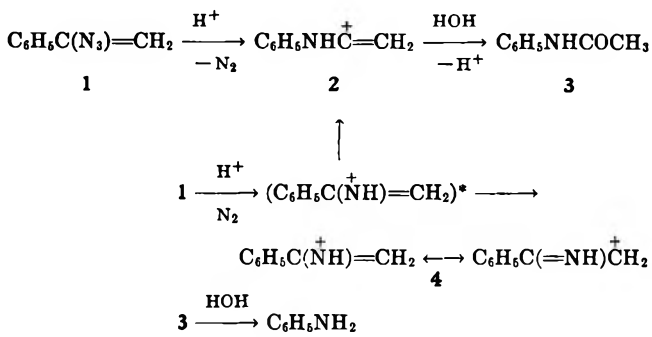
(2) P. A. S. Smith in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 468–471.

(3) A. N. Nesmeyanov and M. I. Rybinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 816 (1962); p 761 reports

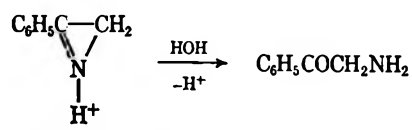


Acid degradation of two vinyl azides, α- (**1**) and β-styryl azide (**5**), has been investigated. In ethanolic sulfuric acid, **1** is nearly quantitatively (94%) transformed into a mixture of acetanilide, **3**, and aniline, presumably formed by hydrolysis of **3** during work-up (Scheme I).[4b] This appears to be a reaction according to path 1 and/or path 2 if in the latter event a "hot" nitrenium ion is produced and rearranged before it loses energy and becomes a resonance hybrid cation. An unrearranged hybrid cation, **4**, was not detected insofar as

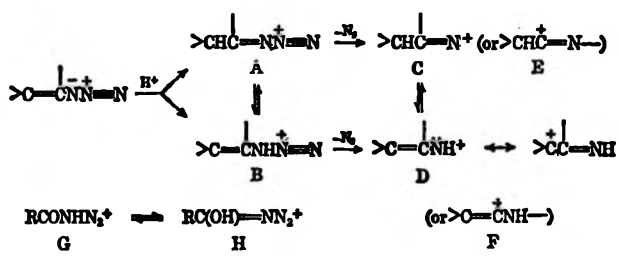
SCHEME I



products of rearrangement from carbon to carbon were not formed[5] and other carbonium ion reactions, *e.g.*, solvation, were not detected. Hydrolysis of the 2-phenylazirinium cation to phenacylamine,[6] without the formation of acetanilide, eliminated path 3 in the acid degradation of **1**.



(4) (a) From the assignment of a higher energy to RNH^+ (from $RNHN_2^+$) relative to RCH_2^+ (from $RCH_2N_2^+$) by R. F. Tietz and W. E. McEwen, *J. Amer. Chem. Soc.*, **77**, 4007 (1955), the hybrid cation, **4** would be expected to react as a carbonium ion excited state. (b) A referee suggested that product formation may require the intermediacy of protonation at carbon rather than at nitrogen. From the recognition that organic azides in general are protonated at nitrogen (P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N.Y., 1966, pp 225–226) we assumed that protonation at carbon in a vinyl azide would be relatively unimportant to account for the observed products. In failing to recognize the two pairs of tautomers, A ⇌ B and C ⇌ D (or the rearranged cations, E ⇌ F), the referee apparently overlooked this intimate relationship of intermediates available from the two conceivable initial steps. This reaction of a vinyl azide is reminiscent of the acid-catalyzed Curtius and the Schmidt reactions where tautomers G and H must each be recognized as a possible intermediate (P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, p 227; P. A. S. Smith in P. de Mayo, "Molecular Rearrangements," Vol. 1, John Wiley & Sons, Inc., New York, N. Y., 1963, p 529; J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 319–321).



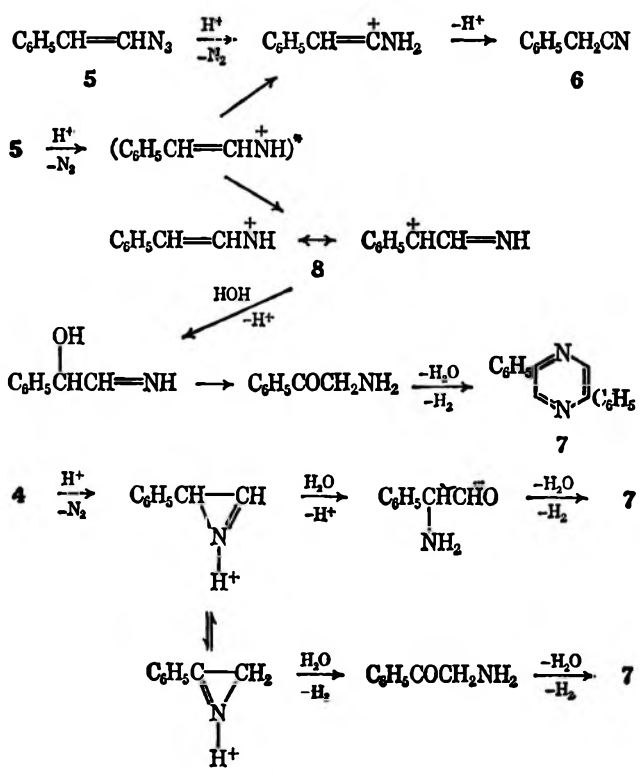
(5) This evidence also eliminates a migration from carbon to carbon concerted with nitrogen elimination.

(6) G. Smolinsky [*J. Org. Chem.*, **27**, 3557 (1962)] reports nmr (solvent unspecified) δ 5.32 (s) and 4.32 (s).

These results required a reevaluation of our earlier work on an acid-catalyzed reaction between acetophenone and an alkyl azide.[7] A resonance cation, for which a vinyl nitrenium and a carbonium ion were contributors and in equilibrium with an azirinium cation, was a proposed intermediate for the formation of benzaldehyde, formaldehyde and a primary amine. We have been unable to repeat the earlier work and it is to be considered inaccurate.

In ethanolic sulfuric acid, β-styryl azide, 5, is transformed into phenylacetonile, 6, 7% yield, a trace amount of 2,5-diphenylpyrazine, 7, and intractable tar (Scheme II). Nitrile 6 appears to be a product from either a rearrangement concerted with nitrogen evolution by path 1 or from a "hot" nitrenium ion, path 2, whereas pyrazine 7 apparently results from the self-condensation of either phenacylamine (the product of an Amadori rearrangement of mandelaldimine) or α-amino-α-phenylacetaldehyde. These in turn may be hydrolysis products of isomeric phenylazirines, path 3. Phenacylamine also may be formed on combination of carbonium ion 8, path 2, with water.

SCHEME II



The sample of β-styryl azide was known to contain about 20% α-chlorostyrene which is transformed by ethanolic sulfuric acid into acetophenone, also isolated.

Experimental Section[8]

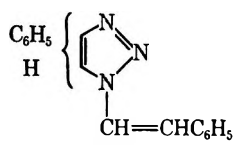
α-Styryl azide was prepared according to Smolinsky:[9] nmr (CCl_4) δ 7.3 (m, phenyl), 5.34 (d, J = 2.3 Hz) and 4.87 (d, J = 2.3 Hz).

1-Phenyl-2-azido-1-ethanol.—A solution of 100 g (0.5 mol) of phenacyl bromide in 375 ml of ethanol and 60 ml of glacial acetic acid was treated with 65 g (1.0 mol) of sodium azide.[9] Without further purification the product of this reaction was treated with 25 g (0.66 mol) of sodium borohydride.[10] Distillation gave a 52.4-g (63%) sample of 1-phenyl-2-azidoethanol: bp 111–114° (0.5 mm); $n^{25}D$ 1.5519; ir (film) 3400 (OH) and 2100 cm^{-1} (N_3); nmr (CCl_4) δ 7.17 (phenyl), 4.57 (q, CHOH), 3.93 (OH, D in DMSO-d_6) and 3.15 (m, CH_2N_3).

Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.71; H, 5.89; N, 25.77.

1-Chloro-1-phenyl-2-azidoethane.—A solution of 17.4 g (0.15 mol) of thionyl chloride in 100 ml of anhydrous ether was added to a solution of 16.5 g (0.1 mol) of 1-phenyl-2-azidoethanol in 100 ml of dry ether and 20 ml of pyridine at 0°. Stirring was continued at 0° for 8 hr and the solution was allowed to stand at room temperature overnight. The organic layer was washed with dilute hydrochloric acid, water and thoroughly with sodium bicarbonate solution to remove all acidic material. It was then dried over magnesium sulfate and evaporated under vacuum. Distillation of the residue gave a 10.1-g (55%) fraction of 1-chloro-1-phenyl-2-azidoethane: bp 78–79° (0.4 mm); $n^{25}D$ 1.5530; ir (film) 2100 cm^{-1} (N_3); nmr (CCl_4) δ 7.18 (m, 5, phenyl), 4.78 (t, 1, CH) and 3.42 (octet, 2, J = 6.8 Hz).

β-Azidostyrene.—A slurry of 8.0 g (70 mmol) of potassium t-butoxide in 200 ml of anhydrous ether was cooled to −25° and a solution of 9.0 g (50 mmol) of 1-chloro-1-phenyl-2-azidoethane was added dropwise. After 2 hr at −25° the solution was allowed to warm to 0° and stored in a refrigerator overnight. The ether solution was washed with water, dried over magnesium sulfate, and concentrated under vacuum to give an oil together with a solid. The solid was separated by filtration and recrystallized from benzene to give 0.2 g (3%) of a yellow solid, mp 186–187.5°, tentatively identified as 1-(β-styryl)-4- (or 5-) phenyl-1,2,3-triazole, recognized as a formal adduct between 5 and $C_6H_5C{\equiv}CH$.



Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.40; H, 5.53; N, 16.92.

The remaining oil was distilled with the pot temperature below 70°, and 1.2 g (17%) of α-chlorostyrene was collected; bp 28–32° (0.6 mm); $n^{25}D$ 1.5606;[11] nmr (CCl_4) δ 7.52, 7.15 (m, 5, phenyl) and 5.59, 5.39 (2d, 2, J = 1.6 Hz, CH_2N_3). The residue was dissolved in n-heptane and chromatographed over alumina to give 3.2 g (44%) of β-azidostyrene: ir (film or $CHCl_3$) 2100 (N_3) and 1645 cm^{-1} (C=C); nmr (CCl_4) δ 7.14 (m, 5, phenyl) and 6.32, 6.11 (2d, 2, J = 14 Hz, probably *trans*-vinyl protons). The azide could not be distilled and decomposed below 70°.[12] It was not submitted to elemental analysis.

α-Azidostyrene with Sulfuric Acid.—Pure α-azidostyrene, 2.9 g (0.02 mol), was added dropwise to a solution of 6 ml of sulfuric acid in 16 ml of absolute ethanol. Care was taken to keep the exothermic reaction under control. When the mixture began to cool a heating mantle was attached and the reaction was heated under reflux for 1 hr. After standing overnight the solution was poured into 75 ml of ice water. Extraction with ether followed by drying over potassium carbonate and evaporation under vacuum gave 0.8 g (29.6%) of a dark solid, mp 110–112° after recrystallization from benzene. This solid was shown by mixture melting point and infrared spectrum to be acetanilide.

The water layer was made basic with excess sodium carbonate and extracted with ether. The combined organic layers were dried over potassium carbonate and evaporated to give 1.2 g (64.6%) of aniline as shown by vpc retention time and infrared spectrum identical with similar data for an authentic sample.

Reaction of β-Azidostyrene with Sulfuric Acid.—A 1.4-g (0.01 mol) sample of β-azidostyrene was added slowly to a solution of 6 ml of sulfuric acid in 16 ml of ethanol. After addition was complete the mixture was heated at 60° for 1 hr and allowed to stand overnight at room temperature. The mixture was poured into 100 ml of ice water and extracted with ether. The combined organic layers were dried over potassium carbonate and evaporated to give 0.6 g of a dark oil. This oil was shown by gas

(7) J. H. Boyer and L. R. Morgan, *J. Amer. Chem. Soc.*, **80**, 2020(1958); **81**, 3369 (1959).

(8) Microanalyses by Microtech Laboratories, Chicago, Ill.

(9) J. H. Boyer and D. Straw, *J. Amer. Chem. Soc.*, **74**, 4506 (1952).

(10) J. H. Boyer and S. E. Ellzey, Jr., *J. Org. Chem.*, **23**, 172 (1958).

(11) K. V. Auwers [*Ber.*, **45**, 2799 (1912)] reports $n^{16.6}D$ 1.5623 and $n^{24.6}D$ 1.5590, bp 83.5–84° (23 mm).

(12) J. H. Boyer, W. E. Krueger, and G. J. Mikol, *J. Amer. Chem. Soc.*, **89**, 5504 (1967).

chromatographic analysis and nmr spectrum to be composed of α-chlorostyrene (*ca.* 16%), acetophenone (43%), and phenylacetonitrile (17%), corresponding to maximum yields of *ca.* 7, 19, and 7%, respectively. Each component was identified by its identical comparison with vpc retention time and nmr spectra for authentic samples.

The water layer was made basic with a large excess of sodium carbonate and extracted with ether to give 0.5 g of a dark oil after combining, drying over potassium carbonate, and evaporating the organic layers. Treatment of this oil with anhyrous hydrogen chloride gave a few milligrams of a yellow solid which was shown to be 2,5-diphenylpyrazine, mp 192–194°, by mixture melting point and infrared spectrum.

Reaction of α-Chlorostyrene with Sulfuric Acid.—A solution of 1.7 g (0.012 mol) of α-chlorostyrene in 6 ml of sulfuric acid and 16 ml of absolute ethanol was heated under reflux for 4 hr and allowed to stand overnight at room temperature before being poured into 200 ml of ice water. The mixture was extracted with ether and the combined extracts were dried over potassium carbonate and evaporated to give 1.1 g (73%) of acetophenone as a dark oil. This assignment was verified by infrared spectrum and vpc retention time.

Registry No.—1-Phenyl-2-azido-1-ethanol, 18756-01-9; 1-chloro-1-phenyl-2-azidoethane, 18756-02-0; 5, 18756-03-1; 1-(β-styryl)-4-phenyl-1,2,3-triazole, 18756-04-2; α-chlorostyrene, 1018-34-8.

Chemistry of Coelenterates. XII.[1a] Hydroxyancepsenolide, a Dilactone from the Octocoral, *Pterogorgia anceps*

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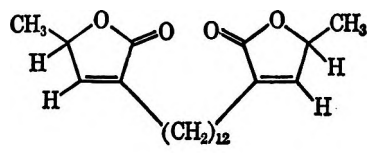
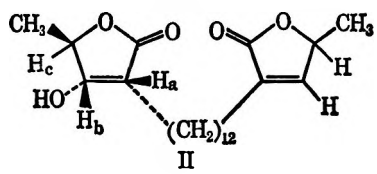
Received August 26, 1968

In an earlier paper,[2] we described the structure elucidation of ancepsenolide, I, a bisbutenolide isolated from the gorgonian, *Pterogorgia anceps* (Pallas).[3] Another dilactone has been isolated from this same organism and in this paper we wish to present evidence which confirms its structure as that shown in II. The new lactone, hydroxyancepsenolide, was isolated by hexane extraction of the dried animal and purified by column chromatography to give a white solid, mp 122.5–123.7°. Mass spectral analysis (*m/e* 380) and combustion data established the molecular formula as $C_{22}H_{36}O_5$. The significant features of the infrared spectrum were a very weak absorption at 3400 cm^{-1} (KBr, hydroxyl) and a strong, broad carbonyl absorption having a maximum at 1750 cm^{-1}. The strong carbonyl absorption at 1750 cm^{-1}, an absorption maximum in the ultraviolet spectrum at 209 mμ with approximately one-half the extinction coefficient (15,800) found for ancepsenolide (28,000), and one-proton multiplets in the nmr spectrum at δ 5.0 and 7.0 ppm identical with ones occurring in the spectrum of ancepsenolide[2] confirmed the presence in hydroxyancepsenolide of one substituted butenolide ring identical with those present in ancepsenolide. The presence of a long methylene chain in hydroxyancepsenolide is indicated by the large absorption peak at δ 1.27 ppm and a long series of peaks in the mass spectrum differing by 14 mass units.

The presence of a hydroxyl group in II was confirmed by the formation of a monoacetate and the secondary nature of this alcohol was inferred from a shift in the nmr spectrum of a one-proton signal (double doublet) centered at δ 4.24 in hydroxyancepsenolide to 5.18 ppm in the corresponding monoacetate.



I



II

Dehydration of II with phosphorus oxychloride in pyridine gave ancepsenolide in good yield. This fact, along with the evidence for the secondary character of the alcohol group, requires that the hydroxyl group of II must be attached to the β carbon of the second five-membered lactone ring. The broad carbonyl absorption in II (1730–1780 cm at one-half peak intensity) is consistent with the presence of both a saturated and an α,β-unsaturated γ-lactone. Hydrogenation of II resulted in the uptake of slightly more than 1 mol of hydrogen and gave a dihydro derivative whose infrared spectrum showed a strong absorption with a maximum at 1765 cm^{-1} (saturated γ-lactone). The nmr spectrum of dihydrohydroxyancepsenolide lacked any vinyl proton absorption and exhibited a complex absorption envelope extending from δ 4.1 to 4.9 ppm which is attributed to a combination of the absorptions due to the three protons attached to carbons bearing oxygen atoms.

The relative stereochemical assignments indicated in structure II for the substituents in the hydroxylated lactone ring are based on coupling-constant data. Proton c of the saturated γ-lactone ring in II appears as a broadened quartet in which the coupling to the methyl group is large, J = 6 cps, and the second splitting attributed to coupling with proton b is small, $J \cong 0.5$–1 cps. The signal assigned to proton b appears as a double doublet in which the small coupling constant, $J \sim 0.5$–1 cps, is consistent with a J_{bc} assignment and the larger J value, 6 cps, must be due to coupling with proton a of the lactone ring. A *trans* orientation of protons b and c imposes a dihedral angle of 105–115° between these protons, and this is consistent with the smaller coupling constant, $J_{bc} \sim 1$ cps.[4] A dihedral angle of close to 0° would be expected between protons a and b if they

(1) (a) Part XI: A. J. Weinheimer, P. H. Washecheck, D. v. d. Helm, and M. B. Hossain, *Chem. Commun.*, in press. (b) To whom inquiries concerning this paper should be addressed.

(2) F. J. Schmitz, K. W. Kraus, L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Tetrahedron Lett.*, 97 (1966).

(3) F. M. Bayer, "The Shallow-Water Octocorallia of the West Indian Region," Martinus Mijhoff, The Hague, Netherlands, 1961, pp 272–277.

(4) For a leading reference, see R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 35–37.

are *cis* to one another and this is consistent with the larger coupling constant assigned to J_{ab}.[4]

In the nmr spectrum of II obtained in deuteriochloroform the absorptions due to the methyl groups are partially masked by the large methylene peak. The lactone methyl absorptions in the acetate of II are shifted upfield to 1.05 ppm (superimposed doublets) when benzene is used as solvent and the integral and J values (6 cps) are easily discernible. In the nmr spectrum of the acetate of dihydrohydroxyancepsenolide obtained in benzene the methyl absorptions appear as doublets centered at δ 0.9 and 1.0 ppm with overlapping peaks at 0.95 ppm.

Experimental Section

Melting points were determined in capillary tubes with a Thomas–Hoover melting apparatus and are corrected. Ultraviolet spectra were measured in 95% ethanol on a Beckman DK-1 spectrophotometer and infrared spectra were taken with a Beckman IR-8 spectrophotometer. Nmr spectra were determined using tetramethylsilane as an internal standard with a Varian A-60 spectrometer.

Isolation of Hydroxyancepsenolide.—Collections of *Pterogorgia anceps* were made along the outside of Boca Chita Key, Miami, Fla., and in Bimini, Bahamas. The air-dried ground gorgonian material (1.9 kg) was extracted consecutively in a continuous percolator–extractor[5] with the following solvents: (1) hexane, 18 hr; (2) hexane, 96 hr; (3) hexane, 48 hr; (4) benzene, 48 hr; (5) benzene, 72 hr; (6) methanol, 28 hr; (7) methanol, 48 hr. The first hexane extract consisted of a complex lipid mixture from which ancepsenolide is isolated by chromatography over alumina[6] or silicic acid.[2] Some hydroxyancepsenolide precipitated from the second hexane extract which contained a total of 1.87 g of material. A 2.84-g sample of crude hydroxyancepsenolide was absorbed on silica gel (140 g, 35 × 653 mm) and eluted with 25% ethyl acetate in benzene (75-ml fractions). Fractions 5–18 contained 1.53 g of white solid which was recrystallized several times from isopropyl alcohol to give white platelets: mp 122.5–123.7°; $[\alpha]^{24}D$ +3.4°;[7] uv max (95% C_2H_5OH) 209 mμ (ϵ 15,800); ir ($CHCl_3$) 3600 very weak (OH), and 1750, broad (lactones); ir (KBr, concentrated) 3600 (OH), 1760, 1720 (lactone C=O's); nmr ($CDCl_3$) δ 7.0 (q, 1, vinyl hydrogen), 5.0 (complex quartet, 1, $CH_3CH(-O^-)CH=$), 4.30–4.73 (broadened q, 1, $-CH(-O^-)CHOH-$), 4.24, (dd, 1, $-CH(-O^-)CHOH-$), 1.1–3.0 ppm (31, $-(CH_2)_{12}-$, $2CH(-O^-)CH_3$, -OH).

Hydroxyancepsenolide Acetate.—Hydroxyancepsenolide (0.266 g, 0.77 mmol) was dissolved in a mixture of 10 ml of pyridine and 1 ml of acetic anhydride and the resulting solution was stirred overnight at room temperature. The reaction mixture was poured into ice water and the product was recovered by extraction into ether. The ether solution was washed with dilute hydrochloric acid, sodium bicarbonate, and water and dried ($MgSO_4$). Evaporation of the ether left 0.288 g of white solid of which 0.180 g was recrystallized four times from isopropyl alcohol, 53 mg, mp 68.3–70.3°.

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.24; H, 9.01. Found: C, 68.23; H, 9.03.

Dihydrohydroxyancepsenolide.—A solution of hydroxyancepsenolide (0.369 g, 0.972 mmol) in ethyl acetate (170 ml) was stirred under hydrogen at atmospheric pressure and room temperature in the presence of prereduced platinum oxide (0.178 g). A fine white precipitate was apparent in the reaction mixture by the time hydrogen uptake ceased after the absorption of slightly more than 1 mol equiv of gas. The catalyst was removed by filtration and washed with warm ethyl acetate to remove the precipitated product. Evaporation of the solvent left a white solid. The mixture of diastereomers expected in this reaction could not be resolved by fractional crystallization, nor could any separation of isomers be detected by tlc under the conditions employed. A sample recrystallized five times from ethyl acetate (29 mg from 148 mg) exhibited a melting point range of 119.3–133.0°. The material recovered from the mother liquors of the first recrystallization attempt had a melting point range of 118.8–125.5° after three recrystallizations from ethyl acetate: ir ($CHCl_3$) 3500, (OH) and 1765 cm^{-1} (saturated γ-lactones); ir (KBr) 3450 (OH), 1760, 1730 (C=O); nmr ($CDCl_3$, sparingly soluble) δ 4.10–4.80 (overlapping multiplets, 3, —CHOHCH(—O⁻), —CHOHCH(—O⁻), —CH_2CH(—O⁻)).

Anal. Calcd for $C_{22}H_{38}O_6$: C, 69.11; H, 9.95. Found: C, 68.90; H, 9.98.

Dihydrohydroxyancepsenolide Acetate.—Acetylation of dihydrohydroxyancepsenolide (0.104 g, 0.271 mmol), mp 117–133°, with pyridine–acetic anhydride as described above for II afforded a solid acetate (0.121 g) which was recrystallized once from isopropyl alcohol and then twice from carbon tetrachloride–hexane to give 57 mg of material: mp 71.2–72.5°; ir ($CHCl_3$) 1765 (saturated lactones) and 1740 cm^{-1} (acetate); nmr ($CDCl_3$) 5.12 (dd, 1, —CHOAcCH(—O⁻)—), 4.15–4.95 (overlapping complex quartets, 2, —CHOAcCH(—O⁻)— and —CH_2CH(—O⁻)—), 2.1 (s, 3, —OC(—O⁻)CH_3).

Dehydration of Hydroxyancepsenolide.—Hydroxyancepsenolide (0.253 g, 0.665 mmol) was stirred overnight with a mixture of 0.2 ml of phosphorus oxychloride and 11 ml of pyridine. The reaction mixture was diluted with four volumes of water and the product recovered by extraction into ether. The ether solution was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). Evaporation of the solvent left a white solid (0.143 g, 60%) which tlc and nmr analysis indicated to be ancepsenolide. The crude product was filtered through silica gel and crystallized once from chloroform to give 0.103 g of ancepsenolide: mp 92.8–94.3°; no depression on admixture with authentic ancepsenolide; $[\alpha]^{24}D$ +7.7°. The infrared and mmr spectra of the dehydration product were identical with those of authentic ancepsenolide.[2]

Registry No.—II, 18634-45-2; acetate of II, 18634-46-3; dihydro derivative of II, 18634-47-4; acetate of dihydro derivative of II, 18634-48-5.

Acknowledgments.—We are pleased to acknowledge the use of the collecting facilities of the Institute of Marine Science, University of Miami, Miami, Fla., and the Lerner Marine Laboratory of the American Museum of Natural History, Bimini, Bahamas, W. I. We wish to thank Mr. Paul Fenessey, Massachusetts Institute of Technology, and Dr. Ronald Grigsby, Continental Oil Co., Ponca City, Okla., for providing mass spectra. This work was supported by NIH Training Grant 5675 from the National Heart Institute.

(5) L. S. Ciereszko, *J. Chem. Educ.*, **43**, 252 (1966).

(6) L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Ann. N. Y. Acad. Sci.*, **90**, 917 (1960).

(7) The sample used to determine the physical properties was isolated from the extracts of a batch of *Pterogorgia anceps* colonies. We have previously noted[2b] variation in the optical rotation of samples of ancepsenolide isolated from different batches of dried animal. We have since observed that a sample of ancepsenolide isolated from a single animal colony of *Pterogorgia anceps* exhibited a rotation of +12.03° (+13.2° originally reported[2b]), while a sample of ancepsenolide isolated from a single colony of another species of this same genus, *Pterogorgia guadalupensis*, exhibited a rotation of +47.9°. All of the above samples appeared to be homogeneous as judged by tlc and nmr, and were found to be identical by virtue of mixture melting points as well as ir, uv and nmr spectral comparisons. Thus the correct value for the optical rotation of ancepsenolide and hydroxyancepsenolide remains uncertain. More individual colonies will be examined in the hope of clarifying this question.

Synthesis and Characterization of Cholesterol β-D-Glucuronide and Derivatives[1]

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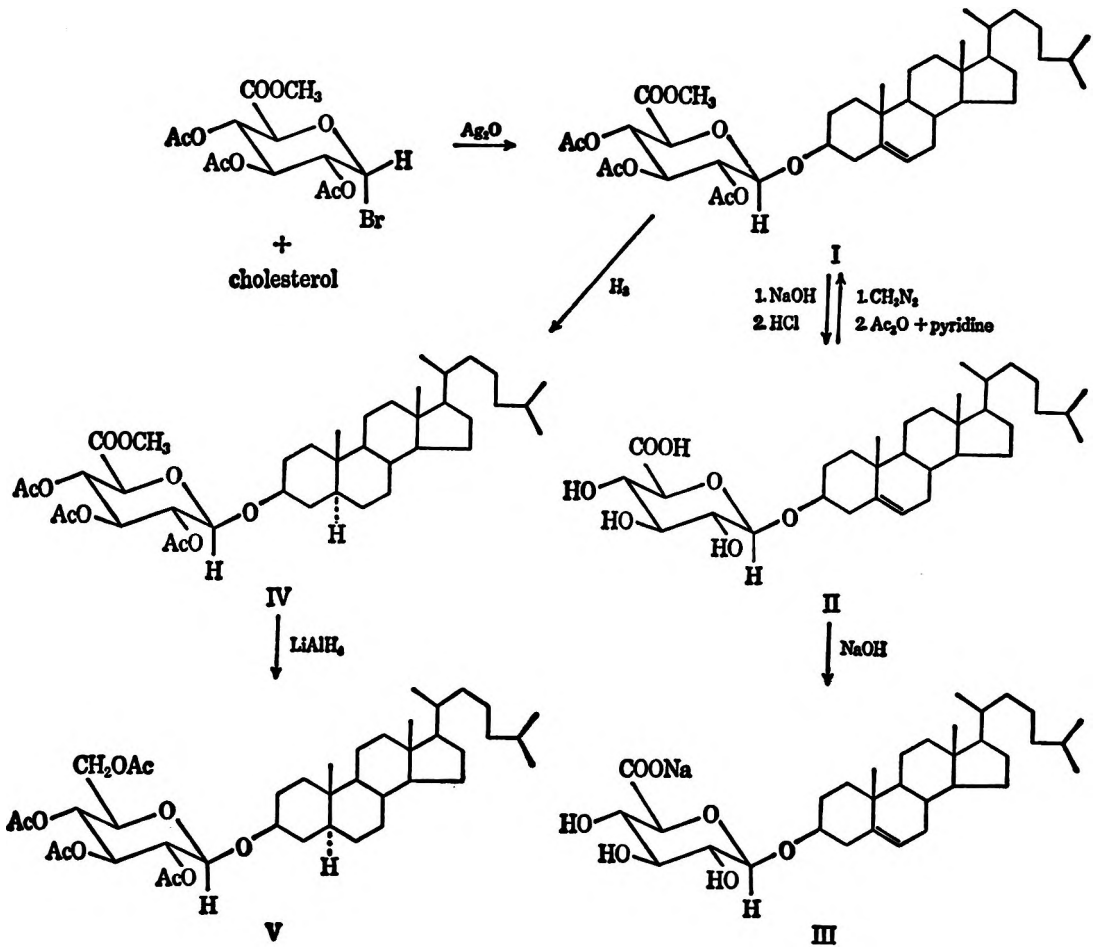
The recent isolation of cholesterol sulfate from human blood plasma[2] and from the urine of normal men[3] has

(1) This work was supported by a research grant, AM 01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) N. M. Drayer and S. Lieberman, *Biochem. Biophys. Res. Commun.*, **18**, 126 (1965).

(3) J. S. D. Winter and A. M. Bongiovanni, *J. Clin. Endocrinol. Metab.*, **28**, 927 (1968).

SCHEME I



led us to consider the possibility that this sterol also is conjugated with glucuronic acid in man. As a preliminary to biochemical studies, it was essential to prepare cholesterol β-D-glucuronide[4] in pure form. This report presents an efficient synthesis of this conjugate *via* its triacetyl methyl ester. Earlier preparative attempts (see Experimental Section) gave in all cases an inadequately characterized product in low yield.

The reactions involved in the synthesis and characterization of cholesterol β-D-glucuronide are outlined in Scheme I. Condensation of methyl 1-bromo-2,3,4-tri-*O*-acetyl-1-deoxy-α-D-glucuronate with cholesterol (the familiar Koenigs–Knorr reaction[5]) was carried out under mild conditions. A benzene solution of the brom methyl ester and cholesterol, in a 3:1 molar ratio, was shaken with silver oxide for 24 hr at room temperature. Following column chromatography on silica gel, methyl [cholest-5-en-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (I) was recovered in a yield of 86% based on the amount of cholesterol used. It was characterized by its elemental analysis and the usual physical constants and, particularly, in terms of its nuclear magnetic resonance and mass spectra.

The chief difficulty in effecting hydrolysis of the triacetyl methyl ester (I) to the trihydroxy acid (II) centered on the very low solubility of the former in alcoholic systems. This difficulty was circumvented by first removing the acetoxyl groups by methanolysis in an anhydrous alkaline methanol–methylene dichloride system, followed by hydrolysis of the carbomethoxyl group in an aqueous alkaline methanol–tetrahydrofuran system. It was found convenient to recover the product as the free acid (II) which, although amorphous rather than crystalline, was easily filtered, washed with water, and dried. Following conversion of acid II into its sodium salt (III), the latter was crystallized from aqueous ethanol. The yield of the twice-crystallized salt was 83% of theory, based on the amount of I employed.

It was not possible to crystallize samples of acid II regenerated from the twice-crystallized sodium salt (III), nor did the triacetoxy acid prepared from II show any inclination to assume crystalline form. The trihydroxy methyl ester, prepared by treating acid II with diazomethane, also proved an unsuitable derivative since it could be crystallized only with difficulty and in low yield, but either acetylation of the crude trihydroxy methyl ester or treatment of the purified acid (II) successively with diazomethane and acetic anhydride–pyridine gave a crystalline product indistinguishable from the triacetyl methyl ester (I) thus serving to interrelate I, II, and III.

Conversion of the primary product (I) into a known compound without rupture of the glycosidic link was achieved by catalytic reduction of I to methyl [5α-chloestan-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (IV) which, on further reduction with

(4) Systematic designations for compounds named trivially in the text are cholesterol, cholest-5-en-3β-ol; cholestanol, 5α-cholestan-3β-ol; cholesterol β-D-glucuronide, cholest-5-en-3β-yl-β-D-glucopyranosiduronic acid; triacetoxy acid, cholest-5-en-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosiduronic acid; trihydroxy methyl ester, methyl [cholest-5-en-3β-yl-β-D-glucopyranosid]uronate. Where required, numbers referring to the carbohydrate moiety are distinguished by priming.

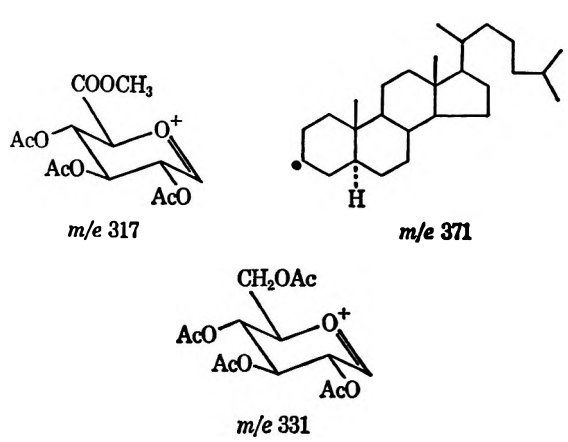
(5) W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).

lithium aluminum hydride followed by reacetylation, furnished 5α-chloestan-3β-yl-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside (V), originally prepared by Linstead.[6]

Nuclear Magnetic Resonance Spectrum of I.—The configuration at the anomeric carbon atom was confirmed by examining a deuteriochloroform solution of the triacetyl methyl ester (I) at 100 and 220 MHz. The sugar moiety attached to C-3 could have only one of two configurations, namely α-D-*C1* or β-D-*C1*, since β-L-*1C* (indistinguishable from β-D-*C1*) is excluded by the nature of the reagent, and α-D-*1C* would be too unstable to exist under normal conditions. If the glucuronide exists in the α-D-*C1* form, the anomeric hydrogen would be equatorially oriented and the rest of the ring protons would be axially situated. Under these conditions the signal due to H-1′ would present a rather narrow pattern since the spin coupling between an equatorial H-1′ and an axial H-2′ would be in the range 2–5 Hz. However, in a β-D sugar, where all the ring hydrogens are in the axial configuration, the H-1′ resonance doublet would be wider because of the greater coupling between two axially oriented protons. Examination of the data obtained at both 100 and 220 MHz shows the presence of doublets at δ 4.64 and 4.00 having coupling constants of 8 and 10 Hz, respectively. These are assigned to the axially oriented protons at C-1′ and C-5′, respectively, on the basis of their chemical shifts. (The deshielding effect of the two oxygen atoms exceeds that due to one oxygen atom and the carbomethoxyl function.)

Mass Spectroscopy Studies.—Analysis of the fragmentation patterns of derivatives I, IV, and V may be summarized as follows. The triacetyl methyl ester (I) furnished a very low intensity molecular (M^+) ion, *m/e* 702. The fragment pair *m/e* 670 and *m/e* 32 (methanol, *via* fission and H transfer) indicates the presence of the methyl ester grouping. The sterol part of the molecule yielded free cholesterol (*m/e* 386),[7] cholesta-3,5-diene (*m/e* 368), and the expected fragments derived from them. The sugar moiety was detected intact as the *m/e* 317 pyronium ion (Scheme II), and also was represented by the ion pair *m/e* 257 and *m/e* 60 (acetic acid or methyl formate). The saturated triacetyl methyl ester (IV) gave an easily detected molecular ion, *m/e* 704. Its fragmentation pattern otherwise differed from that of I only to the extent that the sterol moiety was represented chiefly by the *m/e* 371 neutral fragment. The saturated tetraacetyl glucoside (V) furnished the most intense molecular ion, *m/e* 718. The presence of the acetylated primary hydroxyl group at C-6′ was indicated by the ion pair *m/e* 645 and *m/e* 73 ($CH_3COOCH_2^+$). The cholestanol part of the molecule again yielded the prominent *m/e* 371 neutral fragment. The sugar moiety was represented intact as the *m/e* 331 pyronium ion which is analogous to the *m/e* 317 ion derived from I and IV. Further fragmentation of the *m/e* 331 ion furnished the ion pair *m/e* 257 and *m/e* 74 (methyl acetate, *via* fission and H transfer).

SCHEME II



m/e 317 *m/e* 371 *m/e* 331

(6) R. P. Linstead, *J. Amer. Chem. Soc.*, **62**, 1766 (1940).

(7) The cholesterol ion is regarded a normal fragment ion and not due to contamination of the sample with the free sterol. The cholesterol peak remained constant relative to the higher mass peaks over the entire temperature range. If it was present as an impurity, one would expect to see its spectrum in the absence of higher mass peaks since cholesterol is probably more volatile than the sample itself.

Experimental Section[8]

Synthesis of Methyl [Cholest-5-en-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (I).—To a solution of 4.77 g (12 mmol) of methyl 1-bromo-2 3,4-tri-*O*-acetyl-1-deoxy-α-D-glucuronate and 1.54 g (4 mmol) of cholesterol (purified *via* the dibromide[9]) in 70 ml of benzene (stored over and distilled from phosphorus pentoxide), 1.85 g (8 mmol) of freshly prepared and dried silver oxide was added. The suspension was shaken with a vigorous rotary motion at room temperature in the dark for 24 hr. After the addition of Celite, the suspension was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on a 46 × 960 mm column of silica gel (Davison, grade 923) prepared and developed with a system consisting of ethyl acetate, 200 ml, diluted to 1000 ml with isooctane. Fractions (10 ml) of effluent were collected at a rate of six per hour. Following the emergence of the unreacted cholesterol and traces of the anomer of I, the contents of tubes 451–667 were pooled and evaporated to dryness as above. Two crystallizations from ethyl acetate–methanol gave 2.42 g (86%) of I with the following constants: mp 165–165.5°; $[\alpha]_D$ −33°; ν_{max} 1755 (acetate), 1470, 1438, 1375, 1250–1210 cm^{-1} (acetate) [lit. mp 162–164.5° (7% yield),[10] 188–190° (44% yield),[11] 176–178° (yield unstated)[12]].

Anal. Calcd for $C_{40}H_{62}O_{10}$: C, 68.35; H, 8.89; CH_3CO, 18.37; OCH_3, 4.41. Found: C, 68.22; H, 8.86; CH_3CO, 18.76; OCH_3, 4.80.

Saponification of I to Sodium Cholest-5-en-3β-yl-β-D-glucopyranosiduronate (III).—To a solution of 421 mg (0.6 mmol) of methyl [cholest-5-en-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (I) in 6 ml each of anhydrous methanol and methylene dichloride, 1.2 ml of 0.1 *N* sodium hydroxide in anhydrous methanol (0.12 mmol) was added. After 3 hr at room temperature, 40 ml of tetrahydrofuran was added and stirring was initiated. Aqueous sodium hydroxide (1 *N*, 12 ml) was added in one portion followed by 35 ml of methanol and, gradually, a total of 75 ml of water. Some material separated at this point but returned to solution within 1 hr. After stirring for a total of 4 hr at room temperature, the pH of the solution was adjusted to around 3 by the addition of dilute hydrochloric acid, *t*-butyl alcohol was added to suppress foaming, and the

(8) Melting points were determined with a Fisher-Johns apparatus and are reported uncorrected. Optical rotations were obtained in chloroform solution, at a concentration of around 1%, and at a temperature of 25 ± 2° in a Zeiss 0.005° photoelectric polarimeter. Infrared spectra were determined in KBr dispersion with a Beckman IR-8 instrument. The nuclear magnetic resonance spectra were obtained with Varian HA-100 or HR-220 instruments, using tetramethylsilane as internal standards of reference. Mass spectra were determined by Dr. Robert Schaffer of the Morgan-Schaffer Corp., Montreal, Canada, using a Hitachi–Perkin-Elmer RMU-6D instrument with direct introduction of sample. Elemental analyses were those of Aug. Peisker–Ritter, Brugg, Switzerland. All samples were dried to constant weight at 80–100° under high vacuum over phosphorus pentoxide prior to analysis. The sodium salts were combusted in the presence of vanadium pentoxide.

(9) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 5421 (1953).

(10) E. Shapiro, *Biochem. J.*, **33**, 385 (1939).

(11) H. Pelzer, *Z. Physiol. Chem.*, **314**, 234 (1959).

(12) F. Nagayama, A. Saito, and D. R. Idler, *Can. J. Biochem.*, **44**, 1109 (1966).

solution was concentrated under reduced pressure to a volume of around 20 ml. The suspended acid was recovered by filtration, washed with water, and dried *in vacuo* over anhydrous calcium chloride to give a white powder weighing 344 mg.

The crude acid was suspended in warm aqueous ethanol, and sufficient aqueous sodium hydroxide was added to provide a pH of around 7 at a point where all the acid had dissolved. Additional ethanol was added, and the solution was filtered and concentrated by warming to a volume slightly greater than that which would induce spontaneous crystallization. The sodium salt (III) was recovered as two crops of needles. These were washed with ethanol, and recrystallized from aqueous ethanol to yield a total of 298 mg (83%) of colorless needles: mp 286–287° dec; ν_{max} 3650–3100 (hydroxyl), 1610 cm^{-1} (carboxylate).

Anal. Calcd for $C_{33}H_{53}O_7Na$: C, 67.78; H, 9.14. Found: C, 67.62; H, 9.11.

A 20-mg sample of sodium cholest-5-en-3β-yl-β-D-glucopyranosiduronate (III) in 250 ml of dilute acetate buffer (pH 5, containing 10% ethanol) was incubated for 72 hr at 38° with 100,000 units of β-glucuronidase derived from beef liver. Extraction with chloroform, followed by two crystallizations of the recovered free sterol from ether–methanol, gave 3.2 mg of plates, mp 149–150°. The melting point was unchanged on admixture with an authentic preparation of cholesterol, and the ir spectra of the recovered and reference sterols were identical.

Preparation of Cholest-5-en-3β-yl-β-D-glucopyranosiduronic Acid (II).—Solution of a sample of the twice-crystallized sodium salt (III) in aqueous ethanol, followed by acidification and concentration under reduced pressure, provided a suspension of acid II. The product was recovered by filtration, washed with water, and dried *in vacuo* over anhydrous calcium chloride: mp 232–233° dec; ν_{max} 3600–3100 (hydroxyl), 1735 cm^{-1} (carboxyl).

Anal. Calcd for $C_{33}H_{54}O_7$: C, 70.43; H, 9.67; COOH, 7.99. Found: C, 70.19; H, 9.63; COOH, 7.84.

A sample of purified acid II in tetrahydrofuran was treated with excess ethereal diazomethane. Acetylation of the dried residue or of the crystallized methyl ester (needles, from aqueous tetrahydrofuran) gave, from ethyl acetate–methanol, needles melting at 164–165°. The melting point was unchanged on admixture with an authentic sample of methyl [cholest-5-en-3β-yl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (I), and their ir spectra were identical.

Methyl [5α-Cholestan-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (IV) from I.—A solution of 500 mg of methyl [cholest-5-en-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (I) in 25 ml of ethyl acetate was shaken for 3 hr in a hydrogen atmosphere in the presence of a 5% palladium-on-carbon catalyst (Engelhard Industries). After removal of the catalyst by filtration and the solvent by evaporation in a stream of nitrogen, the residue was crystallized from ethyl acetate–methanol to furnish 427 mg of needles: mp 180–181°; [α]D −5°; ν_{max} 1755 (acetate), 1470, 1440, 1370, 1250–1210 cm^{-1} (acetate).

Anal. Calcd for $C_{40}H_{64}O_{10}$: C, 68.15; H, 9.15; CH_3CO, 18.32; OCH_3, 4.40. Found: C, 68.18; H, 9.14; CH_3CO, 18.07; OCH_3, 4.42.

Saponification of 212 mg (0.3 mmol) of methyl [5α-cholestan-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (IV), as in the preparation of III from I, gave 148 mg of **sodium 5α-cholestan-3β-yl-β-D-glucopyranosiduronate** as needles from aqueous ethanol: mp 286–287° dec; ν_{max} 3650–3100 (hydroxyl), 1610 cm^{-1} (carboxylate).

Anal. Calcd for $C_{33}H_{55}O_7Na$: C, 67.55; H, 9.45. Found: C, 67.40; H, 9.51.

Incubation of a 20-mg sample of sodium 5α-cholestan-3β-yl-β-D-glucopyranosiduronate with β-glucuronidase, as in the previous example, gave 5.0 mg of leaflets from methanol, mp 141–142°. The melting point was unchanged on admixture with an authentic preparation of cholestanol, and the ir spectra of the isolated and reference sterols were identical.[13]

(13) The object of these hydrolyses was to obtain samples of the free sterols for formal identification, but it was apparent from the low recovery of the sterols that both sterol glucuronides are resistant to hydrolysis by β-glucuronidase of hepatic origin. It was reported earlier [K. D. Voigt, M. Lemmer, and J. Tamm, *Biochem. Z.*, **332**, 550 (1960)] that a preparation of cholesterol β-D-glucuronide (supplied by Professor Rudolph Tscheche but not described in the literature) was not hydrolyzed by the same enzyme preparation. The low rate of hydrolysis of cholesterol β-D-glucuronide by β-glucuronidase of limpet origin is evident from the data of Nagayama, *et al.*,[12] who did not, however, comment on the point.

5α-Cholestan-3β-yl-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside (V) from IV.—To a solution of 200 mg of methyl [5α-cholestan-3β-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (IV) in 25 ml of dry ether, 300 mg of lithium aluminum hydride was added. After refluxing for 3 hr, excess reagent was decomposed by the successive addition of ethyl acetate and water. The solution was further diluted with ethyl acetate, washed with acidic and neutral brine, dried with anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. Following reacetylation, the product was crystallized from ethanol, furnishing 95 mg of needles: mp 174.5–175.5°; [α]D +3°; ν_{max} 1750 (acetate), 1468, 1440, 1365, 1250–1210 cm^{-1} (acetate) [lit. for 5α-cholestan-3β-yl-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside (V) mp 175°; [α]D +5° ($CHCl_3$)[6]].

Anal. Calcd for $C_{41}H_{66}O_{10}$: C, 68.49; H, 9.25; CH_3CO, 23.95. Found: C, 68.40; H, 9.23; CH_3CO, 23.07.

Registry No.—II, 17435-78-8; III, 19459-08-6; IV, 19459-09-7; V, 19459-10-0; sodium 5α-cholestan-3β-yl-β-D-glucopyranosiduronate, 19459-11-1.

Acknowledgments.—The two-stage methanolysis–saponification of the triacetyl methyl ester (I) to the sodium salt (III) is based on a technique devised earlier by Dr. Vernon Mattox for similar derivatives. We wish to thank him for offering the method to us prior to its publication. We express also our gratitude to our associate, Dr. Marvin Lewbart, who pointed out the feasibility of reducing the saturated triacetyl methyl ester (IV) to the tetraacetyl glucoside (V) with lithium aluminum hydride. The nuclear magnetic resonance spectra were obtained with instruments in the laboratories of Varian Associates whom we wish to thank for this courtesy.

A New Dimer of Pyridoxol (Vitamin B_6)

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A number of syntheses of pyridoxol (**5**) by Diels–Alder condensations of a variety of dienophiles with 5-ethoxy-4-methyloxazole (**1**) have been described.[1] While examining the conversion of adduct **3** of this oxazole and *cis*-1,4-diacetoxybutene-2 (**2**) to pyridoxol in moist acetic acid solvent (Scheme I), we have observed that a high yield of product is obtained from dilute solutions of adduct, but that the yield falls off rapidly as the initial concentration of adduct is increased. However, the apparent yield when measured by the intensity of the pyridoxol chromophore in the total reaction mixture appears essentially independent of concentration (Table I). The bulk of this difference can be accounted for by the presence of a new dimer **6**, N-(5-desoxypyridoxolyl)pyridoxol, isolated from the reaction mixture by ion-exchange chromatography.

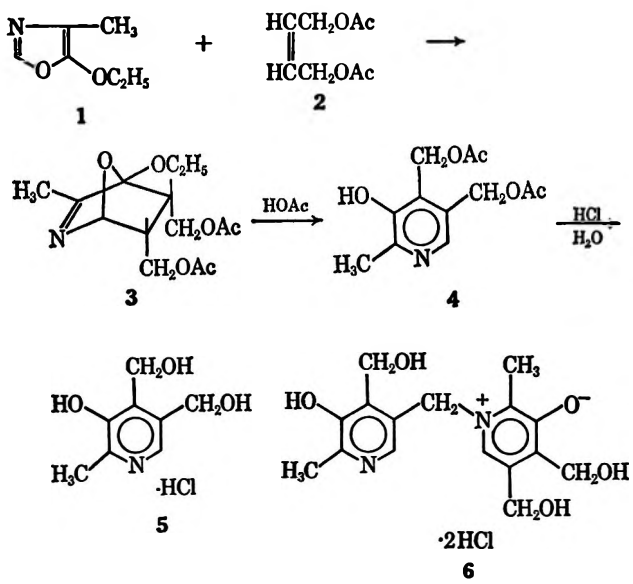
(1) E. E. Harris, R. A. Firestone, K. Pfister, 3rd, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.*, **27**, 2705 (1962); W. Kimel and W. Leimgruber, U. S. Patent 3,250,778 (1966); T. Naito and T. Yoshikawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 918 (1966); R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967).

TABLE I
YIELDS OF PYRIDOXOL

[S], M^a	Apparent yield,[b] %	True yield,[c] %
0.019	100	89
0.093	91	75
0.465	93	53
0.930	92	30

[a] Initial concentration in acetic acid. [b] Per cent of theory by uv absorbance of the crude reaction mixture at 292 nm in 0.1 *N* HCl. [c] By quantitative paper chromatography.

SCHEME I



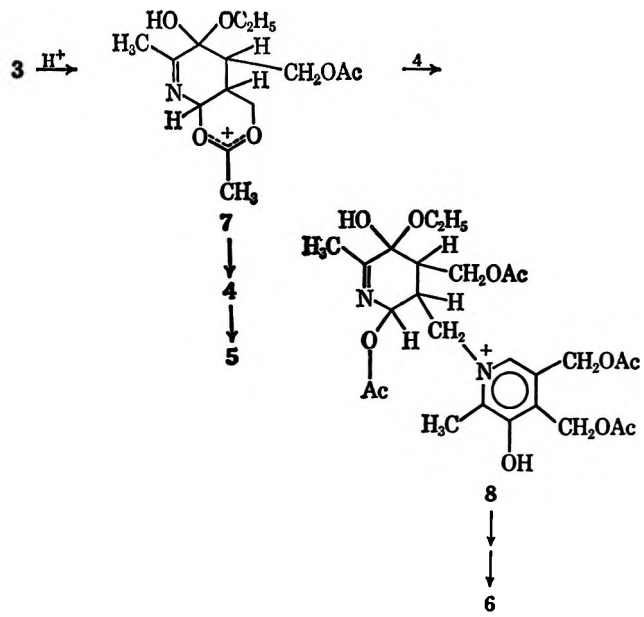
The structure of the dimer **6** was established by elemental analysis of its dihydrochloride, mp 194–197°, which corresponds to the empirical formula $C_{16}H_{20}N_2O_5 \cdot 2HCl$, by its equivalent weight, by a positive Gibbs test indicative of an unsubstituted position *para* to a phenolic hydroxyl,[2] and by its nmr and ultraviolet spectra.

The 60-Mc nmr spectrum of the dimer in D_2O–DCl (Table II) resembles the sum of two nearly equivalent pyridoxol-like molecules,[3] except for the deshielding by 70 cps of one pair of C-5 methylene protons by the quaternary nitrogen and a 40-cps upfield shift of one aromatic proton. In 1 *N* NaOD in D_2O the spectrum exhibits in one of the two methyl groups the exchange of protons typical of quaternized pyridoxine derivatives,[4] while that of the methiodide of **6** shows this exchange in both of the C-2 methyl groups under these conditions.

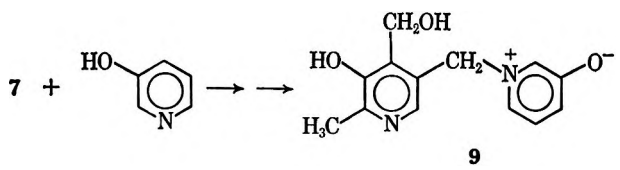
The ultraviolet absorption spectrum of **6** (Table III) at pH 7 shows in phosphate buffer the twin maxima in the 255- and 325-nm region characteristic of pyridoxine derivatives and exhibits in borate buffer the single peak near 295 nm expected only[5] for those derivatives which contain both the free 3-hydroxyl and the free 4-hydroxymethylene functions which permit formation of a cyclic borate ester. These positions are free in both segments of the dimer and no absorbance maxima are observed near 255 and 325 nm.

Pyridoxol diacetate (**4**) alone does not dimerize in the reaction medium. A rational pathway to the dimer must involve the adduct and might well proceed by way of the carboxonium ion **7** which, in addition to the expected aromatization to **4**, would be susceptible to nucleophilic attack at the incipient C-5 methylene carbon[6] by previously formed **4** to yield **8** and ultimately **6** by aromatization through loss of the elements of acetic acid and ethanol and subsequent hydrolysis (Scheme II). High initial concentrations of **3** afford greater concentrations of **4** during the later stages of the reaction, which would increasingly favor dimer formation, as is observed. Clearly nucleophiles other than **4** should attack **7** in this same manner, and indeed

SCHEME II



when the adduct was treated with acetic acid in the presence of added 3-hydroxypyridine a high yield of the analogous mixed product **9** was obtained. The



structural assignment is supported by its elemental analysis, nmr spectrum (Table II), and ultraviolet spectrum (Table III), which shows in borate buffer the presence of both the complexed 292-nm peak and the pair at 248 and 322 nm derived from the 3-hydroxypyridine moiety.

A different dimer of pyridoxol has been isolated from autoclaved solutions of pyridoxol free base by Harris.[7] Because it formed only a monomethiodide, he assigned to it the structure **10**, differing from **6** only by the presence of a C-4 rather than a C-5 methylene linkage to the quaternary nitrogen; more recently Hüttenrauch

(2) H. D. Gibbs, *J. Biol. Chem.* **72**, 649 (1927); E. T. Stiller, J. C. Keresztesy, and J. R. Stevens, *J. Amer. Chem. Soc.*, **61**, 1237 (1939).
(3) W. Korytnyk and B. Paul, *J. Heterocycl. Chem.*, **2**, 481 (1965).
(4) W. Korytnyk and R. P. Singh, *J. Amer. Chem. Soc.*, **85**, 2813 (1963).
(5) J. V. Scudi, W. A. Bastedo, and T. J. Webb, *J. Biol. Chem.*, **136**, 399 (1940).
(6) L. J. Dolby, C. N. Lieske, D. R. Rosencrantz, and M. J. Schwarz, *J. Amer. Chem. Soc.*, **85**, 47 (1963); L. J. Dolby and M. J. Schwarz, *J. Org. Chem.*, **30**, 3581 (1965); O. K. J. Kovács, Gy. Schneider, L. K. Láng, and J. Apjok, *Tetrahedron*, **23**, 4181 (1967); R. J. Oullette and R. D. Robins, *Tetrahedron Lett.* 397 (1968).
(7) S. A. Harris, *J. Amer. Chem. Soc.*, **63**, 3363 (1941).

TABLE II

60-MC NMR SPECTRA[a]

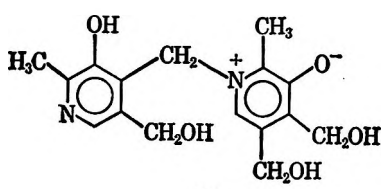
Compd	Solvent	2-Methyl	4-Methylene	5-Methylene	6-H	DOH	Other
Pyridoxol·HCl	D_2O–DCl	163 (3)	307[b] (2)	294[b] (2)	497 (1)	346	
Dimer 6·2HCl	D_2O–DCl	160 (3)	307 (2)	291 (2)	457 (1)	348	
		164 (3)	309 (2)	364 (2)	502 (1)		
Dimer 6	D_2O–1 *N* NaOD	140 (3)		292 (2, estd)	457 (1)	284	
		150[c] (3)	*d*	336 (2)	412 (1)		
Dimer 6 methiodide	D_2O	162 (3)	304 (2)	292 (2)	462 (1)	280	
		164 (3)	308 (2)	364 (2)	500 (1)		252[e] (3)
Dimer 6 methiodide	D_2O–1 *N* NaOD	148[c]		292	406	284	238[e]
		152[c]	*d*	348	464		
Compound 9	D_2O–DCl	167 (3)	302 (2)	369 (2)	497 (1)		Multiplet at 513(2) Multiplet at 482 (2)
Dimer 11	D_2O–DCl	161 (6)	302 (2)	284 (2)	504 (1)		
			310 (2)	292 (2)			
Dimer 11	D_2O–1 *N* NaOD	134[f] (3)		241 (2)	457 (1)	292	
		139[f] (3)	*d*	279 (2)			

[a] Data are cps downfield from DSS internal standard. Figures in parentheses are number of protons by integration. [b] Assigned by Korytnyk and Paul. [c] Exchanged rapidly. [d] Masked by DOH. [e] Quaternary methyl. [f] Did not exchange.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA IN AQUEOUS SYSTEMS

Compd	Solvent	λ_{max}, nm	$E^{1\%}_{1cm}$
Pyridoxol·HCl	0.1 *N* HCl	292	425
	pH 7 phosphate buffer	324, 254	345, 182
	pH 7 borate buffer	292	300
Dimer 6·2HCl	0.1 *N* HCl	296	466
	pH 7 phosphate buffer	332, 258	286, 209
	pH 7 borate buffer	296	293
4-Methyl ether of pyridoxol·HCl	pH 7 borate buffer	327, 253	344, 177
Compound 9 free base	pH 7 borate buffer	248, 292, 322	328, 190, 284



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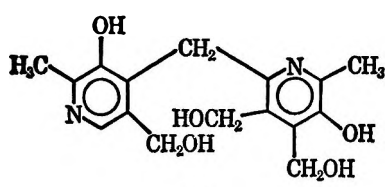

11

and Zahn[8] have interpreted its relatively facile oxidation by triphenyltetrazolium chloride as support for this N-alkylpyridinium-4-carbinol structure. However, the nmr spectra (Table II) indicate the presence of only one aromatic proton and the absence of a quaternary linkage, since the methyl protons did not exchange in base. In consequence, this dimer is better formulated as Harris' alternative, but less favored, structure **11**.

Experimental Section[9]

Diels–Alder Adduct 3.—A mixture of 127 g (1.0 mol) of 5-ethoxy-4-methyloxazole,[1] 516 g (3.0 mol) of *cis*-1,4-diacetoxybutene-2,[10] and 15 g of powdered calcium oxide was stirred under nitrogen for 30 hr at 115°. The reaction mixture, which contained 30% of unreacted oxazole by glpc (20% DC-200 on Chromasorb W), was filtered and stripped free of oxazole and diacetoxybutene at 0.5-mm pressure, and the residual crude adduct, obtained in almost quantitative yield based on oxazole consumed, was doubly distilled at 0.1 mm and 100° in a falling-film molecular still: no ultraviolet absorbance; nmr ($CDCl_3$) downfield from TMS, 78 (t, CH_3CH_2), 124 cps (s, $2CH_3CO$), 129 cps (s, $CH_3C{=}N$), envelope 148–288 cps (8 protons), 339 cps (d, bridgehead H).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 55.69; H, 6.67; N, 4.91.

Pyridoxol Hydrochloride (5).—Ten grams (0.0334 mol) of crude adduct **3** in 1670 ml of acetic acid 0.4 *M* in water was heated at 50° for 2 hr, freed of acetic acid under reduced pressure, and heated in 100 ml of 0.45 *N* hydrochloric acid at 95° for 2.5 hr. The apparent yield of product calculated from the ultraviolet absorbance of an aliquot of this solution at 292 nm in 0.1 *N* hydrochloric acid was 100%. The yield of pyridoxol determined by quantitative paper chromatography (Whatman No. 4, wet with pH 7 borate buffer and developed 18 hr with *n*-butyl alcohol saturated with the same buffer, the spot corresponding to pyridoxol eluted with borate buffer and evaluated by ultraviolet absorbance) was 89%. Values at other concentrations were determined in the same manner.

Dimer 6.—Eighty-five grams (0.28 mol) of crude adduct **3** in 280 ml of acetic acid 0.4 *M* in water was heated to 50° for 2 hr. The dark mixture was stripped free of acetic acid *in vacuo* and the residue was heated in 800 ml of 0.475 *N* hydrochloric acid at 95° for 2.5 hr to afford a 30% yield of pyridoxol and 33% of dimer **6** by quantitative paper chromatography. The hydrolysis solution was charged to 500 g of Amberlite IR-120 resin on the hydrogen cycle. The resin was washed with water to remove color bodies and eluted with 12 l. of 2 *N* hydrochloric acid. The first 6 l. afforded upon concentration *in vacuo* 17.5 g (30%) of crystalline pyridoxol hydrochloride identical in all respects with an authentic sample. The remaining 6 l. contained 8.4 g of material with a pyridoxinelike uv absorption which was shown by tlc on silica gel in 1:1 $CHCl_3$–MeOH to be mostly dimer **6**.

(8) R. Hüttenrauch and U. Zahn, *Arch. Pharm.*, **300**, 385 (1967).

(9) Melting points are uncorrected. Microanalyses were run by Mr. R. N. Boos. Nmr spectra were run by Mr. R. C. Zerfing on a Varian A-60A instrument.

(10) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, **21**, 328 (1956).

This solution was concentrated *in vacuo* to an oily residue which upon trituration with ethanol gave 5.4 g of crude dimer **6**.

Two recrystallizations from 95% ethanol afforded 3.0 g of pure dimer **6** as its dihydrochloride: mp 194–197°; equiv wt, 204 (calcd 196); nmr and uv spectra as given in Tables II and III; blue color with 2,6-dichloroquinone chlorimide (Gibbs test).[2]

Anal. Calcd for $C_{16}H_{20}N_2O_5 \cdot 2HCl$: C, 48.86; H, 5.64; N, 7.12; Cl, 18.03. Found: C, 48.46; H, 5.70; N, 6.85; Cl, 18.43.

Under these same conditions pyridoxol-4,5-diacetate[11] was converted quantitatively in to pyridoxol hydrochloride.

Methiodide of Dimer 6.—A mixture of 100 mg of dimer **6**, 5 ml of methyl alcohol, 5 ml of methyl iodide, and 10 ml of benzene was heated at 50° for 20 hr, then concentrated to dryness. The crude methiodide exhibited in pH 7 borate buffer an absorption maximum at 310 nm ($E^{1\%}_{1cm}$ 307).

Compound 9.—Ten grams (0.0334 mol) of crude adduct **3** and 17.7 g (0.186 mol) of 3-hydroxypyridine was stirred in 250 ml of acetic acid 0.4 *M* in water at room temperature for 18 hr. The reaction mixture was concentrated, diluted with 100 ml of 2.3 *N* hydrochloric acid, heated at 95° for 2.5 hr, treated with 1.4 g of Darco KB charcoal at 95° for 2 hr, and filtered. The filtrate was charged to 200 g of Amberlite IR-120 resin on the hydrogen cycle. Excess 3-hydroxypyridine was eluted with 2 *N* hydrochloric acid, the column was washed to neutrality with water, and the product was eluted with 1 l. of 2 *N* ammonia water. This eluate was concentrated to dryness *in vacuo*, affording 6.0 g (77%) of solid compound **9**, single spot by tlc, which was converted into its dihydrochloride in ethanolic hydrogen chloride and recrystallized from aqueous ethanol, mp 191–192°; uv and nmr spectra are in the tables.

Anal. Calcd for $C_{13}H_{14}N_2O_3 \cdot 2HCl$: C, 48.91; H, 5.05; N, 8.78. Found: C, 48.87; H, 5.08; N, 9.06.

Registry No.—**3**, 19206-42-9; **5**·HCl, 58-56-0; **5**·HCl 4-methyl ether, 3131-27-9; **6**, 19203-53-3; **6**·2HCl, 19598-93-7; **6** methiodide, 19245-01-3; **9**, 19203-54-4; **9**·2HCl, 19598-94-8; **11**, 19203-56-6.

(11) S. A. Harris, *J. Amer. Chem. Soc.*, **62**, 3203 (1940).

The Base Cyclization of *trans*-S-(1-Butenyl)-L-cysteine S-Oxide

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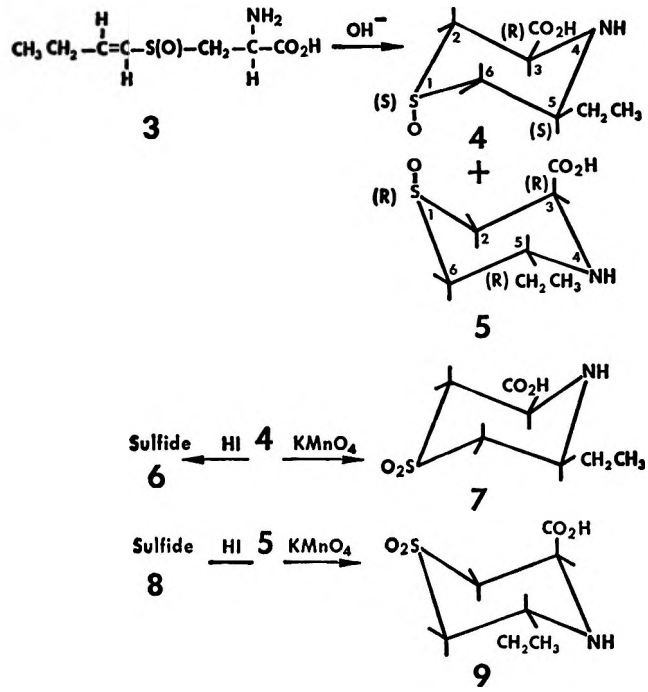
trans-S-(1-Propenyl)-L-cysteine S-oxide, the naturally occurring flavor precursor in the onion,[2] cyclizes in aqueous base to give cycloalliin[3] (**1**) in high yield as the only isolable product. The corresponding *cis* compound,[4] however, under the same conditions yields cycloalliin (**1**) and an isomeric cyclic sulfoxide[5] **2**. We now report that *trans*-S-(1-butenyl)-L-cysteine S-oxide (**3**) cyclizes in an analogous manner to give the isomeric cyclic sulfoxides **4** and **5** (Scheme I).

trans-S-(1-Butenyl)-L-cysteine S-oxide (**3**) was prepared by oxidation of the corresponding sulfide with hydrogen peroxide in aqueous solution. The oxidation

SCHEME I



product could not be separated into the two diastereomers, but a fairly pure sample of the dextrorotatory sulfoxide, $[\alpha]^{25}D$ +61° (water), was obtained in small yields.[7] A solution of the mixed sulfoxides **3** in 2 *N* ammonium hydroxide after 5–7 days at room temperature yielded 13% 3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane S-oxide (**4**) and 30% 3-(*R*)-carboxy-5-(*R*)-ethyl-1,4-thiazane S-oxide (**5**).

The structures of the new compounds and configuration at C-5 were established by oxidation of the cyclic sulfoxides to sulfones of known configuration[6] previously established by nmr. Oxidation of **4** yielded a sulfone identical with **7** which establishes the (*S*) configuration for C-5.[8] Similarly, isomer **5** by oxidation is correlated with sulfone **9** and therefore the configuration of C-5 is (*R*).

Evidence that the sulfoxide in **4** is axial and therefore (*S*) as in cycloalliin follows from a comparison of the D-line rotational changes on reduction of sulfoxide to sulfide. When **4** is reduced to the sulfide **6** by hydriodic acid, the molecular rotation in acid decreases in a positive sense: $[M]D$ −43.4° (3 *N* hydrochloric acid) for sulfoxide → $[M]D$ −59.2° (3 *N* hydrochloric acid) for sulfide. Conversion of cycloalliin to its sulfide in the same manner results in a change in the same direction: $[M]D$ −19° (hydrochloric acid) for cycloalliin → $[M]D$ −38.5° for sulfide. Rotational changes in water were also both in the same direction. Since no drastic ring conformational changes are expected in these reactions, the configuration of the sulfoxide in **4** should be the same as in cycloalliin.

By a similar argument the sulfoxide of **5** is axial with the (*R*) configuration. Thus, reduction of sulfoxide **5** to sulfide **8** is accompanied by an increase

(1) A Laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) A. I. Virtanen and C. G. Spåre, *Suomen Kemistilehti, B*, **34**, 72 (1961).

(3) A. I. Virtanen and E. J. Matikkala, *Acta Chem. Scand.*, **13**, 623 (1959).

(4) J. F. Carson and Lois E. Boggs, *J. Org. Chem.*, **31**, 2862 (1966).

(5) Cycloalliin (**1**) and its isomer **2** are the methyl homologs of **4** and **5**, respectively.[6]

(6) J. F. Carson, L. Boggs, and R. E. Lundin, *J. Org. Chem.*, **33**, 3739 (1968).

(7) A. L. Müller and A. I. Virtanen, *Acta Chem. Scand.*, **20**, 1163 (1966), prepared the sulfoxide by oxidation of the cysteine derivative with perbenzoic acid and apparently experienced similar difficulties in isolating a pure product. These investigators failed to isolate cyclization products from reaction of their sulfoxide preparation in ammoniacal solution.

(8) C-3 is known to be (*R*) in both isomers because of their formation from a derivative of L-cysteine.

TABLE I

NMR SPECTRAL DATA[a] FOR 3-(*R*)-CARBOXY-5-(*R*)-ETHYL-1,4-THIAZANE S-(R)-OXIDE (5) IN TFA–20% D_2O AT 65° AND 3-(*R*)-CARBOXY-5-(*R*)-METHYL-1,4-THIAZANE S-(*R*)-OXIDE (2) IN TFA AT 60°

	5		2	
Proton	δ'[b]	*J*, Hz	δ[c]	*J*, Hz
CH_3	0.69 t	*J* 7.51	0.88 d	*J* 6.8
H-6(a)	2.61 d of t	$J_{66'}$ 15.2 (g)	2.43 q	$J_{66'}$ 15.4 (g)
		J_{56} 11.8 (aa)		J_{56} 11.2 (aa)
H-6(e)	2.98 d of t	$J_{66'}$ 15.0 (g)	2.68 d of t	$J_{e6'}$ 15.4 (g)
		J_{56} 2.5 (ae)		J_{5e} 2.5 (ae)
		J_{26} 2.5 (lr)		J_{26} 2.5 (lr)
H-5(a)	4.00 m		4.00 m	
H-2(a)	2.91 q	$J_{22'}$ 15.4 (g)	2.69 q	$J_{22'}$ 15.8 (g)
		J_{23} 5.7 (ae)		J_{23} 5.5 (ae)
H-2(e)	3.57 d of t	$J_{22'}$ 15.4 (g)	3.35 d of t	$J_{22'}$ 15.8 (g)
		J_{23} 2.7 (ee)		J_{23} 2.5 (ee)
		J_{26} 2.7 (lr)		J_{26} 2.5 (lr)
H-3(e)	4.31 q	J_{23} 5.7 (ae), 2.7 (ee)	4.16 q	J_{23} 5.5 (ae), 2.5 (ee)

[a] Obtained at 100 MHz: d = doublet, t = triplet, q = quartet, d of t = doublet of triplets, m = multiplet, g = *gem*, lr = long range. [b] Chemical shifts for **5** are in parts per million downfield from pivalic acid. [c] Chemical shifts for **2** are in parts per million downfield from tetramethylsilane.

in rotation in the positive sense: $[M]_D$ −126.6° (hydrochloric acid) for sulfoxide → $[M]_D$ −97.3° for sulfide. Reduction of the cycloalliin isomer **2** yielded a rotational change in the same direction: $[M]_D$ −144° (hydrochloric acid) for sulfoxide → $[M]_D$ −113° for sulfide. The argument is more doubtful in this case since a ring inversion could conceivably occur during reduction to sulfide for one sulfoxide and not for the other. However, the good agreement in the changes in molecular rotation (+29.3° for **5** → **8** and +31° for reduction of **2**) strengthens the applicability of the principle to this case.

That sulfoxide **5** has the same ring conformation, at least in trifluoroacetic acid (TFA), as the cycloalliin isomer **2** was shown by nmr. Table I shows spectral data for the two compounds. The large coupling constants, J_{56} = 11.8 Hz for **5** and 11.2 Hz for **2**, require a *trans*-diaxial relation between the C-5 proton and one C-6 proton in each compound. The coupling constants between the C-2 and C-3 protons, J_{23} = 5.7 and 2.7 Hz for **5** and J_{23} = 5.5 and 2.5 Hz for **2**, require that no diaxial relation can exist between C-2 and C-3 protons in each case, in agreement with the assigned conformations in TFA.

Experimental Section[9]

trans-**S-(1-Butenyl)-L-cysteine S-Oxide (3).**—An aqueous solution of 2.57 g (0.0147 mol) of *trans*-S-(1-butenyl)-L-cysteine was oxidized with hydrogen peroxide as previously described.[4] Concentration of the oxidation solution to *ca.* 20 ml yielded 360 mg of cystine, apparently a decomposition product since the cystine content of the original amino acid was 1%. Occasionally, the yield of cystine reaches 25%. The solution, freed of cystine upon the addition of acetone (8:1) yielded 1.78 g of amorphous product. Four recrystallizations from acetone–water yielded 147 mg of the (+) isomer as very fine crystals: mp 119–121° dec; rotation unchanged on recrystallization; $[\alpha]^{25}D$ +61.2° (*c* 1.8, water); relative R_f with respect to alanine, 1.88; ir, 1580 (ionized carboxyl), 1030 (sulfoxide), and 962 cm^{-1} (*trans* double bond).

Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.7; H, 6.95; N, 7.20.

Although slightly levorotatory fractions could be isolated from the mother liquor, a pure chromatographically homogeneous (−)-sulfoxide could not be isolated.

Preparation of Mixed Crotyl- and Butenylcysteine Sulfoxides 3 and Cyclization to 4 and 5.—Because of the difficulty of separating mixtures of crotyl- and butenylcysteines, it was advantageous to oxidize the mixture to the sulfoxides and to cyclize the crude product as here described. A suspension of 20 g (0.114 mol) of a mixture of 40% 1-butenyl- and 60% 2-butenyl-L-cysteines in 900 ml of water was oxidized with 16 ml of 30% hydrogen peroxide for 27 hr at 25°. Cyclization of the crude dried product was accomplished in 1000 ml of 2 *N* ammonium hydroxide (7 days at 25°).

Crotylcysteine sulfoxide and other primary amino compounds were removed from the product by reaction with sodium 2,4,6-trinitrobenzene sulfonate as described previously.[4] Salts were removed in the usual manner with Dowex 50 (H^+) and the ammoniacal eluate from the ion exchanger on concentration yielded 2.66 g of 5 (30.6% based on the 1-butenyl content of the starting material). Recrystallization from 50% aqueous ethanol gave pure **3-(*R*)-carboxy-5-(*R*)-ethyl-1,4-thiazine S-(*R*)-oxide** (5) as tiny prisms: dec pt 270°; $[\alpha]^{26}D$ −66.2° (*c* 2, 2.5 *N* hydrochloric acid), −101.2° (c 2, water); ir, strong at 1640 (ionized carboxyl) and at 1022 cm^{-1} (sulfoxide).

Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 44.0; H, 6.74; N, 7.30.

Compound 5 did not form a crystalline hydrochloride. On paper chromatography the compound moved with an R_f relative to alanine of 0.91, and gave an extremely weak yellow spot with the copper ninhydrin reagent.

The mother liquor after removal of 5 was acidified with hydrochloric acid, taken to dryness *in vacuo*, and crystallized from water–acetone (1:8) to yield 1.36 g of **4** as the hydrochloride (13% based on the original 1-butenylcysteine content). Recrystallization from aqueous acetone yielded pure **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane S-(*S*)-oxide hydrochloride** (4): mp 230–238° dec; ir, strong at 1745 (un-ionized carboxyl) and at 1005, 1024, and 1035 cm^{-1} (sulfoxide region).

Anal. Calcd for $C_7H_{13}NO_3S \cdot HCl$: C, 36.92; H, 6.20; N, 6.15; Cl, 15.57. Found: C, 37.0; H, 6.19; N, 6.16; Cl, 15.6.

The hydrochloride of **4** was converted to the free amino acid which was crystallized from water–acetone (1:10) as large coarse prisms: mp 243–245° dec; $[\alpha]^{25}D$ −22.7° (*c* 2.5, 3 *N* hydrochloric acid) and −32.5° (*c* 2, water); ir, strong at 1640 (ionized carboxyl) and at 1027 cm^{-1} (sulfoxide).

Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.8; H, 6.95; N, 7.28.

Paper chromatography with the solvent system already described gives an extremely faint yellow spot with copper–ninhydrin reagent; relative R_f with respect to alanine, 1.26.

Cyclization of (±)-*trans*-S-(1-Butenyl)-L-cysteine Sulfoxide

(9) Infrared spectra were determined as potassium bromide disks in a Perkin-Elmer Model 237 spectrophotometer. All nmr spectra were taken on a Varian Associates HR-100 spectrometer to which had been added an internal field-frequency lock built at this laboratory. Paper chromatograms were run on Whatman No. 1 paper with butanol–acetic acid–water (63:10:27) and compounds were detected with the copper–ninhydrin spray reagent of E. D. Moffat and R. I. Lytle [*Anal. Chem.*, **31**, 926 (1959)]. Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

(3) to 4 and 5.—A solution of 2.70 g (0.0141 mol) of 3 ($[\alpha]^{25}D$ +5°) in 500 ml of 2 *N* ammonium hydroxide was allowed to stand 5 days at 25° and the products were isolated as before. Yields of 492 mg (18.2%) of isomer 4 and 370 mg (11.5%) of 5 hydrochloride were obtained.

Oxidation of Sulfoxides 4 and 5 to the Corresponding Sulfones 7 and 9.—A solution of 700 mg (0.00366 mol) of 5 in 120 ml of 0.25 *N* sulfuric acid was oxidized with 464 mg of potassium permanganate. After removal of sulfate and manganese dioxide and purification with a cation exchanger, a yield of 312 mg of **3-(*R*)-carboxy-5-(*R*)-ethyl-1,4-thiazane S-dioxide** (9) was obtained, identified by ir and nmr.

Oxidation of a sample of 4 (200 mg) in a similar manner yielded 70 mg of **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane S-dioxide** (7), established by ir.

Reduction of Sulfoxide 4 to Sulfide 6.—Hydriodic acid reduction of 1.30 g (0.0057 mol) of 4 HCl gave 902 mg (89%) as the free amino acid. Recrystallization from water–ethanol (1:4) yielded pure **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane** (6) as large lathlike crystals: mp 256 dec; ir, no sulfoxide absorption; $[\alpha]^{26}D$ −58.8° (*c* 2, water), $[\alpha]^{25}D$ −33.8° (*c* 2.5, 1 *N* hydrochloric acid).

Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48. Found: C, 47.8; H, 7.31.

Reduction of Sulfoxide 5 to Sulfide 8.—A sample of 1.496 g (0.00782 mol) of 5 was reduced and the product was crystallized from water–ethanol (1:5) to yield the sulfide, **3-(*R*)-carboxy-5-(*R*)-ethyl-1,4-thiazane** (8) (77%), as rectangular prisms: mp 275–277° dec (phase change above 230°, prisms → needles); sulfoxide absent by ir; $[\alpha]^{25}D$ −82.5° (*c* 1.8, water), −61.07° (*c* 2.2, in 3 *N* hydrochloric acid).

Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48; N, 7.99. Found: C, 48.0; H, 7.45; N, 7.98.

Registry No.—2, 19206-35-0; 3, 19206-36-1; 4, 19206-37-2; 4 HCl, 19206-38-3; 5, 19206-39-4; 6, 19206-40-7; 8, 19206-41-8.

Acknowledgment.—We are grateful to Nancy Bennett for assistance with nmr spectra and to L. M. White and Geraldine Secor for analyses.

The Reductic Acid-^{14}C Derived from D-Xylose-1-^{14}C and 2-Furaldehyde-α-^{14}C[1,2]

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In addition to its formation from hexuronic acids and polyuronides, reductic acid (2,3-dihydroxy-2-cyclopenten-1-one) has been reported to be formed from both D-xylose[3] and its structurally related dehydration product, 2-furaldehyde.[4] Subsequent to these reports, several investigators[5-7] have attempted to explain the mechanism of formation of this compound from both D-xylose and 2-furaldehyde, and, in all cases, these suggestions predict that C-1 of D-xylose and the α-carbon atom of 2-furaldehyde should ultimately reside at C-2 of reductic acid.

TABLE I

% DISTRIBUTION OF ISOTOPE IN REDUCTIC ACID-^{14}C

Source	C-2[a]	C-1 and C-3[b]	C-4 and C-5[b]
D-Xylose-1-^{14}C	58.8	41.2	0.3
2-Furaldehyde-α-^{14}C	57.0	42.0	1.0

[a] Determined by difference after conversion of reductic acid-^{14}C into succinic acid-^{14}C. [b] Determined by difference after the conversion of succinic acid-^{14}C into ethylene diamine *via* a Curtius degradation.

In this work, some yield figures and structural relationships between reactants and product were determined using D-xylose-1-^{14}C and 2-furaldehyde-α-^{14}C as starting materials in the conversion. The former compound was obtained commercially and the latter was prepared from D-xylose-1-^{14}C, a conversion which is known[8] to give 2-furaldehyde exclusively labeled at the α-carbon atom. These compounds were converted into reductic acid at 150° in 5% sulfuric acid in low yield (0.24% in the case of D-xylose, calculated from isotope dilution figures). Structural relationships were investigated by systematic degradation of the reductic acid-^{14}C obtained from these precursors. Conversion of reductic acid into succinic acid allowed a determination of the radiochemical activity present at C-2 of reductic acid and since, in the reductic acid molecule, the oxygen-bearing carbon atoms 1 and 3 are equivalent as are the methylene carbon atoms 4 and 5 and are represented by, respectively, the carboxyl carbon atoms and the methylene carbon atoms of succinic acid, a determination of the specific activity of the ethylene diamine derived from succinic acid of known activity *via* a Curtius degradation allowed the determination of the radiochemical activity residing in both pairs of carbon atoms. Degradation of the reductic acid-^{14}C obtained from either D-xylose-1-^{14}C or 2-furaldehyde-α-^{14}C gave identical results (Table I) with about 60% of the activity at C-2 and 40% at C-1 and C-3. In both cases, negligible activity was found in the methylene carbon atoms 4 and 5.

The identical label distribution in the reductic acid indicates a common primary source and suggests that it is 2-furaldehyde derived, since the latter is readily formed from D-xylose under the conditions of formation of reductic acid. That pentoses are sources of reductic acid has been widely accepted exclusively on the basis of the experimental findings of Reichstein and Oppenauer[3] who reported its isolation, in crystalline form, in about 0.5% yield starting from D-xylose.

In a recent study of the formation of reductic acid from D-galacturonic acid,[9] it was found that, in 90% of the reaction product, C-1 of the uronic acid corresponded to C-2 of reductic acid, indicating that this fraction of the product arose in a manner consistent with mechanism proposals on this subject.[5-7] In 10% of the product, however, C-1 of the uronic acid was found at C-1–C-3 of reductic acid and represented an un-

(1) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) Journal Paper No. 5506, Missouri Agricultural Experiment Station.

(3) T. Reichstein and R. Oppenaur, *Helv. Chim. Acta*, **16**, 988 (1933); **17**, 390 (1934).

(4) Dutch Patent 61,296 (1948); *Chem. Abstr.*, **42**, 7788 (1948).

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(6) E. Stutz and H. Deuel, *Helv. Chim. Acta*, **41**, 1722 (1958).

(7) H. S. Isbell, *J. Res. Natl. Bur. Std.*, **33**, 45 (1944).

(8) W. A. Bonner and M. R. Roth, *J. Amer. Chem. Soc.*, **81**, 5454 (1959).

(9) M. S. Feather and J. F. Harris, *J. Org. Chem.*, **31**, 4018 (1966).

explained reaction pathway. Since, at the reaction conditions used, considerable 2-furaldehyde is evolved from uronic acids, it must also contribute to product formation in this reaction. Assuming that all of the reductic acid labeled at C-1–C-3 formed during uronic acid decomposition is 2-furaldehyde derived and using the radioisotopic label distribution figures obtained herein, it can be concluded that, of the reductic acid-^{14}C formed from D-galacturonic acid-1-^{14}C, all of the C-1–C-3-labeled product and 15% of the C-2-labeled product are derived from 2-furaldehyde. The remaining 75%, labeled exclusively at C-2, must be formed by a mechanism unique to hexuronic acids.

Experimental Section

Materials and Methods.—Specific activities of labeled compounds were determined on a Model No. 3003 Packard Tricarb spectrometer using an internal toluene-^{14}C standard. D-Xylose-1-^{14}C was obtained from CalBiochem, Los Angeles, Calif. Radiochemically inert reductic acid was prepared from pectin as described in a previous report[9] and had mp 211–212°, λ_{max} 267 mμ (ε 13,300) (95% ethanol). Thin layer chromatography was performed on silica gel GF coated glass plates and spots were detected with either aniline hydrogen phthalate spray reagent or uv irradiation.

Reductic Acid-^{14}C From D-Xylose-1-^{14}C.—To an 8-mm pyrex glass tube was added 25 μCi of D-xylose-1-^{14}C (200 mg) and 1.0 ml of 5% sulfuric acid. The tube was sealed and heated at 150° for 2 hr and the contents were then transferred to a beaker and neutralized with barium carbonate. The resulting solution, after filtration through Celite, was passed through a column of Dowex 50 (hydrogen form) and evaporated to dryness. Thin layer chromatograms of the residue using chloroform–acetic acid (9:1) as irrigant indicated that reductic acid was the major product. To the residue was added 1.50 g of radiochemically inert reductic acid and the sample was recrystallized from N,N-dimethylformamide: yield 1.37 g. The resulting crystals were sublimed five times at 140° (0.1 mm), whereupon a constant specific activity of 4.20×10^{-3} μCi/mmol was attained.

Reductic Acid-^{14}C from 2-Furaldehyde-α-^{14}C.—The 2-furaldehyde-α-^{14}C used in this experiment was prepared essentially by the method described by Hughs and Acree.[10] To 750 ml of 5.0 *N* sulfuric acid was added 75 μCi (3.0 g) of D-xylose-1-^{14}C and the solution was slowly distilled. At the end of 6 hr, 250 ml of distillate (containing the 2-furaldehyde-α-^{14}C) was collected. This solution was made 5% in sulfuric acid and was heated 1.5 hr at 150° in a glass-lined Parr bomb. Reductic acid was qualitatively detected, isolated, and purified as described above with 3.0 g of inert reductic acid being used as diluent. The pure product (2.0 g) had a specific activity of 1.98×10^{-3} μCi/mmol.

Chemical Degradation of the Reductic Acids-^{14}C.—A 1.2-g sample of reductic acid-^{14}C (specific activity 4.20×10^{-3} μCi/mmol) derived from D-xylose-1-^{14}C was converted into succinic acid by permanganate oxidation as described in a previous report.[9] After recrystallization from water, the succinic acid (mp and mmp 182°) had a specific activity of 1.74×10^{-3} μCi/mmol. This material (500 mg) was subjected to a Curtius degradation as described by Benson and Bassham[11] to give crystalline ethylenediamine dihydrochloride (mp and mmp 203°) having a specific activity of 1.40×10^{-5} μCi/mmol. Repetition of the above experiments using 2-furaldehyde-α-^{14}C derived reductic acid-^{14}C (specific activity 1.90×10^{-3} μCi/mmol) gave succinic acid having a specific activity of 0.82×10^{-3} μCi/mmol and subsequently, ethylenediamine dihydrochloride having a specific activity of 2.2×10^{-5} μCi/mmol.

Registry No.—2,3-Dihydroxy-2-cyclopenten-1-one-2-^{14}C, 19214-81-4; D-xylose-1-^{14}C, 19588-10-4; 2-furaldehyde-α-^{14}C, 19238-30-3.

(10) E. E. Hughes and S. F. Acree, *J. Res. Natl. Bur. Std.*, **21**, 327 (1938); **23**, 293 (1939).

(11) A. A. Benson and J. A. Bassham, *J. Amer. Chem. Soc.*, **70**, 3939 (1948).

Rearrangement of Azidoquinones. III. Reaction of 1,4-Benzoquinone with Sodium Azide

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In 1915, Oliveri-Mandalá and Calderao[1,2] showed that 1,4-benzoquinone reacts with hydrazoic acid in benzene to give 2-azido-1,4-benzohydroquinone (**1**). Twenty years later Fieser and Hartwell[3] obtained an azidohydroquinone, believed to be the same as that reported in the earlier work,[1,2] when an acetic acid solution of 1,4-benzoquinone was treated with sodium azide. We have reinvestigated this latter reaction and find the product to be 2,5-diazido-1,4-benzohydroquinone (**2**). The structure of **2** is based upon its spectral properties and upon its conversion into a diacetate (**3**), 2-amino-5-azido-1,4-benzoquinone (**4**), 2,5-diamino-1,4-benzoquinone (**5**), and the γ-cyanomethylene-$\Delta^{\alpha,\beta}$-butenolide (**6**).

Addition of excess sodium azide to an acetic acid solution of 1,4-benzoquinone resulted in a mildly exothermic reaction followed by the precipitation of diazide **2** in 33% isolated yield. The nmr spectrum of this *highly explosive* compound is consistent for the diazide structure, showing only one sharp singlet at δ 6.53 for the two equivalent aromatic protons. The ir spectrum of **2** shows characteristic absorptions for the phenolic hydroxyl and azide groups at 3300 and 2120 cm^{-1}, respectively. The hydroquinone structure was confirmed by the formation of a diacetate derivative, **3**, in 92% yield when **2** was treated with acetic anhydride. The spectral (nmr, ir, and mass spectrum) properties and combustion analysis of **3** are in agreement with its formulation. This diacetate is a relatively stable compound, melting with decomposition at 160–161°. The diacetate reported by Oliveri-Mandalá and Calderao[2] for monoazidehydroquinone **1** melted from 115 to 120° and decomposed at 140°.

These data, although consistent for **2** as the structure of the diazidohydroquinone, do not rule out other possible formulations, particularly with regard to the orientation of the two azide substituents. In order to establish this relationship, diazide **2** was converted into a known compound, 2,5-diamino-1,4-benzoquinone[4] (**5**) and to γ-lactone **6** (Scheme I). The key intermediate in both of these transformations is 2-amino-5-azide-1,4-benzoquinone (**4**). We have previously shown[5] that azidohydroquinones readily disproportionate to give aminoquinones and, when this reaction was applied to the azidohydroquinone, **2**, the required 2-amino-5-azido-1,4-benzoquinone (**4**) was obtained in 75% yield. The nmr spectrum of **4** strongly indicates that the azido and amino groups are in the 2 and 5 positions since the

(1) E. Oliveri-Mandalá and E. Calderao, *Gazz. Chim. Ital.*, **45**, 307 (1915).

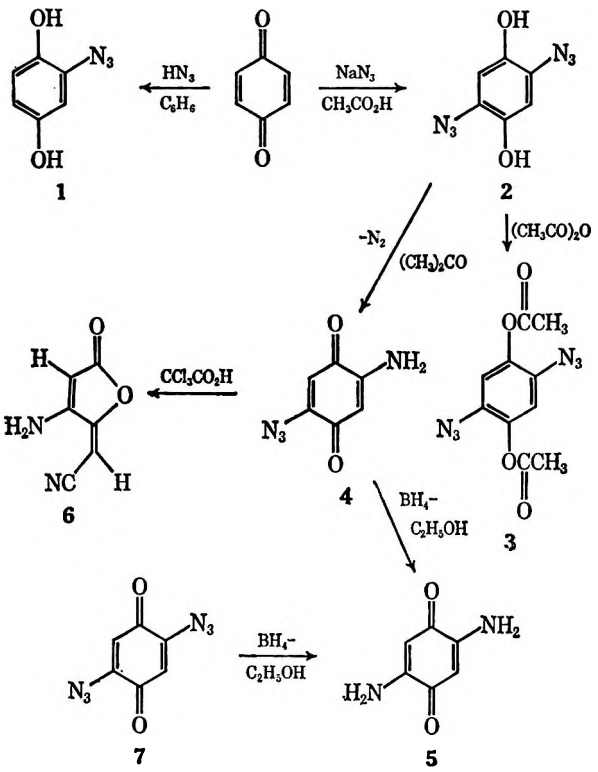
(2) E. Oliveri-Mandalá and E. Calderao, *ibid.*, **45**, 120 (1915).

(3) L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.*, **57**, 1482 (1935).

(4) F. Kehrman and G. Betsch, *Ber.*, **30**, 2095 (1897).

(5) H. W. Moore and H. R. Shelden, *J. Org. Chem.*, **33**, 4019 (1968).

SCHEME I



vinyl protons appear as sharp singlets at δ 6.00 and 5.68.[6] The ir spectrum of **4** also gives critical structural data for the azidoaminoquinone, showing absorptions for the primary amino group at 3310 and 3110 cm^{-1}, an azide group at 2140 cm^{-1} and quinone carbonyl at 1660 cm^{-1}.

Sodium borohydride reduction of **4** gives 2,5-diamino-1,4-benzoquinone[4] (**5**). However, this compound did not melt under 360° even though the reported melting point is 325–330°.[4] Only a color change from deep purple to black was observed at the latter temperature. The spectral properties of **5** are in complete agreement with its structure. The nmr spectrum of **5** shows singlet absorptions for the four amino protons and for the two equivalent vinyl protons at δ 7.35 and 5.32, respectively. The ir spectrum shows characteristic absorptions for the amino group at 3410 and 3315 cm^{-1} and for the quinone carbonyl at 1560 cm^{-1}. The mass spectrum of **5** shows a molecular ion at *m/e* 138, consistent with the formulation $C_6H_6N_2O_2$. 2,5-Diamino-1,4-benzoquinone was prepared by an independent pathway involving borohydride reduction of 2,5-diazido-1,4-benzoquinone (**7**), and was shown to be identical in all respects with compound **5** described above.

Azidoquinones undergo a highly stereoselective rearrangement in acidic medium to give γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides.[7] The isomer obtained is the one in which the nitrile group is *trans* to the lactone oxygen. The other substituent on the exocyclic double bond is the one which was originally adjacent to the azide group in the starting quinone. In order to confirm the structure of **4** and, therefore, also of **2** and **5**, this reaction was carried out with **4** in trichloroacetic acid, and γ-lactone **6** was obtained in 44% yield. The oreintation of the protons in **6** and thus of the azido and amino groups in **4** are assigned from the nmr spectrum of the lactone. These vinyl protons in **6** give rise to an AB pattern centered at δ 5.62 showing a coupling constant of 1.6 cps. This observed coupling is characteristic of protons in a 1,4-*trans–trans* relationship on the butadiene moiety of the γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolide ring system.[7] This is in complete agreement with the work of Bothner-By, *et al.*,[8–12] who have investigated long-range coupling in a large number of butadienes and found that 1,4-vinyl protons in the *trans–trans* configuration to show coupling constants ranging between 1.3 and 1.9 cps. All other long-range couplings were found to be appreciably smaller. The ir and mass spectra and C and H analyses of **6** are also in agreement with its structure.

Experimental Section

2,5-Diazido-1,4-benzohydroquinone (**2**).—A solution of 10 g (0.093 mol) of 1,4-benzoquinone in 100 ml of glacial acetic acid was cooled to 10°, and 20 ml of an aqueous solution containing 13.5 g (0.208 mol) of sodium azide was then added in one portion. After a few minutes the reaction solution was filtered to remove any unreacted sodium azide and the mother liquor cooled. 2,5-Diazido-1,4-benzohydroquinone (**2**) precipitated as white crystalline needles. An additional fraction of the product was obtained by pouring the mother liquor into water. The combined fractions were dried to give 5.9 g (33% yield) of diazide **2**. This compound is quite thermally and photolytically unstable which prevented satisfactory combustion analysis. It violently *explodes* at 100° and rapidly turns red upon exposure to laboratory light.

1,4-Diacetoxy-2,5-diazidobenzene (**3**).—2,5-Diazido-1,4-benzohydroquinone (**2**, 1 g, 0.0052 mol) was dissolved in 80 ml of warm acetic anhydride and the solution was allowed to stand at room temperature for 6 hr. The resulting white precipitate was collected and dried to give 1.3 g (91% yield) of diacetate **3**, mp 160–161° dec.

The nmr spectrum ($CDCl_3$) of **3** shows two absorptions in the ratio of 2:6 at, respectively, δ 6.89 and 2.28. The ir spectrum (Nujol) shows absorptions for acetate carbonyl at 1760 cm^{-1} and for azide at 2120 cm^{-1}. The mass spectrum of **3** shows a molecular ion at *m/e* 276 in accord with the formulation $C_{10}H_8N_6O_4$.

Anal. Calcd for $C_{10}H_8N_6O_4$: C, 43.47; H, 2.90; N, 30.43. Found: C, 43.27; H, 2.92; N, 30.39.

2-Amino-5-azido-1,4-benzoquinone (**4**).—2,5-Diazido-1,4-benzohydroquinone (**2**, 5.8 g, 0.03 mol), was dissolved in 500 ml of spectrograde acetone. The solution immediately became purple with the simultaneous evolution of nitrogen. After nitrogen evolution ceased, the solution was filtered to remove a small amount of 2,5-diamino-1,4-benzoquinone (**5**) which had formed. The solution was then concentrated *in vacuo* at 40° to the point where azide **4** began to precipitate. The solution was then cooled and the precipitate collected to give 3.7 g (75% yield) of the purple crystalline 2-amino-5-azido-1,4-benzoquinone (**4**). It was impossible to obtain a melting point on this product. The compound did not melt when it was slowly heated to 360° and it *violently decomposed* when placed in a bath at 200°. The spectral data (ir, nmr) *vida infra* for **4** are in complete agreement with its formulation. The mass spectrum of **4** does not show a molecular ion peak, but the second most intense (47%) peak is at *m/e* 136, corresponding to the loss of nitrogen from azidoaminoquinone **4**.

2,5-Diamino-1,4-benzoquinone (**5**).—2,5-Diazido-1,4-benzoquinone (**7**, 1 g, 0.005 mol) was dissolved in 50 ml of 95% ethanol. Excess sodium borohydride was added and the reaction solution

(6) R. K. Norris and S. Sternhell [*Aust. J. Chem.*, **19**, 617 (1966)] have investigated long-range coupling quinones and found no observable coupling between protons in positions 2 and 5.

(7) H. W. Moore and H. R. Shelden, *Tetrahedron Lett.*, 5431 (1968).

(8) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3455 (1965).

(9) A. A. Bothner-By and R. K. Harris, *ibid.*, **87**, 3445 (1965).

(10) A. A. Bothner-By and D. Jung, *ibid.*, **90**, 2342 (1968).

(11) A. A. Bothner-By and E. Moser, *ibid.*, **90**, 2347 (1968).

(12) A. A. Bothner-By and D. F. Koster, *ibid.*, **90**, 2351 (1968).

was maintained at 20° by means of an external ice bath. The purple product precipitated from the solution and was collected to give 426 mg (62% yield) of 2,5-diamino-1,4-benzoquinone (**5**), mp >360° (lit.[4] mp 325–330°). The spectral data (ir, nmr, and mass spectra), *vida infra*, are in complete agreement with structure **5**.

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.35. Found: C, 51.94; H, 4.53.

2,5-Diamino-1,4-benzoquinone (**5**) was also prepared in 31% yield from 2-amino-5-azido-1,4-benzoquinone (**4**) according to the above procedure. The compounds prepared by both methods were shown to be identical in all respects.

2,5-Diazido-1,4-benzoquinone (**7**).—A solution of 5 g (0.028 mol) of 2,5-dichloro-1,4-benzoquinone in 60 ml of dimethylformamide and 20 ml of acetone was cooled to 15°. An aqueous solution of 4 g (0.061 mol) of sodium azide in 20 ml of water was slowly added keeping the temperature below 18°. The bright orange diazide, **7**, precipitated from the reaction solution in 94% yield. Recrystallization from warm ethanol gave pure 2,5-diazido-1,4-benzoquinone (**7**), mp 93–94° dec. The nmr spectrum of **7** ($CDCl_3$) shows only one peak at δ 6.20. The ir spectrum (Nujol) shows characteristic absorptions at 2150 and 2110 (azide) and 1660 cm^{-1} (quinone carbonyl). The mass spectrum of **7** showed a molecular ion at *m/e* 190 in accord with the molecular formula $C_6H_2N_6O_2$. Reliable combustion analysis could not be obtained owing to the instability of the diazide.

β-Amino-γ-cyanomethylene-$\Delta^{\alpha,\beta}$-butenolide (**6**).—2-Amino-5-azido-1,4-benzoquinone (**4**, 0.02 g, 0.0013 mol) was added in small portions to 3 g of trichloroacetic acid at 65° over a period of 30 min. During this time the solution became dark and nitrogen was evolved. The reaction solution was then poured into 10 ml of ice–water and cooled; the product was collected by filtration giving 0.08 g (44% yield) of β-amino-γ-cyanomethylene-$\Delta^{\alpha,\beta}$-butenolide (**6**), mp 201–204°. Recrystallization from aqueous ethanol gave an analytical sample of **6** as a white crystalline solid, mp 204°.

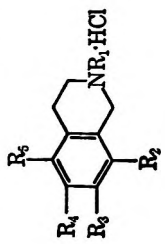
Anal. Calcd for $C_6H_4N_2O_2$: C, 52.94; H, 2.94; N, 20.59. Found: C, 52.93; H, 2.99; N, 20.68.

The ir spectrum of **6** shows characteristic absorptions at 3490, 3200 and 3300 (NH_2), 2250 (CN), and 1780 and 1760 cm^{-1} (C=O). The mass spectrum of **6** shows a molecular ion at *m/e* 136 (59%) in accord with the formulation $C_6H_4N_2O_2$.

Registry No.—1,4-Benzoquinone, 106-51-4; sodium azide, 12136-89-9; **2**, 19462-75-0; **3**, 19462-76-1; **4**, 19462-77-2; **6**, 19459-07-5; **7**, 19462-78-3.

Acknowledgment.—The authors are grateful to the National Science Foundation for partial support of this work from Grant G.P. 8706.

TABLE I
1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd	R_1	R_2	R_3	R_4	R_5	Yields,[a] %	Mp, °C	Lit. mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Cl
5	CH_3	OH	OCH_3	H	H	68	212–214	*b*	57.47	7.02	6.09	15.43	57.03	6.74	6.22	15.36
6	CH_3	H	OCH_3	OH	H	26	286–288	285–290[c]								
7	CH_3	OH	OCH_3	OCH_3	H	63	236–238	*d*	55.49	6.96	5.39	13.68	55.37	6.71	5.83	13.83
8	CH_3	OH	OH	H	H	30	228–230		60.11	7.06	7.01	17.75	59.78	7.09	6.64	17.25
9	H	OH	OCH_3	H	H	42	281–283	282–283[e]								
10	H	OH	OCH_3	OCH_3	H	63	257–258	258[f]								
11	CH_3	OH	OCH_3	H	CH_3	50	282–284		59.14	7.45	5.74	14.55	59.13	7.44	5.90	14.94

[a] Yields are calculated on the basis of the starting phenols. [b] Compound **5** was prepared in 70% over-all yield by our published procedure[5] and was identical with this sample. [c] J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *J. Org. Chem.*, **32**, 2225 (1967). [d] Free base prepared by neutralization, mp 130–132° [E. Späth and A. Becke, *Ber.*, **68**, 944 (1935)] reported mp 131–133°). [e] See ref 3. [f] E. Kauder, *Arch. Pharm.*, **237**, 190 (1899); A. Hefiter, *Ber.* **34**, 3004 (1901) (as cited in ref 9 of the former).

Synthesis of Isoquinolines. IX. 1,2,3,4-Tetrahydroisoquinolines *via* the Mannich Condensation[1]

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In recent years, we have developed and explored a facile synthesis of simple oxygenated isoquinolines, based upon modifications of the Pomeranz–Fritsch reactions.[3] These modifications have involved the

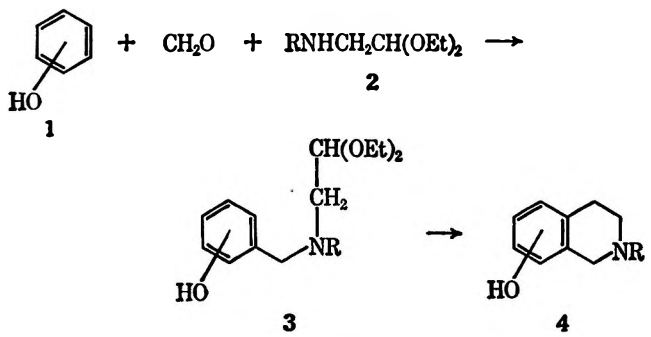
(1) Paper VIII: J. M. Bobbitt and T. E. Moore, *J. Org. Chem.*, **33**, 2958 (1968). This work was sponsored, in part, by Contract DA-49-193-MD-2948 from the U. S. Army Medical Research and Development Command, Publication 513 from the Army Research Program on Malaria.

(2) Recipient of a Fullbright Travel Grant, 1966.

(3) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965). See also preceeding papers in this series.

acid-catalyzed cleavage, ring closure, and reduction of benzyl amino acetals formed by reductive alkylation of aminoacetaldehyde acetal with suitable aromatic aldehydes. We have now been able to prepare the benzyl amino acetals by a simple Mannich reaction on suitable phenols.[4] The method has been especially useful for preparation of 6,7,8-trioxygenated isoquinolines.

The appropriate phenols (**1**) were allowed to react with formaldehyde and suitably substituted amino acetals (**2**, R = H or CH_3) to yield the benzyl amino



acetals (**3**) which were converted into isoquinolines (**4**) by acid treatment followed by hydrogenation over palladium on carbon.[3] The Mannich bases were not isolated. The results are given in Table I. Two products (**5** and **6**) were obtained when the reaction was carried out with guaiacol, but they were easily separable by crystallization and the combined yield was nearly quantitative. The Mannich condensations with methyl amino acetal were carried out at room temperature,[5] but those with amino acetal required reflux temperature in ethanol.

Two of the compounds, **7** and **10**, are known alkaloids, anhalidine and anhalamine, respectively.[6] Methylation of **10** with diazomethane led to the alkaloid, anhalinine (6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline). All three alkaloids were synthesized by a more laborious method by Späth and his coworkers.[7,8] Anhalamine and anhalidine have been prepared more recently by Brossi and his coworkers.[9] Compound **11** was prepared from vanillin. The 5-methyl group was formed by reduction of the aldehyde group during the hydrogenation step. The nmr spectra of all of the compounds, known and unknown, were measured and are in agreement with the assigned structures.

Experimental Section[10]

Reaction of Guaiacol to Yield 5 and 6.—A mixture of guaiacol (2.48 g, 0.02 mol), 3.00 g of 40% aqueous formaldehyde (0.04 mol), and 3.60 g of methylaminoacetaldehyde dimethyl acetal (0.03 mol) in 25 ml of ethanol was stirred at room temperature for 24 hr. The solvent was removed on a rotary evaporator and the resulting thick oil was dissolved in 50 ml of cold 6 *N* HCl and washed with ether. The acidic solution was stirred at room temperature for 15 hr. The last traces of ether were removed on a rotary evaporator and the solution was hydrogenated over 4 g of 5% palladium on carbon at room temperature and atmospheric pressure until no more hydrogen was absorbed (about 0.02 mol). The catalyst was removed by filtration and the solution was concentrated on a rotary evaporator to a yellow syrup. The syrup was treated with 50 ml of hot ethanol and cooled. Crystals formed and were collected to yield 1.20 g of the crude hydrochloride of **6**, (26%) mp 281–284°. The compound was recrystallized from methanol.

The mother liquor after the removal of **6** was concentrated and cooled to yield the crystalline crude hydrochloride of **5** (3.12 g, 68%), mp 208–212°. The analytical sample, mp 212–214°, was crystallized from absolute ethanol.

Preparation of Mannich Bases (3). General Procedure.[5]—The tertiary bases (**3**, R = CH_3) were prepared by stirring a mixture of the phenol (0.02 mol), formaldehyde (0.04 mol of 40% aqueous), and methylaminoacetaldehyde dimethyl acetal[11] (0.03 mol) in 25 ml of ethanol for 24 hr at room temperature. The secondary amines (**3**, R = H) were prepared by stirring similar mixtures (with aminoacetaldehyde dimethyl acetal[11]) at reflux temperature for 6–8 hr. In each case, the solvent was removed on a rotary evaporator and the crude Mannich bases were not purified.

1,2,3,4-Tetrahydroisoquinolines (4).—The crude Mannich bases were dissolved in 50 ml of cold 6 *N* HCl, washed three times with ether, and stirred at room temperature for 15 (leading to **9**) or 36 hr (leading to **7**, **8**, **10**, and **11**). The last traces of ether were removed, and the acid solutions were hydrogenated as described above. The catalyst was removed by filtration, and the solutions were evaporated on a rotary evaporator to yield slightly colored syrups. The syrups were treated with hot absolute ethanol (50 ml) and evaporated again. In some cases, this procedure was repeated twice more. The products crystallized during the evaporation or upon alcohol addition. They were collected by filtration and washed with cold absolute ethanol. Analytical samples were prepared by recrystallization from ethanol.

6,7,8-Trimethoxy-1,2,3,4-tetrahydroisoquinoline (Anhalinine).—Compound **10** (0.3 g) was treated with the diazomethane from 5 g of nitrosomethylurea. The mixture was allowed to stand in a refrigerator for 5 days and was evaporated to a syrup. The sryup was taken up in ether again, washed with 5% aqueous NaOH, dried over Na_2SO_4, and saturated with gaseous HCl. The crude hydrochloride (0.18 g) precipitated and was collected and recrystallized from absolute ethanol to yield anhalinine hydrochloride, mp 248–250° (lit.[7] mp 248–250°).

Registry No.—**5**, 19462-72-7; **8**, 19462-73-8; **11**, 19462-74-9.

(4) This research was suggested during a lecture given at Connecticut by Professor J. H. Burckhalter of the University of Michigan.

(5) E. L. Eliel, *J. Amer. Chem. Soc.*, **73**, 43 (1951).

(6) See L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, New York, N. Y., 1954. p 7.

(7) E. Späth and I. Roder, *Monatsh.*, **42**, 97 (1921); **43**, 93 (1922); *Chem. Abstr.*, **16**, 100, 3303 (1922).

(8) See footnote *d*, Table I.

(9) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).

(10) Melting points were measured on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich and the Baron Consulting Co. of Orange, Conn.

(11) Sometimes the diethyl acetal was used with similar results.

The Formation of Tetramethylpyrazine and 2-Isopropyl-4,5-dimethyl-3-oxazoline in the Strecker Degradation of DL-Valine with 2,3-Butanedione

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Received November 13, 1968

The Strecker degradation is a well-documented reaction in which an α-amino acid is simultaneously decarboxylated and deaminated to yield a structurally related aldehyde containing one less carbon atom.[1] The reaction is usually observed when α-amino acids are heated in the presence of 1,2-di- or 1,2,3-tricarbonyl

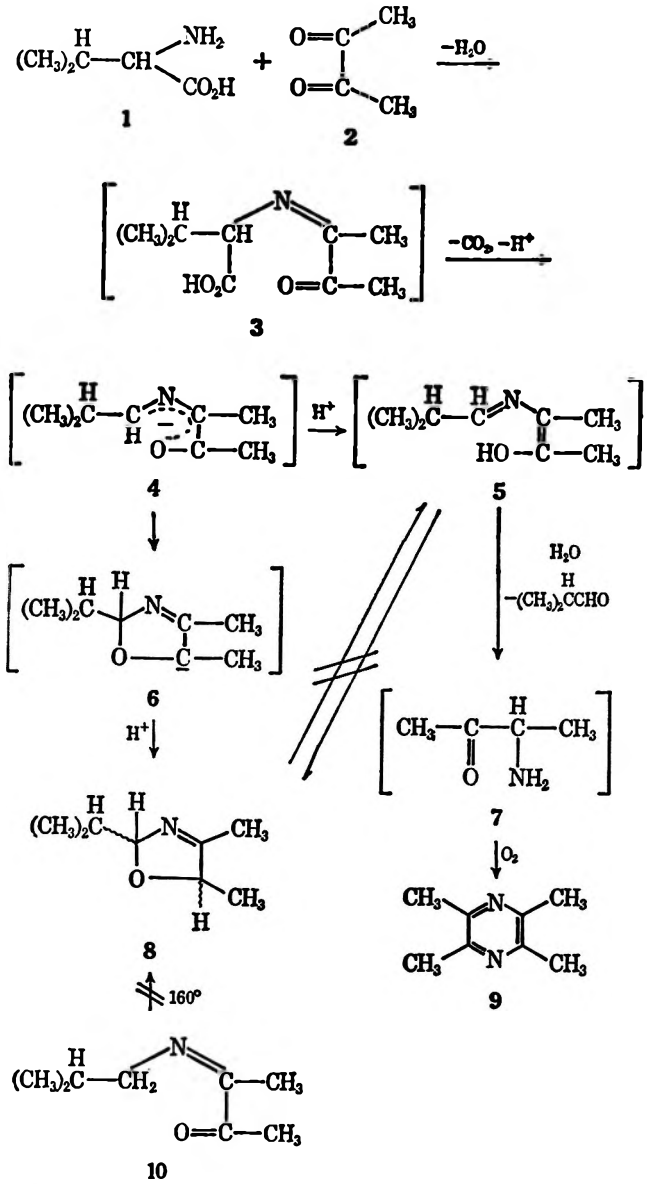
(1) A. Schönberg and R. Moubacher, *Chem. Rev.*, **50**, 261 (1952).

compounds. Historically the Strecker degradation has been studied as an "aldehyde-forming" process, and the fate of the amino acid nitrogen has not received much attention. A general reaction mechanism proposed by Schönberg, *et al.*,[2] suggested that reductive amination of the di- or polycarbonyl moiety takes place. An example of the evidence cited for this type of reductive amination is the formation of Ruhemann's purple in the α-amino acid–ninhydrin reaction.[3] In this Note we wish to present additional data to substantiate and elaborate Schönberg's reductive amination mechanism.

When equimolar amounts of DL-valine (**1**) and 2,3-butanedione (**2**) were refluxed in diglyme (*ca.* 160°), carbon dioxide was rapidly evolved and the diketone was completely consumed after 45 min as evidenced by the disappearance of its characteristic yellow color. The reaction mixture was steam distilled to separate volatile reaction products. Besides diglyme, the distillate contained isobutyraldehyde, tetramethylpyrazine (**9**, 9%),[4] and a mixture of *cis*- and *trans*-2-isopropyl-4,5-dimethyl-3-oxazoline (**8**, 4%). Compound **8** apparently represents the first example of a simple 3-oxazoline to be reported in the literature.[5,5a] The oxazoline structure was established by ir and nmr spectroscopy and from the fact that dehydrogenation of **8** with chloranil produced 2-isopropyl-4,5-dimethyloxazole in high yield. The nmr spectrum of **8** served to distinguish the 3-oxazoline from the otherwise possible 2-oxazoline isomer. A doublet centered at δ 1.29 ppm (J = 6 Hz) was attributed to the 5-methyl group. The hydrogen atom at C-5 gave a broad quartet centered at δ 4.48 ppm (J = 6 Hz). The methyl substituent at C-4 appeared as two sharp singlets at δ 1.92 and 1.94 ppm which together integrated for three protons.

A plausible explanation for the formation of the novel Strecker degradation products is shown in Scheme I. Initially **1** and **2** react with elimination of water to form a thermally unstable Schiff base **3**.[2] Decarboxylation of **3** probably leads to the mesomeric species **4**,[6] which, after protonation and hydrolysis, is transformed into isobutyraldehyde and 3-amino-2-butanone (**7**). The reductive amination product **7** was not observed, but, as expected,[7] underwent self-condensation and oxidation with molecular oxygen to yield **9**. The formation of **8** is still not clearly understood. Compound **8** could have been formed by ring–chain tautomerism involving **5**. This seemed unlikely, however, since no **9** formed when **8** was heated at 160° in aqueous diglyme. If **8** and **5** existed in equilibrium at 160°, part of the **5** present would likely have undergone hydrolysis to yield **7** and thence **9**. The fact that no **9** was formed suggested that

SCHEME I



equilibration of **5** and **8** did not occur under our reaction conditions. Ketimine **10** which could have been formed by decarboxylation of **3** was also shown not to be a precursor of **8**. A sample of **10** prepared by an alternate route gave no **8** upon heating for 1 hr at 160° in a sealed tube. In addition, **8** and **9** were not formed when an equimolar mixture of isobutylamine and **2** were subjected to the original Strecker degradation conditions. A more likely mechanism for the formation of **8** could involve cyclization of **4** followed by protonation of the resulting 3-oxazolinide ion **6**.

Experimental Section[8]

Reaction of DL-Valine (1) and 2,3-Butanedione (2).—A mixture containing 17.55 g of reagent grade **1** (0.150 mol), 12.00 ml

(2) A. Schönberg, R. Moubacher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948).

(3) M. Friedman and C. W. Sigel, *Biochemistry*, **5**, 478 (1966).

(4) Under similar conditions benzil and alanine produced tetraphenylpyrazine; *cf.* C. D. Hurd and C. M. Buess, *J. Amer. Chem. Soc.*, **78**, 5667 (1956).

(5) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience Publishers, New York, N. Y., 1967, p 316.

(5a) NOTE ADDED IN PROOF.—2,4,5-Trimethyl-3-oxazoline was recently reported to be a flavor constituent in boiled beef; *cf.* S. S. Chang, *et al.*, *Chem. Ind.* (London), 1639 (1968).

(6) F. G. Baddar, *J. Chem. Soc.*, S163 (1949). It is also possible that **5** may have been formed directly from **3** *via* a concerted process involving a cyclic transition state.

(7) Compound **7** was expected to yield **9** by analogy with 2-amino-1-phenyl-3-butanone which undergoes spontaneous conversion into 2,5-dibenzyl-3,6-dimethylpyrazine in high yield; *cf.* P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **79**, 95 (1928).

(8) Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord spectrophotometer. Samples were examined as liquid films unless otherwise noted. Ir absorption maxima data were rounded off to the nearest 0.05 μ. Nmr spectra were obtained using Varian HA-100 and A-60 instruments. Samples were run as 5–10% solutions in the solvents indicated and the data are recorded as follows: chemical shift in δ units downfield from tetramethylsilane (multiplicity, integrated number of protons, coupling constant, structural assignment). Multiplicity is indicated by letters: s = singlet, d = doublet, t = triplet, q = quartet, and m = complex multiplet. The mass spectrum of compound **8** was taken on an Atlas Model CH-4 spectrometer. Melting points were observed in open capillaries and are uncorrected. Microanalyses were performed by Mr. T. Atanovich and associates of these laboratories.

of redistilled **2** (0.137 mol) and 50 ml of freshly redistilled diglyme was stirred and refluxed for 45 min under N_2. The cooled reaction mixture was steam distilled and the 300 ml of pale yellow distillate obtained was saturated with NaCl and extracted three times with ether. The ether solution was dried ($MgSO_4$), concentrated and distilled to yield 7.56 g of oil, bp 52–70° (19 mm). Glpc analysis on a 5 ft × 0.25 in. column packed with 30/60 mesh Chromosorb W containing 15% Carbowax 20M indicated three compounds: isobutyraldehyde,[9] 0.3%, retention time (R_T) at 107°, 1.0 min; diglyme, 88%, R_T 15.2 min; and **8**, 11%, R_T 10.4 min. Samples of each substance were condensed from the glpc effluent (He) at Dry Ice temperature for characterization. Isobutyraldehyde and diglyme were identified by R_T and by their ir spectra. Compound **8** was a colorless, mobile liquid with a peculiar vegetablelike odor: ir 3.40, 3.50, 6.0 (C=N), 6.85, 7.00, 7.25, 7.30, 7.85, 8.15, 9.10, 9.30, 10.00 and 10.50 μ; 100 MHz nmr (CCl_4) δ 0.94 [d, 6, J = 6 Hz, $(CH_3)_2CH$], 1.29 (d, 3, J = 6 Hz, $CHCH_3$), 1.78 (broad m, 1, J = 6 Hz, >CH–), 1.92 and 1.94[10] (s, 3, CH_3C=), 4.48 (broad q, 1, J = 6 Hz, $>CHCH_3$) and 5.08 ppm [m, 1, –(O)CHN=]; mass spectrum (70 eV) m/e 141 (molecular ion) 139, 124, 98 (base peak), 97, 82, 71, 55, 56, 43, 42, 41, 39.

Anal. Calcd for $C_8H_{15}NO$: N, 9.92. Found: N, 9.9.

Treatment of the original distillation residue with excess picric acid in ethanol at 25° gave 3.62 g (9%) of **9** dipicrate, mp 185–190°. Recrystallization from ethanol gave yellow needles, mp 196.5–198° (lit.[11] mp 198.5–199.5°).

Anal. Calcd for $C_{20}H_{18}N_8O_{14}$: C, 40.41; H, 3.05; N, 18.84. Found: C, 39.9; H, 3.0; N, 18.7.

Decomposition of the picrate with aqueous NH_3 gave pure **9** whose ir spectrum (CS_2) was identical with that of an authentic specimen.

Chloranil Dehydrogenation of 8.—A solution of **8** (0.380 g, 0.00270 mol) in 4 ml of diglyme was treated with 0.749 g (0.00304 mol) of freshly recrystallized chloranil. The mixture was stirred and heated to 100° for 1 hr. On cooling, 0.688 g of solid (presumably tetrachlorohydroquinone) was filtered off and the filtrate was distilled. A single product was formed which codistilled with diglyme, bp 60.5–64.5° (14 mm). The compound was separated by preparative glpc using the column described above and was shown to be 2-isopropyl-4,5-dimethyloxazole by comparing ir and R_T data with those of the authentic substance. The oxazole was formed in 80% yield.

2-Isopropyl-4,5-dimethyloxazole was prepared by the method of Theilig[12] from isobutyramide and 3-bromo-2-butanone (Eastman Organic Chemicals, Rochester, N.Y.). The compound was a colorless liquid: bp 76–77° (20 mm); yield 70%; ir (CH_2Cl_2) 3.45, 6.05, 6.40, 7.25, 8.35, 8.85, 9.15, 9.40, 10.15 and 10.50 μ; 100 MHz nmr ($CDCl_3$) δ 1.28 [d, 6, J = 7 Hz, $(CH_3)_2CH$], 2.00 (s, 3, ring CH_3), 2.14 (s, 3, ring CH_3) and 2.94 ppm [m, 1, J = 7 Hz, $(CH_3)_2CH$].

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.6; H, 9.2; N, 9.5.

N-(1-Methyl-2-oxopropylidene)isobutylamine (10).—A solution containing 4.00 ml (0.0457 mol) of **2** in 100 ml of benezene was treated with 4.55 ml (0.0457 mol) of isobutylamine and refluxed under a Dean-Stark water separator for 1 hr (0.92 ml of water separated). The benezene solution was concentrated and the residue was distilled giving 3.13 g (49%) of **10**: bp 65–67° (16 mm); ir 3.40, 5.85 (C=O), 6.10 (C=N), 6.80, 7.40, 7.75, 9.00 and 10.20 μ; 60 MHz nmr ($CDCl_3$) δ 0.95 [d, 6, J = 6 Hz, $(CH_3)_2CH$], 1.80 and 1.82 [s, 4, (includes isopropyl methine H), CH_3C=N], 1.93 (m, J = 6 Hz, $>CHCH_2$), 2.22 (s, 3, $CH_3C(=O)$–), 3.10 and 3.12[13] (d, 2, J = 7 Hz, $=NCH_2$).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.4; H, 10.6; N, 10.3.

(9) No attempt was made to recover the bulk of the isobutyraldehyde which was presumably lost during distillation.

(10) Two nearly superimposed sharp singlets were observed, apparently due to a difference in chemical shifts of the 4-methyl group hydrogens in *cis* and *trans* **8**. The isomers of **8** were partially resolved on a 10 ft × 0.125 in. glpc column packed with 60/80 mesh Chromosorb W (HMDS treated) containing 15% SF-96.

(11) T. Ishiguro, E. Kitamura, and M. Matsumura, *Yakugaku Zasshi*, **78**, 150 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

(12) G. Theilig, *Chem. Ber.*, **86**, 96 (1953).

(13) Two singlets and two doublets believed due to *syn* and *anti* forms of the imine; *cf.* G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).

Registry No.—**1**, 516-06-3; **2**, 431-03-8; **8** (*cis*), 19519-42-7; **8** (*trans*), 19519-43-8; **9**, 1124-11-4; **10**, 19519-44-9; 2-isopropyl-4,5-dimethyloxazole, 19519-45-0.

Addition of Thiobenzophenone to Benzenediazonium-2-carboxylate[1]

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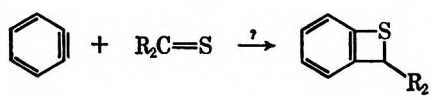
One possible way to prepare benzothietes[2] is by a 1,2 cycloaddition of a thiocarbonyl group to benzyne(1,2-dehydrobenzene). Examples are known of the cycloaddition of a thiocarbonyl group to double bonds,[3] but



the only reported interaction with a benzyne occurs with formation of a benzothiazole.[4] A number of 1,2 cycloadditions of benzyne with other types of compounds are known.[5]

To check the feasibility of adding thiocarbonyl groups to benzyne, thiobenzophenone and propylene oxide were added to a solution of the hydrochloride of benzenediazonium-2-carboxylate in 1,2-dichloroethane[6] and the solution was refluxed. Gas and heat were evolved and a white solid was obtained (44.5% yield, purified) which was identified as 2,2-diphenyl-3,1-benzoxathian-4-one (**1**), the δ-lactone of *o*-[(α-hydroxybenzhydryl)thio]benzoic acid, which has not been prepared before although a number of 3,1-benzoxathian-4-ones have been synthesized by other methods.[7] The identification was accomplished by determination of the compound's molecular weight, its empirical formula by analysis for elements, its mass spectrum, infrared

(1) This work was aided by Grant GP 5513 of the National Science Foundation and by Grant CA 08250 of the National Cancer Institute, National Institutes of Health.

(2) These compounds are interesting because of the possibility that their anions might show relative stabilization (they are formally 10-π-electron systems). The intervention of an anion in the reduction of a naphthothiete sulfone has been considered: D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964). Several substituted benzothiete derivatives not suited for the preparation of thiete anions have been prepared by the reduction of sulfones: L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965).

(3) H. Staudinger, *Helv. Chim. Acta*, **8**, 862 (1920); E. T. Kaiser and T. F. Wulfers, *J. Amer. Chem. Soc.*, **86**, 1897 (1964); W. J. Middleton, *J. Org. Chem.*, **30**, 1395 (1965); G. Tsuchihashi, M. Yamauchi, and M. Fukuyama, *Tetrahedron Lett.*, 1971 (1967); P. Rioult and J. Vialle, *Bull. Soc. Chim. Fr.*, 2883 (1967); K. Yamada, M. Yoshioka and N. Sugiyama, *J. Org. Chem.*, **33**, 1240 (1968).

(4) B. F. Hrutford and J. F. Bunnett, *J. Amer. Chem. Soc.*, **80**, 2021 (1958).

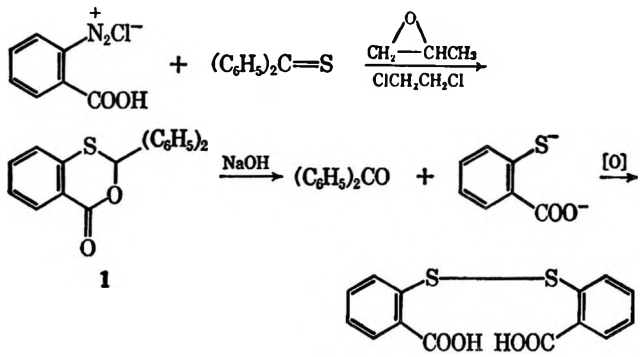
(5) (a) Reviewed by R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967; (b) L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience Publishers, New York, N. Y., 1967.

(6) For this method of preparation of benzyne, see L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).

(7) (a) D. T. Mowry, W. H. Yanko and E. L. Ringwald, *ibid.*, **69**, 2358 (1947); (b) A. Senning and S.-O. Lawesson, *Acta Chem. Scand.*, **14**, 2230 (1960); *Arkiv Kemi*, **17**, 261, 387, 489 (1961), and **18**, 95 (1961); (c) W. G. Bentrude and J. C. Martin, *J. Amer. Chem. Soc.*, **84**, 1564 (1962). See also references cited in these publications.

spectrum, ultraviolet spectrum, and proton nmr spectrum. Hydrolysis with base gave benzophenone, which was identified as its 2,4-dinitrophenylhydrazone, and 2,2′-dicarboxyphenyl disulfide, derived from 2-mercaptobenzoic acid which is oxidized by air (Scheme I). The disulfide was identical with a known sample with respect to its melting point and infrared (ir) spectrum.

SCHEME I

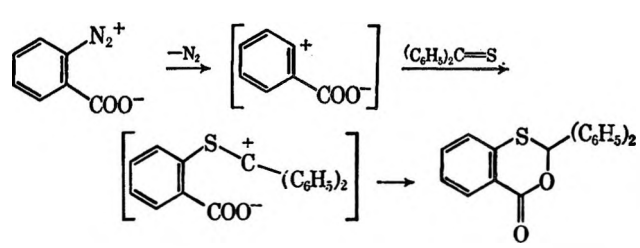


The mass spectrum of the benzoxathian-4-one had a prominent parent peak (P) at *m/e* 318. The base peak was at *m/e* 136 [P − $(C_6H_5)_2CO$], and other prominent peaks were at *m/e* 108 [P − $(C_6H_5)_2COCO$] and *m/e* 105 [P − $(C_6H_5)_2COS$ + H)] These fragments support the structure assignment.

Absorption in the ir spectrum at 1730 cm^{-1} is consistent with the absorption at 1724 cm^{-1} (5.80 μ) reported for several 3,1-benzoxathian-4-ones.[7b] The ultraviolet (uv) spectrum in methanol showed absorptions at 233, 265, and 330 mμ which are not inconsistent with those expected of an *o*-thio-substituted benzoic acid derivative.[8] The proton nmr spectrum showed only absorption centered at δ 7.4, attributable to aromatic protons.

Formation of 2,2-diphenyl-3,1-benzoxathian-4-one suggests that an intermediate in benzyne formation from benzenediazonium-2-carboxylate is being trapped by the thiobenzophenone. A possible mechanism is shown in Scheme II. Recently, evidence has been

SCHEME II



obtained for a two-step mechanism in the formation of benzyne[9] and there have been earlier indications of the nonsynchronous loss of nitrogen and carbon dioxide from benzenediazonium-2-carboxylate.[10]

(8) The uv spectrum of *o*-thioalkyl benzoate esters appear not to have been reported, but (2-carboxyphenyl)thioglycolic acid is reported to have maxima at 223, 258, and 316 mμ and *o*-mercaptobenzoic acid has absorption at 220 and 313 mμ: "Absorption Spectra in the Ultraviolet and Visible Region," Vol. 1, L. Lang, Ed., Academic Press, New York, N. Y., 1961, pp 95, 99.

(9) R. Gompper, G. Seybold, and B. Schmolke, *Angew. Chem. Intern. Ed. Engl.*, **7**, 389 (1968).

(10) M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, **82**, 3802 (1960); S. Yaroslavsky, *Tetrahedron Lett.*, 1503 (1965); R. Knorr, *Chem. Ber.*, **98**, 4038 (1965); S. Yaroslavsky, *Chem. Ind.* (London), 765 (1965); M. Kise, T. Asari, N. Furukawa and S. Oae, *ibid.*, 276 (1967). See also ref 5a.

Experimental Section

Benzenediazonium-2-carboxylate Hydrochloride.[6]—Anthranilic acid (10.95 g, 8 × 10^{-2} mol) was dissolved in 120 ml of absolute ethanol in a 400-ml beaker. The solution was stirred magnetically in a dish containing ice. To this was added 8 ml of concentrated hydrochloric acid followed by 20 ml of isoamyl nitrite. The reaction mixture was stirred for 10 min and 120 ml of absolute ether was added. Pale pink crystals precipitated from solution as stirring was continued for an additional 5 min. The crystals were filtered through a polyethylene funnel and washed with 150 ml of absolute ether. The product was dried in air to give 14.1 g (7.58 × 10^{-2} mol, 95%).

2,2-Diphenyl-3,1-benzoxathian-4-one.—A 250-ml, three-necked, round-bottomed flask was fitted with a condenser, ground-glass stopper, and a standard taper stopcock. The flask was swept with nitrogen for 20 min and the flow was continued throughout the reaction. A solution of benzenediazonium-2-carboxylate hydrochloride (4.0 g, 2.17 × 10^{-2} mol) in 100 ml of 1,2-dichloroethane was added to the flask. In rapid succession thiobenzophenone[11] (5.0 g, 2.52 × 10^{-2} mol) and propylene oxide (3.9 ml, 5.46 × 10^{-2} mol) were added, and the reaction mixture was refluxed for 24 hr. The solution turned wine-red 0.5 hr after the final addition was complete. The reaction mixture was cooled and the solvent was removed by means of a rotating evaporator leaving a wine-red oil. The oil was dissolved in a minimum amount of benzene and chromatographed on a Florisil (100–200 mesh) column. Elution with benzene gave a number of bands. A blue and purple band ran together and came off the column first. The solvent was evaporated over a steam bath in a nitrogen atmosphere leaving a deep violet oil. This oil was dissolved in a minimum amount of benzene and chromatographed on a Florisil (100–200 mesh) column. Elution with 2:1 ligroin–benzene afforded the following bands in their order of elution: dark blue, tan, clear, orange, and pink.

The first band yielded a blue oil after the evaporation of solvent under nitrogen. Recrystallization from petroleum ether afforded 1.12 g of deep violet needles, mp 51–52° (uncor), identified as thiobenzophenone by mixture melting point, 51–52° (lit.[11] mp 53–54°), with an authentic sample. This represents a return of 5.7 × 10^{-3} mol or 22.4% of the starting material.

After the evaporation of solvent the tan band left a pale tan oil. Crystallization and subsequent recrystallization from ethanol yielded 0.17 g (1.13 × 10^{-3} mol, 5.2%) of tan solid, mp 109° (uncor). The solid was identified as biphenylene by comparison of infrared (ir) spectra and mixture melting point,[12] 108.5–109° (lit.[13] mp 109–110°).

The clear band afforded a white solid after the removal of solvent. Two recrystallizations from methanol yielded 3.16 g (9.95 × 10^{-3} mol, 44.5%) of pure 2,2-diphenyl-3,1-benzoxathian-4-one: mp 185° (uncor); λ_{max}^{MeOH} 233, 265, and 330 mμ.

Anal. Calcd for $C_{20}H_{14}O_2S$: C, 75.47; H, 4.40; O, 10.10; S, 10.10; mol wt, 318. Found: C, 75.67; H, 4.40; O, 10.00; S, 9.89; mol wt, 320 (osmometric).

Molecular weight determination using the mass spectrometer gave a value of 318. The ir absorptions are as follows: 1730 (s), 1600 (m), 1490 (m), 1480 (m), 1445 (m), 1270 (m), 1240 (m), 1215 (m), 1170 (m), 1125 (m), 1105 (m), 1050 (m), 1030 (m), 1000 (m), 960 (w), 955 (w), 938 (w), 928 (w), 915 (w), 905 (w), 887 (w), 857 (w), 850 (w), 835 (w), 819 (w), 810 (w), 797 (m), 753 (s), 747 (s), 720 (w), and 695 (s) cm^{-1}. The nmr spectrum shows only one absorption, a multiplet centered at δ 7.4 (60 MHz).

Hydrolysis of 2,2-Diphenyl-3,1-benzoxathian-4-one.—A 50-ml, one-necked, round-bottomed flask was fitted with a condenser and magnetic stir bar. A mixture of 15 ml of 1,4-dioxane and 15 ml of 6 *N* sodium hydroxide was placed in the flask. To this was added 2,2-diphenyl-3,1-benzoxathian-4-one (0.376 g, 1.18 × 10^{-3} mol) and the solution was refluxed for 15 hr. The reaction mixture was cooled and the aqueous layer was separated. The organic layer was washed twice with two 20-ml portions of 6 *N* sodium hydroxide which were added to the aqueous layer collected previously. This was acidified with concentrated hydro-

(11) B. F. Gofton and E. A. Braude, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 927.

(12) We are indebted to J. M. Balquist for an authentic sample and spectrum of biphenylene.

(13) W. C. Lothrop, *J. Amer. Chem. Soc.*, **63**, 1187 (1941).

chloric acid. A white inorganic solid, which did not burn, precipitated on cooling. Its ir spectrum showed the following absorptions: 3000 (m), 2640 (m), 2540 (m), 1675 (s), 1580 (m), 1550 (m), 1455 (m), 1425 (m, sh), 1410 (m), 1305 (m), 1280 (m), 1255 (s), 1200–1030 (s, broad), 900 (m), 810 (m), 740 (s), and 690 (m) cm^{-1}. The solid was refluxed for 24 hr in 50 ml of concentrated hydrochloric acid. A tan solid precipitated when the solution was cooled. The filtrate was washed with two 50-ml portions of chloroform which were combined and evaporated to dryness leaving an additional amount of the tan solid. Recrystallization from methanol–water afforded 0.287 g (8.98×10^{-4} mol, 79.9%) of pure tan solid, mp 302–303° (uncor). The ir spectrum showed the following absorptions: 3000–2800 (m), 2640 (w), 2540 (w), 1680 (s), 1580 (m), 1555 (m), 1455 (m), 1410 (m), 1305 (m), 1285 (m), 1255 (s), 1165 (w), 1145 (m), 1115 (w), 1055 (m), 1035 (m), 960 (w), 900 (m, broad), 810 (m), 740 (s), and 693 (m) cm^{-1}. Based on the ir spectrum and a mixture melting point, 301.5–302.5° (authentic sample from Aldrich Chemical Co., mp 304°), the compound was identified as 2,2′-dicarboxyphenyl disulfide.

The dioxane was removed by means of a rotating evaporator leaving 0.153 g (8.42×10^{-4} mol, 71.2%) of a clear oil. A comparison of the ir spectrum of the oil with an authentic sample of benzophenone indicated that the two compounds were identical. Treatment with an acidic solution of 2,4-dinitrophenylhydrazine gave a bright orange solid. This was dissolved in a minimum amount of chloroform and chromatographed on a Florisil (100–200 mesh) column. The column was eluted with chloroform. Two bands separated with the first being bright orange and the second a deep red. After evaporation of solvent and recrystallization from chloroform–ethanol the first band afforded benzophenone 2,4-dinitrophenylhydrazone, mp 237–238°, mmp 237–238°. An authentic sample of the 2,4-dinitrophenylhydrazone was prepared from benzophenone and its ir spectrum and melting point (238°) were identical with those of the hydrazone obtained from the product of hydrolysis of the 2,2-diphenyl-3,1-benzoxathian-4-one. The red band afforded 2,4-dinitrophenylhydrazine, mp 199°.

Registry No.—Thiobenzophenone, 1450-31-3; benzenediazonium-2-carboxylate, 18761-40-5; **1**, 19185-81-0.

2,4,5-Triphenyl-2H-1,3-oxathiole from Desyl Thiocyanate[1]

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Received September 12, 1968

A pale yellow solid, $C_{21}H_{16}OS$ (55% yield, mp 77–78°), was obtained when desyl thiocyanate (2-thiocyanato-2-phenylacetophenone) was treated with excess sodium hydride in 1,2-dimethoxyethane. *cis*-Dibenzoylstilbene episulfide (2,3-dibenzoyl-2,3-diphenylthiirane, 32%) and *cis*-dibenzoylstilbene (8%) were isolated also from the reaction mixture. When the sodium hydride was not in excess, a 75–85% yield of yellow *cis*-dibenzoylstilbene episulfide was obtained, as had been reported previously.[2]

The data for compound $C_{21}H_{16}OS$ are consistent with the structure 2,4,5-triphenyl-2H-1,3-oxathiole (**1**). Few simple 1,3-oxathioles are known,[3] and this new method may be applicable generally to the synthesis of 2,4,5-triaryl-1,3-oxathioles. The structure of the oxathiole was deduced from an analysis for elements, a molecular weight determination, the infrared, ultraviolet, and proton nmr spectra, and the mass spectrum. The infrared spectrum showed absorption at 3030 (aromatic protons), 2880 (benzylic proton), 1620 (carbon–carbon double bond), 1245 (asymmetric carbon–oxygen stretching), and 1060 cm^{-1} (symmetric carbon–oxygen stretching). Absorption in the infrared spectrum of 2-trichloromethyl-4,5-diphenyl-1,3-dioxole at 1667, 1250, and 1124 cm^{-1} has been ascribed to the carbon–carbon double bond and to the carbon–oxygen bonds, respectively.[4] In 1,3-dioxole itself there is absorption at 1631, 1176–1156, and 1087–1075 cm^{-1}.[5] The ultraviolet spectrum of the oxathiole in 95% ethanol shows maxima at 225 mμ (ε 18,600) and 342 mμ (ε 6760). The ultraviolet spectrum of 5,6-dihydro-1,4-oxathiin has an absorption maximum at 229 mμ (ε 3820)[6] and 2,3-diphenyl-5,6-dihydrooxathiin is reported to be pale yellow[7] but spectroscopic data were not given.

The proton nmr spectrum (60 MHz, $CDCl_3$) shows a complex multiplet at 433 Hz and a singlet at 418 Hz relative to tetramethylsilane. The ratio of the areas of the two absorptions was 14.4:1 which is close to the 15:1 ratio calculated for the oxathiole. The benzylic proton presumably causes the absorption at 418 Hz; it is at low field because it is adjacent to an oxygen atom, a sulfur atom, and a phenyl ring. Diamagnetic anisotropy effects of the carbon–carbon double bond, the sulfur atom, and the phenyl rings probably have a role in deshielding the benzylic proton. The absorption of the aliphatic proton in 2-trichloromethyl-4,5-diphenyl-1,3-dioxole appears at 373 Hz.[4]

Mass spectrometry (Scheme I) supports the molecular formula $C_{21}H_{16}OS$. The molecular ion (P) was also the base peak and prominent fragments occurred at *m/e* 284 (P − S), 283 (P − SH), 239 (P − C_6H_5), 211 (P − C_6H_5CO), 210 (P − C_6H_5CHO), 178 (P − C_6H_5CHO − S), 167 and 165. The fragments at *m/e* 165 and 167 may be fluorenyl-type ions whose formation would involve a migration of a phenyl group. Treatment of a small amount of the oxathiole with refluxing ethanolic hydrogen chloride gave hydrogen

(1) This work was aided by Grant GP-5513 of the National Science Foundation and by Grant CA 08250 of the National Cancer Institute, National Institutes of Health.

(2) D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, **30**, 636 (1965); D. C. Dittmer, G. E. Kuhlmann, G. C. Levy, and R. Keene, paper in preparation.

(3) For a recent review of 1,3-oxathioles, see D. S. Breslow and H. Skolnik, "Heterocyclic Compounds, Multisulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles," Part One, A. Weissburger, Ed., Interscience Publishers, Inc., New York, N. Y., 1966, p 203 ff.

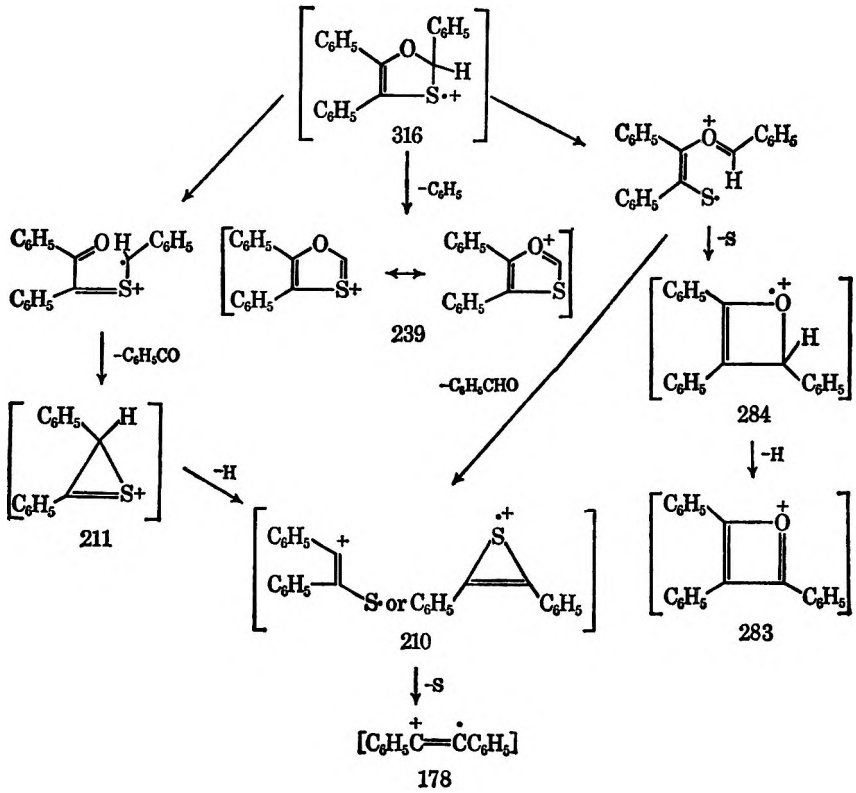
(4) H. J. Dietrich and J. V. Karabinos, *J. Org. Chem.*, **31**, 1127 (1966).

(5) N. D. Field, *J. Amer. Chem. Soc.*, **83**, 3504 (1961).

(6) W. E. Parham, I. Gordon, and J. D. Swalen, *ibid.*, **74**, 1824 (1952).

(7) J. R. Marshall and H. A. Stevenson, *J. Chem. Soc.*, 2360 (1959).

SCHEME I

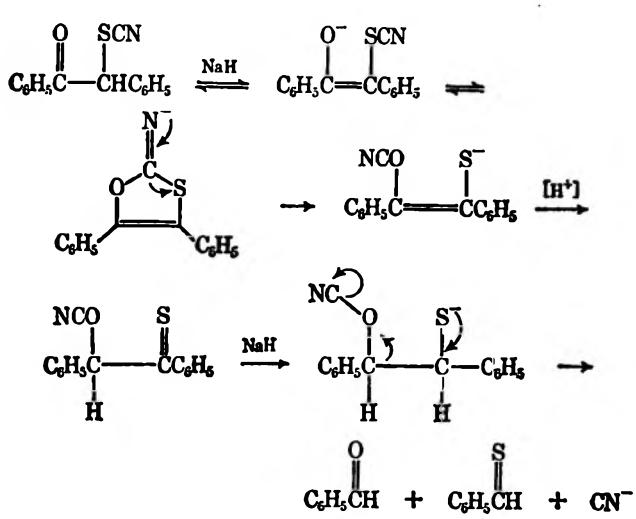


sulfide [a result consistent with hydrolysis of the oxathiole to monothiobenzoin (2-mercapto-2-phenylacetophenone) and loss of sulfur by hydrolysis] and benzaldehyde, which was identified as a 2,4-dinitrophenylhydrazone. Thin layer chromatography of the hydrolysis products indicated the presence of the benzaldehyde and benzoin. A third spot of unknown origin was observed.

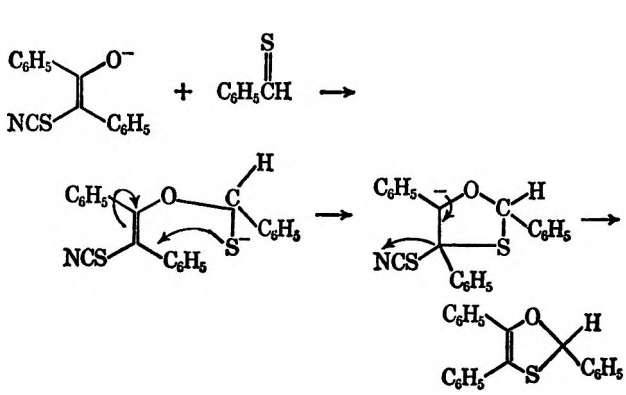
Alternate structures, 3,4,5-triphenyl-3H-1,2-oxathiole and 3,4,5-triphenyl-5H-1,2-oxathiole, are less in accord with the data. The ultraviolet spectra of these derivatives should be similar to the spectra of vinyl sulfides or vinyl ethers, none of which has absorption at as high a wavelength as the compound obtained from desyl thiocyanate in which both oxygen and sulfur are conjugated with the carbon–carbon double bond. The oxathiole does not give a test with acidified potassium iodide and starch paper as sulfenate esters (thioperoxides) are reported to do.[8] Formation of benzaldehyde on hydrolysis of the oxathiole is more difficult to rationalize on the basis of the 1,2-oxathiole structures.

Schemes II and II show the formation of the oxathiole under the reaction conditions used beginning with the enolization of desyl thiocyanate. This enol can give 1-mercapto-2-cyanato-1,2-diphenylethane[9] which may decompose to thiobenzaldehyde and benzaldehyde. The thiobenzaldehyde, presumably being more reactive than benzaldehyde,[10] may react with the enolate anion of desyl thiocyanate with formation of the oxathiole. Desyl thiocyanate may be the source of protons used in Scheme III.

SCHEME II



SCHEME III



(8) T. L. Moore and D. E. O'Connor, *J. Org. Chem.*, **31**, 3587 (1966).

(9) Compare the scheme for the formation of episulfides from epoxides by treatment with thiocyanate ions: E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951).

(10) J. C. Powers and F. H. Westheimer, *ibid.*, **82**, 5431 (1960).

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer and ultraviolet spectra were taken on a Perkin-Elmer Model 202 spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrometer, and mass spectra on a Perkin-Elmer Hitachi RMU-6E spectrometer. Melting points were taken on a Fisher-Johns melting point apparatus. The analysis for elements was done by Galbraith Laboratories, Inc., Knoxville, Tenn., and by the Scandinavian Micro-Analytical Laboratory, Herlev, Denmark. Desyl thiocyanate was prepared from desyl chloride and potassium thiocyanate.[2]

2,4,5-Triphenyl-2H-1,3-oxathiole (1).—Sodium hydride (13.4 g, 0.312 mol, 56% dispersion in mineral oil) was added to 100 ml of dry dimethoxyethane. A solution of desyl thiocyanate (48.7 g, 0.192 mol) in 200 ml of dimethoxyethane was cooled to −10° and added in three portions over a 20-min period to the sodium hydride which also was cooled to −10°. The temperature quickly rose to room temperature. Stirring was continued for 90 min. Water (3 ml) was added to destroy any remaining sodium hydride, and the inorganic salts were removed by filtration and washed with two 30-ml portions of ether. The solvents were then removed on a rotary evaporator, the residue was dissolved in 350 ml of ether and washed with two 25-ml portions of water, and the ether solution was dried over anhydrous magnesium sulfate overnight. Evaporation of the solvent to about 200 ml precipitated *cis*-dibenzoylstilbene (3.10 g, 0.00795 mol, 8.3%) after several hours. Recrystallization from glacial acetic acid gave white crystals, mp 211–212° and mmp 209.5–211° (lit.[11] mp 210.0–210.8°). The olefin was further identified by thin layer chromatography (tlc) and its infrared and ultraviolet spectra which were the same as those reported.[11,12] The material remaining in the ether solution was chromatographed on a silicic acid column with benzene as eluent. A light yellow band, which preceded the band of *cis*-dibenzoylstilbene episulfide, was collected. A total of 11.1 g of crude 2,4,5-triphenyl-2H-1,3-oxathiole (0.0352 mol, 55%) and episulfide (13.1 g, 0.0311 mol, 32%) was collected. The oxathiole was recrystallized from petroleum ether (66–78°) several times and purified on a silicic acid column using a 4:1 pentane–benzene mixture as the eluent. Yellow crystals, mp 77–78°, were obtained which gave only one spot (R_f 0.67) on a tlc plate (Merck silica gel GF_{254}, benzene eluent). *Anal.* Calcd for $C_{21}H_{16}OS$: C, 79.71; H, 5.10; S, 10.13; mol wt, 316. Found: C, 79.57; H, 5.16; S, 10.19; mol wt, 328 (osmometry in acetone). The infrared spectrum of the oxathiole (KBr disk) exhibited bands at 3030 (w), 2880 (w), 1620 (m), 1600 (m), 1570 (m), 1495 (m), 1440 (m), 1350 (w), 1315 (w), 1245 (s), 1210 (m), 1175 (w), 1155 (w), 1080 (m), 1070 (m), 1060 (s), 1020 (m), 990 (m), 955 (m), 920 (w), 910 (w), 875 (m), 827 (w), 781 (w), 765 (m), 750 (s), 710 (s), and 691 (s) cm^{-1}. The ultraviolet spectrum was obtained in two solvents: $\lambda_{max}^{CH_3CN}$ 226, 342 mμ; $\lambda_{max}^{95\%C_2H_5OH}$ 225 mμ (ε 18,600), 342 mμ (ε 6760).

Mass spectrometry also was used to establish the empirical formula of the oxathiole using the isotope abundances of the molecular ion *m/e* 316 (P) at *m/e* 317 (P + 1) and *m/e* 318 (P + 2). *Anal.* Calcd[13] for $C_{21}H_{16}OS$: 100[(P + 1)/P], 23.8; 100[(P + 2)/P], 7.1. Found: 100[(P + 1)/P], 22.6; 100[(P + 2)/P], 7.3. The mass spectrum of the oxathiole was obtained at 110° using the direct inlet at 20-ev ionizing potential:[14] *m/e* 318 (7.62), 317 (26.3), 316 (100), 284 (15.5), 283 (5.50), 239 (5.47), 212 (6.58), 211 (38.8), 210 (20.4), 179 (6.66), 178 (28.4), 167 (23.4), 166 (5.28), 165 (26.0), 121 (7.86), 106 (7.95), 105 (9.54).

The proton nmr spectrum (60 MHz in $CDCl_3$) of the oxathiole had a complex multiplet centered at 433 Hz and a sharp resonance absorption at 418 Hz relative to tetramethylsilane. The ratio of the high-field absorbance to the low-field absorbance was 1:14.4 (calcd 1:15).

When the oxathiole (0.051 g, 0.00016 mol) was refluxed in 20 ml of 95% ethanol and 1 ml of concentrated hydrochloric acid, hydrogen sulfide was evolved as detected by lead acetate paper. Thin layer chromatography indicated also the presence of benzaldehyde, benzoin, and possibly monothiobenzoin. The solution from hydrolysis of the oxathiole was treated with an amount of 2,4-dinitrophenylhydrazine reagent[15] sufficient only to react with the benzaldehyde. The orange precipitate was filtered and recrystallized from a commercial mixture of xylenes to give benzaldehyde 2,4-dinitrophenylhydrazone, mp 240–241° (lit.[16] mp 239–240°). The infrared spectrum of the derivative was identical with that of authentic benzaldehyde 2,4-dinitrophenylhydrazone.[17]

Registry No.—**1**, 19206-52-1; desyl thiocyanate, 19203-00-0.

(11) N. M. Bikales and E. I. Becker, *J. Org. Chem.*, **21**, 1405 (1956).
(12) R. E. Lutz, W. J. Welstead, Jr., R. G. Bass, and J. I. Dale, *ibid.*, **27**, 1111 (1962).
(13) J. H. Beynon and A. E. Williams, "Mass Abundance Tables for Use in Mass Spectroscopy," Elsevier Publishing Co., New York, N. Y., 1963.
(14) Percentage of base peak is given in parenthesis. Only fragments which were 5% or greater of the base peak and above *m/e* 104 are tabulated.
(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 219.
(16) G. D. Johnson, *J. Amer. Chem. Soc.*, **75**, 2720 (1953).
(17) "Sadtler Standard Spectra," Midget ed, The Sadtler Research Laboratories, Philadelphia, Pa., 1962, No. 4156.

Hydrolysis and Decarboxylation of Diethyl 1-Methyl-4-nitro-5-imidazolylmalonate

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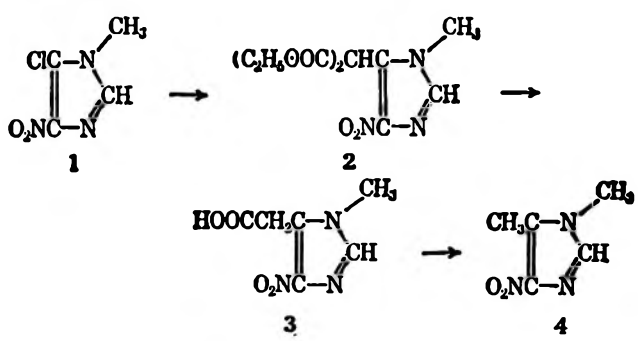
During a study of certain imidazole derivatives, 1-methyl-4-nitro-5-imidazolylacetic acid (**3**) was desired. A convenient route appeared to be the conversion of 5-chloro-1-methyl-4-nitroimidazole (**1**)[2] into its corresponding diethyl 5-imidazolylmalonate (**2**) followed by hydrolysis and decarboxylation. Starting



compound **1** was prepared by nitration of 5-chloro-1-methylimidazole.[3–5]

The formation of the substituted malonic ester **2** was achieved in good yield by a malonic ester condensation reaction. However, when acid hydrolysis (1.2 *N* aqueous HCl) of **2** was attempted, 1,5-dimethyl-4-nitroimidazole (**4**)[6] was isolated as the sole product in high yield.[7]

(1) Deceased.
(2) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).
(3) O. Wallach and A. Boehringer, *Ann.*, **184**, 50 (1877).
(4) O. Wallach, *ibid.*, **214**, 257 (1882).
(5) F. F. Blicke and H. C. Godt, Jr., *J. Amer. Chem. Soc.*, **76**, 3653 (1954).
(6) A. Windaus [*Ber.*, **42**, 758 (1909)] prepared this compound by nitrating 1,5-dimethylimidazole with fuming nitric acid.

If **3** is formed but decarboxylates rapidly to **4** through its carbanion,[7] carrying out the reaction in stronger acid concentration should inhibit the conversion of **3** into **4** and permit the isolation of **3**. Nmr studies of the reaction in various acid concentrations aided in establishing the best conditions for obtaining **3**. When the reaction was performed in 6 *N* aqueous HCl, **3** was isolated in high yield.

Experimental Section

The nmr spectral data were obtained on a Varian A-60 nmr spectrophotometer using dimethyl sulfoxide-d_6 as solvent. Chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS).

5-Chloro-1-methylimidazole[5] had the following nmr analysis: δ 3.60 ppm (CH_3, 1 position, 3 H, doublet, J = 0.9 Hz), 7.76 ppm (H, 2 position, 1 H), 7.00 ppm (H, 4 position, 1 H, doublet, J = 1.0 Hz).

5-Chloro-1-methyl-4-nitroimidazole (1)[2] had the following nmr analysis: δ 3.76 ppm (CH_3, 1 position, 3 H, doublet, J = 0.4 Hz), 8.02 ppm (H, 2 position, 1 H, unresolved multiplet).

Diethyl 1-Methyl-4-nitro-5-imidazolylmalonate (2).—Diethyl malonate (144 g, 0.9 mol) was added dropwise with stirring to a solution of sodium metal (17.4 g, 0.75 g-atom) in 750 ml of absolute ethanol. A Soxhlet extractor, containing 48.3 g (0.3 mol) of **1** in its thimble, was attached to the reaction flask, and the reaction mixture was refluxed for 12 hr after all of **1** had dissolved. The ethanol was removed under reduced pressure (steam bath). The residue was dissolved in 750 ml of water extracted with ether, and acidified with dilute hydrochloric acid. The aqueous layer was separated from the orange oil, and extracted with chloroform. The oil and chloroform extract were combined and filtered. After stripping of the chloroform, the oil solidified on cooling. The product was recrystallized from diisopropyl ether–ethanol (3:1): yield, 70.5 g (82.4%); mp 67°.

Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 46.31; H, 5.30; N, 14.73. Found: C, 46.60; H, 5.19; N, 14.65.

Nmr analysis showed δ 3.84 ppm (CH_3, 1 position, 3 H, doublet, J = 0.3 Hz), 7.93 ppm (H, 2 position, 1 H, unresolved multiplet), 5.94 ppm (CH, 5 position, 1 H, singlet), 4.28 ppm (CH_2, ester, 4 H, quartet), 1.22 ppm (CH_3, ester, 6 H, triplet).

1,5-Dimethyl-4-nitroimidazole (4).—Compound **2** (17.1 g, 0.06 mol) and 250 ml of 1.2 *N* aqueous HCl were refluxed (100°) for 12 hr. The solution was cooled to 25° and made basic with solid sodium carbonate. The precipitated product was filtered, and the aqueous filtrate extracted with chloroform. The solid obtained by evaporation of the chloroform extract was combined with the rest of the product, and recrystallized from water: yield, 6.8 g (80%); mp 162° (lit.[6] mp 160–161°).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.92; H, 5.18; N, 29.60.

Nmr analysis showed δ 3.68 ppm (CH_3, 1 position, 3 H, doublet, J = ~0.3 Hz), 7.74 ppm (H, 2 position, 1 H, unresolved multiplet), 2.57 ppm (CH_3, 5 position, 3 H, singlet).

Following the course of the above reaction in refluxing 1.2 *N* aqueous HCl by nmr,[8] **3** had formed in large amounts within 30 min. Also **4** was present in significant amounts by this time. After 12 hr, essentially complete conversion into **4** had occurred.

1-Methyl-4-nitro-5-imidazolylacetic Acid (3).—A solution of **2** (8.5 g, 0.03 mol) in 85 ml of 6 *N* aqueous HCl was refluxed (104°) for 25 min. The reaction mixture was cooled to 0° and neutralized to pH of 2.5 (pH meter) using solid sodium carbonate. The product **3** precipitated and was filtered. Purification was achieved by dissolving in 10% sodium carbonate solution at 10°, filtering, and precipitating the product with 6 *N* aqueous HCl. The product was filtered, washed with water, and dried: yield, 4.8 g (87.3%); mp 144° dec.

Anal. Calcd for $C_6H_7N_3O_4$: C, 38.92; H, 3.81; N, 22.70; neut equiv, 185.1. Found: C, 38.65; H, 3.87; N, 22.73; neut equiv, 185.3.

Nmr analysis showed δ 3.70 ppm (CH_3, 1 position, 3 H), 4.13 ppm (CH_2, 5 position, 2 H), 7.69 ppm (H, 2 position, 1 H). Neither spin coupling nor carboxyl hydrogen was observed.

The course of the above reaction in refluxing 6 *N* aqueous HCl was followed by nmr. Compound **3** was present in greatest amount within 30 min after reflux had begun with no **2** or **4** evident. Only after 5 hr at reflux did **4** become apparent. By this time, the nmr spectrum showed evidence of competing reactions taking place with only a small buildup of **4**. After 12 hr at reflux, only 5.9% **4** was isolated from the reaction mixture. The nmr spectrum still indicated the presence of a significant amount of **3**.

Registry No.—II, 7464-80-4.

Acknowledgment.—The authors thank Drs. M. W. Dietrich and M. D. Wolfinger for assistance with the nmr spectral data.

(7) Several other nitrogen-containing heterocyclic-substituted carboxylic and acetic acids are known to undergo decarboxylations with relative ease. For a review with references and mechanistic considerations, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 348–351.

(8) Aqueous HCl (6 *N*) was added to the initial aliquots, after cooling, to clarify the solutions.

Oxidation of Some Cyclic Benzylic Hydrazines Derived from Naphthalene, Acenaphthene, and Diphenylmethane

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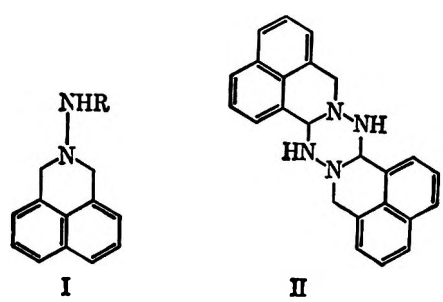
Although the oxidation of 1,1-dibenzylhydrazines with the formation of hydrocarbon products appears to be a general reaction, oxidation of cyclic benzylic hydrazine I (R = H) by means of mercuric oxide or other oxidants gave none of the expected acenaphthene.[1] Instead only the corresponding tetrazene was isolated.



I II

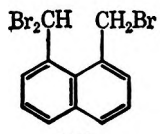
It has now been found that treatment of the *p*-toluenesulfonyl derivative (I, R = $SO_2C_6H_4CH_3$-*p*) with sodium ethoxide in ethanol, or simply by warming in ethanol alone, yields neither acenaphthene nor the tetrazene but rather the high melting compound II.[2] Structure II was established by an alternate synthesis involving treatment of tribromide III with hydrazine according to the method used by Schmitz[3] to obtain the analogous hexahydro-*s*-tetrazine IV from 2-(2-bromo-

(1) L. A. Carpino, *J. Amer. Chem. Soc.*, **85**, 2144 (1963).

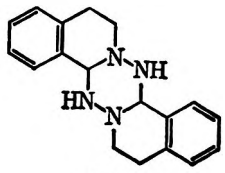
(2) Depending on the specific case there may or may not be a correspondence between the products obtained by direct oxidation of a 1,1-disubstituted hydrazine and those obtained by alkaline degradation of the *p*-toluenesulfonyl derivative. See also D. M. Lemal, T. W. Rave, and S. D. McGregor, *J. Amer. Chem. Soc.*, **85**, 1944 (1963).

(3) E. Schmitz, *Ber.*, **91**, 1495 (1958). Several attempts to obtain an 8-halomethyl-1-naphthaldehyde having been unsuccessful, tribromodimethylnaphthalene was used as a convenient substitute.

ethyl)benzaldehyde. Tetrazine IV is also formed by oxidation[4] of N-aminotetrahydroisoquinoline and alkaline degradation of its *p*-toluenesulfonyl derivarive.

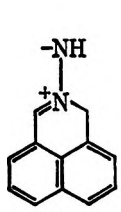


III

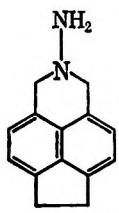


IV

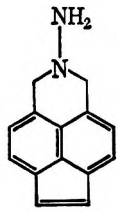
Formation of II from III presumably involves the dipolar intermediate V or some closely related species.[5]



V



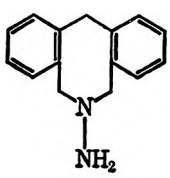
VI



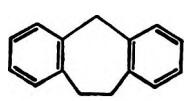
VII

Ionization[6] of I (R = $SO_2C_6H_4CH_3$-*p*) followed by deprotonation at carbon rather than nitrogen would lead to the same intermediate.

The results of an examination of three additional benzylic hydrazines (VI–VIII) provide a rationale for



VIII



IX

the supposedly anomalous lack of conversion of I into acenaphthene. Whereas oxidation of VI[7] by means of activated manganese dioxide gave none of the expected hydrocarbon, pyracene, similar treatment of VII[7] gave 1,2-dihydropyracylene, albeit in very low yield (8–15%). This suggests that in the latter case reaction can occur, at least to a limited extent, through a pathway involving fragmentation of the intermediate azamine to the 1,8-quinodimethane.[7] In the case of I and VI such a pathway is not available. Nevertheless it has been difficult to understand why reaction in these two cases could not proceed through a transition state similar to that which is involved in the case of simple acyclic benzylic hydrazines. An interesting case is provided by VIII which cannot undergo fragmentation to a quinodimethane but is far more flexible than I. In fact alkaline degradation of the *p*-toluenesulfonyl derivative of VIII has been found to give the corresponding hydrocarbon (IX) in good yield. One possible explanation for the lack of conversion of I into asenaphthene can therefore be given in terms of the compression involved in the transition state for collapse of the intermediate azamine to the strained[8] acenaphthene system.[9] Since this strain should be even greater in the conversion of VII into 1,2-dihydropyracylene the importance of an alternate fragmentation pathway to hydrocarbon products is clearly indicated. For the same reason N-aminodihydroisoindoles are readily converted into the still more highly strained benzocyclobutenes and in this case the fragmentation pathway is confirmed by the stereochemistry of the reaction.[10]

(4) E. Höft and A. Rieche, *Angew. Chem.*, **73**, 807 (1961).

(5) Compare D. M. Lemal and T. W. Rave, *J. Amer. Chem. Soc.*, **87**, 393 (1965); D. M. Lemal, F. Menger, and E. Coats, *ibid.*, **86**, 2395 (1964).

(6) D. M. Lemal, C. D. Underbrink, and T. W. Rave, *Tetrahedron Lett.*, 1955 (1964).

(7) L. A. Carpino and S. Göwecke, *J. Org. Chem.*, **29**, 2824 (1964).

Experimental Section[11]

Thermal Decomposition of 2-*p*-Toluenesulfonylamino-2,3-dihydro-1H-benz[*d*,*e*]isoquinoline.—A solution of 0.5 g of I (R = *p*-$CH_3C_6H_4SO_2$) in 55 ml of commercial absolute ethanol was refluxed for 9 hr. Filtration gave 0.2 g (74.5%) of II, mp 255–257° dec (sintering at 235°). Because of its insolubility no solvent could be found for recrystallization. The crude material was found to be analytically pure.

Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.84; H, 5.87; N, 15.10.

Treatment of α,α,α'-Tribromo-1,8-dimethylnaphthalene with Hydrazine.—To a solution of 0.6 g of III[12] (mp 105–108°) in 15 ml of ethanol was added 0.4 ml of 64% hydrazine. Addition of 20 ml of water and filtration gave 0.13 g (47%) of II, identified by infrared comparison with the sample obtained by thermal decomposition of I (R = *p*-$CH_3C_6H_4SO_2$).

2-*p*-Toluenesulfonylamino-1,2,3,4-tetrahydroisoquinoline.—Treatment of the hydrochloride of 2-amino-1,2,3,4-tetrahydroisoquinoline with *p*-toluenesulfonyl chloride and triethylamine in DMF solution gave the tosyl derivative (60%) which after recrystallization from nitromethane and benzene had mp 129–131°.

Anal. Calcd for $C_{16}H_{18}N_2SO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.90; H, 6.30; N, 9.01.

Treatment of the tosyl derivative with aqueous sodium hydroxide for a few minutes resulted in the precipitation of 97% IV, mp 249–251° dec, identified by comparison with authentic samples prepared by oxidation[4,13] of the free hydrazine and reaction of 2-(2-bromoethyl)benzaldehyde with hydrazine.[3]

Oxidation of VII.—Under a stream of nitrogen a solution of 0.5004 g of VII in 100 ml of methylene dichloride was treated over 5 min with 2 g of activated manganese dioxide with magnetic stirring. The mixture was stirred for an additional 5 min, allowed to settle and poured onto a column of basic alumina (Schuchardt, activity No. 1, Brockmann). Elution with methylene dichloride and evaporation of the solvent under a stream of nitrogen gave a residue which after recrystallization from ligroin (bp 60–70°) gave 0.0336 g (7.7%) of 1,2-dihydropyracylene, mp 154–156° (lit.[14] mp 155–156°). The compound was identified by comparison of its infrared spectrum with that of an authentic sample.[14] In other runs under the same conditions the yield varied from 8 to 15%. A similar attempt to oxidize VI gave no pyracene. In neither case did treatment of the corresponding *p*-toluenesulfonyl derivative with alkali give any hydrocarbon products.

Benzophenone-2,2'-dicarboxylic Acid.—A mixture of 92.6 g of

(8) A. G. Anderson, Jr., and R. H. Wada, *J. Amer. Chem. Soc.*, **74**, 2274 (1952).

(9) We are indebted to a referee for the suggestion that the loss of nitrogen from the azamine derived from I or VI might be hindered relative to the case of VIII because of severe steric hindrance to coplanarity in the developing biradicals assumed to be involved. Evaluation of this interesting suggestion must await further data on the extent to which radical (or ionic) character is important in the transition state for conversion of an azamine (acyclic as well as cyclic) into hydrocarbon products.

(10) L. A. Carpino, *Chem. Commun.*, 494 (1966).

(11) Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument using TMS as internal standard. Infrared spectra were recorded on Perkin-Elmer 21 237B and Beckman IR-5 instruments. Elemental analyses are by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt, Mülheim (Ruhr), Germany.

(12) W. Ried, H. Boden, U. Ludwig, and H. Neidhart, *Ber.*, **91**, 2479 (1958).

(13) We are indebted to Dr. Höft who kindly supplied an infrared spectrum of IV for comparison purposes.

(14) A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, **23**, 517 (1958).

2-(2-methylbenzoyl)benzoic acid[16] in 1700 ml of water and 0.2 g of NaOH was heated on a steam bath with stirring and then carefully treated with solid $KMnO_4$ in small portions over 0.5 hr, after which time the vigorous foaming had subsided. Over the following 8 hr a total of 230 g of $KMnO_4$ was added portionwise. After an additional 15 hr of heating the mixture was cooled, treated with excess $NaHSO_3$ and filtered through Celite. The MnO_2 was washed with two 1-l. portions of hot water and the combined decolorized filtrates were acidified with hydrochloric acid to give 80.3 g (77%) of the acid, mp 185°, resolidification and final mp 212–213.5° [lit.[16] mp 210° (final)].

6-(*t*-Butyloxycarbonylamino)-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine.—A solution of 26.3 g of 2,2′-bis(bromomethyl)diphenylmethane (obtained from benzophenone-2,2′-dicarboxylic acid by the method of Bergmann and Pelchowicz[16]) and 9.9 g of *t*-butyl carbazate in 150 ml of DMF was warmed to 50° and 15.2 g of triethylamine added dropwise with stirring at a rate to keep the temperature < 60°. After the mixture was allowed to stir overnight 400 ml of water was added and the gummy solid extracted with CH_2Cl_2. Evaporation of the solvent followed by recrystallization from cyclohexane gave 13 g (53%) of the azocine: mp 104–105°; nmr δ (CCl_4) 1.38 s (*t*-Bu, 9 H), 4.3 m (CH_2, 6 H), 7.1 m (phenyl, 8 H).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.99; H, 7.41; N, 8.50.

6-Amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine.—A solution of 1.3 g of the carbo-*t*-butoxy derivative above in 25 ml of methanol was added to 75 ml of methanol which had been saturated with hydrogen chloride in an ice bath. The solution was allowed to stir overnight and evaporated to dryness and the residue recrystallized from methanol–ether to give 0.6 g (58%) of the hydrochloride, mp 210–214° dec (softening at 209°).

Anal. Calcd for $C_{15}H_{17}N_2Cl$: C, 69.08; H, 6.57; N, 10.74; Cl, 13.59. Found: C, 69.01; H, 6.62; N, 10.56; Cl, 13.66.

Conversion to the **free base** was effected by shaking with CH_2Cl_2 and $NaHCO_3$ solution. Recrystallization of the crude product from petroleum ether gave 72% of the hydrazine, mp 114–116°.

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.10; H, 7.34; N, 12.27.

The **benzal** derivative, recrystallized from ethanol, had mp 165–166.5°.

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.57; H, 6.33; N, 9.01.

The ***p*-toluenesulfonyl** derivative, recrystallized from benzene–hexane had mp 146–148.5° dec.

Anal. Calcd for $C_{22}H_{22}N_2SO_2$: C, 69.82; H, 5.87; N, 7.40; S, 8.46. Found: C, 70.04; H, 6.01; N, 7.58; S, 8.42.

10,11-Dihydro-5H-dibenzo[*a*,*d*]cycloheptene.—A mixture of 20 ml of 20% NaOH and 2.5 g of the *p*-toluenesulfonyl derivative of VIII was heated for 10 min on a steam bath and cooled to room temperature and the oil extracted with CH_2Cl_2. Evaporation and recrystallization from methanol gave 1.1 g (85%) of the hydrocarbon, mp 74–76.5° (lit.[17] mp 78–79°), which was identified by comparison with an authentic sample.

Registry No.—II, 19406-76-9; 2-*p*-toluenesulfonylamino-1,2,3,4-tetrahydroisoquinoline, 19350-92-6; 6-(*t*-butyloxycarbonylamino)-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine, 19350-93-7; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine, 19350-94-8; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine hydrochloride, 19350-95-9; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine benzal derivative, 19350-96-0; 6-amino-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine *p*-toluenesulfonyl derivative, 19350-97-1.

Acknowledgment.—This work was supported by a grant (NSF GP-4283) from the National Science Foundation. We are indebted to Mr. Robert Kirkley for checking the oxidation of VII.

(15) M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, **63**, 1537 (1941).

(16) E. D. Bergmann and Z. Pelchowicz, *ibid.*, **75**, 4281 (1953).

(17) W. Treibs and H. J. Klinkhammer, *Ber.*, **83**, 367 (1950).

Reaction of 6-Hydroxy-2-pyridone with Diazomethane. Isolation of a Novel Product

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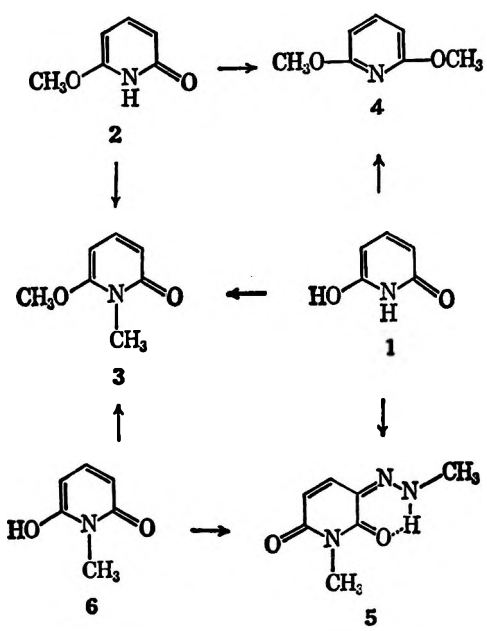
Alkylation reactions of nitrogenous heterocycles have been investigated extensively because of the biological importance of such reactions.[3] In the course of a study of the tautomerism and reactivity of 2,6-disubstituted pyridines, we investigated the reaction of 6-hydroxy-2-pyridone (**1**) (glutaconimide) with diazomethane. In addition to the expected N- and O-methylated products [6-methoxy-2-pyridone (**2**), 6-methoxy-1-methyl-2-pyridone (**3**), and 2,6-dimethoxypyridine (**4**)], an additional substance was observed upon thin layer chromatography. When a large ratio of diazomethane to 6-hydroxy-2-pyridone (**1**) was used (100:1), this product was the one isolated in largest yield. It has been assigned the structure of 1-methyl-1,2,3,6-tetrahydropyridine-2,3,6-trione 3-methylhydrazone (**5**) on the basis of the evidence discussed below. To our knowledge, the isolation of **5** represents the first reported example of substitution of a methylazo group on an aromatic or heterocyclic ring with diazomethane. We feel that this report is not a unique example of this type of substitution but that it may have occurred in methylations of phenols[4] and pyridones[5] with diazomethane and that the corresponding products have been overlooked as minor impurities.

Products **2**, **3**, and **4** were identified by comparison of their ir spectra and/or melting points with those of authentic samples.[6]



(1) New York University special Predoctoral Fellow, 1966–1967.

(2) Inquiries should be addressed to this author.

(3) A. Loveless, "Genetic and Allied Effects of Alkylating Agents," The Pennsylvania State University Press, University Park, Pa., 1966.

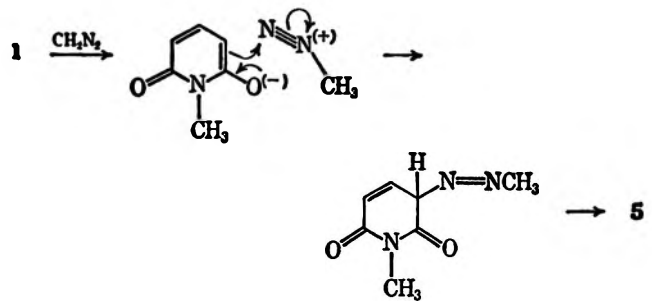
(4) H. von Pechmann, *Chem. Ber.*, **28**, 857 (1895).

(5) N. Kornblum and G. P. Coffey, *J. Org. Chem.*, **31**, 3447 (1966).

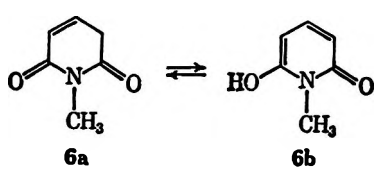
(6) A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc., B*, 562 (1966).

The elemental analysis of **5** indicated that it had been produced by monomethylation and addition of CH_2N_2 to **1**. The presence of a CH_3N_2 group conjugated with the heterocyclic ring was suggested by the yellow color of **5** (λ_{max} 270 and 374 mμ) and supported by a positive test for an N–N linkage (Zn–HCl, then *p*-dimethylaminobenzaldehyde).[7] The nmr spectrum revealed the presence of two *ortho* protons (τ 2.79 and 3.88, J = 10.0 Hz), a strongly hydrogen-bonded exchangeable proton (τ − 4.50) and two N-methyl groups (τ 6.52 and 6.70). The N-methyl absorbance at τ 6.52 appeared as a doublet (J = 4.2 Hz) in $CDCl_3$. On addition of D_2O, this collapsed to a singlet over 1 hr, as the hydrogen-bonded proton exchanged. This indicated that **5** existed as the hydrozone tautomer rather than in an isomeric methylazo form. A similar effect has been observed in the 1-arylazo-2-naphthol series.[8,9] The major mass spectral fragmentation patterns of **5**—P − 15 (CH_3), P − 28 (C=O),[10] and P − 42 (CH_2CO or CH_2N_2)—were consistent with the proposed structure. Additional evidence supporting the assigned structure of **5** came from the following experiments: reaction of 6-methoxy-2-pyridone (**2**) with diazomethane, and reaction of 6-hydroxy-1-methyl-2-pyridone (**6**) with diazomethane. The products of the first reaction were **3** and **4**. The products of the second reaction were **3** and **5**.

A mechanism which accounts for the formation of **5** is illustrated below. In the reaction of **1** with diazomethane, it was also possible that ring methylation occurred after substitution by CH_2N_2.



The existence of **5** as the diketohydrazone tautomer in $CDCl_3$ has caused us to reinvestigate the tautomerism of the related compound **6** by nmr. Katritzky, *et al.*, studied the tautomerism of this compound by pK_a determinations and ultraviolet spectroscopy, and found that **6** existed to an equal extent in both tautomers, **6a** and **6b**, in aqueous solution. We now wish to report that in $CDCl_3$, only the diketo tautomer, **6a**, was observed.



6a **6b**

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 or Beckman DU spectrophotometer, infrared spectra with a Perkin-Elmer Model 137 spectrophotometer, and nuclear magnetic resonance spectra with a Varian A-60 spectrometer using tetramethylsilane as internal reference (τ 10.0). Analyses were performed by Mr George Robertson, Jr., Florham Park, N. J. Mass spectra were determined with a Varian M-66 double-focusing cycloidal mass spectrometer at 70 eV. Thin layer chromatography was performed on plates prepared with Merck silica gel (Brinkmann Instruments, Westbury, N. Y.) to which approximately 5% Radelin phosphor GS-115 had been incorporated. The plates were visualized with an ultraviolet lamp equipped with a short-wave filter.

Reaction of 6-Hydroxy-2-pyridone with Diazomethane.—To a stirred mixture of 1.0 g (9 mmol) of 6-hydroxy-2-pyridone (**1**)[11] and 60 ml of ethyl ether, under a nitrogen atmosphere, was added 900 mmol of ethereal diazomethane. The reaction was allowed to proceed, with stirring, for 30 min at 0° (ice bath) and then for 14 hr at room temperature. Nitrogen was then bubbled into the reaction mixture to remove the unreacted diazomethane. The yellow solution was filtered and the filtrate evaporated to a thick brown oil. This oil was subjected to thin layer chromatography on twenty-five 1.00-mm silica plates employing a solvent system of chloroform–methanol, 95/5 (v/v). The plates exhibited four major bands, R_f 0.15, 0.30, 0.85 and 0.99, which were cut out separately and extracted with dichloromethane–methanol. The fractions produced by this were worked up in the manner indicated below.

Fraction I (R_f 0.15).—The crude material obtained from the extraction was recrystallized from hexane–benzene to yield 25.0 mg (2%), large colorless plates, mp 103–104.5° (lit.[6] mp 102–104°) of 6-methoxy-2-pyridone (**2**), mmp 103–105° with an authentic sample of **2**. This material had an infrared spectrum identical with that of an authentic sample of **2**:[6] nmr ($CDCl_3$) τ − 4.51 (broad s, 1, NH), 2.57 (d of d, 1, J_{34} = 8.8 Hz, J_{45} = 7.7 Hz, H-4), 3.75 (d of d, 1, J_{34} = 8.8 Hz, J_{35} = 0.8 Hz, H-5), 6.16 (s, 3, CH_3O).

Fraction II (R_f 0.30).—The crude material from the extraction was recrystallized from hexane–benzene with Norit A. This yielded 49.0 mg (4%), colorless plates, mp 59–72°, of hydrated 6-methoxy-1-methyl-2-pyridone (**3**). This material was dissolved in dry chloroform and dried over Linde Molecular Sieve 4X to give a colorless crystalline solid, mp 78–79.5° (lit.[6] mp 52–54°). An elemental analysis showed that the material was still hydrated. Both the nmr and ir of this material agreed with those of an authentic sample of **3**:[6] nmr ($CDCl_3$) τ 2.68 (d of d, 1, J_{34} = 9.1 Hz, J_{45} = 7.7 Hz, H-4), 3.79 (d of d, 1, J_{34} = 9.1 Hz, J_{35} = 1.1 Hz, H-3), 4.45 (d of d, 1, J_{45} = 7.7 Hz, J_{35} = 1.1 Hz, H-5), 6.10 (s, 3, CH_3O), 6.53 (s, 3, CH_3N).

Fraction III (R_f 0.85).—The crude extracts were recrystallized from hexane to yield 204.1 mg (14%), yellow plates, mp 163° (sealed tube), of 1-methyl-1,2,3,6-tetrahydropyridine-2,3,6-trione-3-methylhydrazone (**5**): λ_{max}^{MeOH} 270 mμ (ϵ 8980), 374 (20,700); ir (KBr) 1678, 1621, 1493, 1393, 1307, 1277, 1247, 1101, 1047, 990, 840, 794 cm^{-1}; nmr ($CDCl_3$) τ − 4.50 (m, 1, NH), 2.79 (d, 1, J_{45} = 10.0 Hz, H-4), 3.88 (d, 1, J_{45} = 10.0 Hz, H-5) 6.52 (d, 3, J = 4.2 Hz, CH_3NH), 6.70 (s, 3, CH_3N); mass spectrum *m/e* (relative intensity) 168 (10), 167 (89), 152 (42), 139 (98), 125 (34), 124 (24), 97 (19), 96 (100), 95 (14). Only absorbances above *m/e* 94 have been reported.

Anal. Calcd for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14; mol wt, 167.069. Found: C, 50.70; H, 5.65; N, 25.41; mol ion, 167.067.

Fraction IV (R_f 0.99).—The crude extracts were rechromatographed on silica using a solvent system of pure chloroform. The band corresponding to the product (R_f 0.81) was extracted with chloroform and the chloroform evaporated to yield 100.2 mg (8%), colorless oil of 2,6-dimethoxypyridine (**4**). The infrared spectrum of this material was identical with that of an authentic sample (Baker Chemical) of **4**.

Reaction of 6-Methoxy-2-pyridone (2) with Diazomethane.—Pyridone **2**, 10 mg (0.08 mmol), was treated with diazomethane (8 mmol) in the manner described above. Thin layer chromatography with the above-mentioned systems indicated that three products were present: unreacted **2**, **3**, and **4**.

Reaction of 6-Hydroxy-1-methyl-2-pyridone (6) with Diazo-

(7) F. Feigl, "Spot Tests in Organic Chemistry," 6th ed, Elsevier Publishing Co., New York, N. Y., 1960, pp 179, 278.
(8) D. Hadzi, *J. Chem. Soc.*, 2143 (1956).
(9) A. Burawoy, H. G. Salem, and A. R. Thompson, *ibid.*, 4793 (1952).
(10) R. Lawrence and E. S. Waight, *ibid.*, *B*, 1 (1968).
(11) This material was prepared by the sublimation–decomposition of 2,6-dihydroxypyridine hydrochloride (Koch-Light Ltd., Colnbrook, England).

methane.—Pyridone **6**, 10 mg (0.08 mmol), was treated with diazomethane (8 mmol) in the manner described above. Thin layer chromatography with the above-mentioned systems indicated that two products were present: **3** and **5**.

The nmr spectrum of 6-hydroxy-1-methyl-2-pyridone (**6**) in deuteriochloroform is as follows: τ 3.26 (d of t, 1, J_{34} = 10.0 Hz, J_{45} = 3.5 Hz, H-4), 3.76 (d of t, 1, J_{34} = 10.0 Hz, J_{35} = 2.0 Hz, H-3), 6.55 (d of d, 2, J_{45} = 3.5 Hz, J_{35} = 2.0 Hz, H-5), 6.70 (s, 3, CH_3–N).

Registry No.—**1**, 14346-45-3; **5**, 19350-90-4; **6**, 6231-17-0; diazomethane, 334-88-3.

3-Benzylidene-2,5-diketopiperazine

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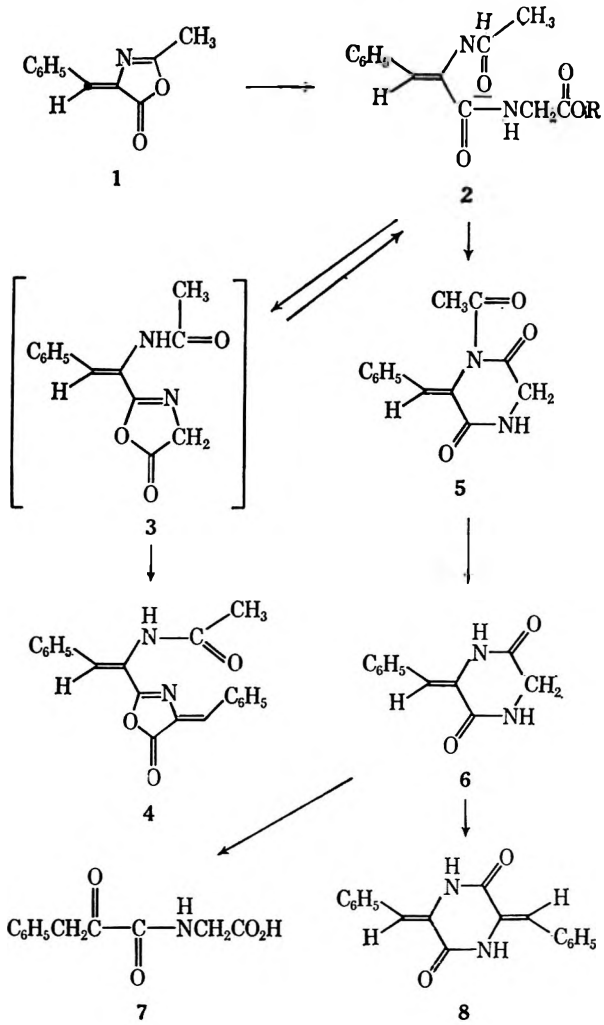
Although 3,6-dibenzylidene-2,5-diketopiperazine (**8**) has been known since 1921,[1] 44 years prior to its isolation as a natural product,[2] the monobenzylidene derivative **6** has not previously been described. As both this compound and the process by which it is produced have a variety of potential synthetic uses,[3] we wish to report our observation of its synthesis.

Fruton and Bergman,[4] in their extensive investigations of dehydropeptides, reported that the azlactone, 2-methyl-4-benzal-5-oxazalone (**1**), condensed with glycine to afford acetyldehydrophenylalanylglycine (**2**, R = H) which upon treatment with benzaldehyde, acetic ahydride, and sodium acetate produced the unsaturated azlactone peptide derivative **4**. In an attempt to obtain the assumed intermediate saturated peptide azlactone (**3**) of the above reaction, we carried out the process with the omission of benzaldehyde. The expected intermediate **3** was not produced; instead N-acetylmonobenzylidinediketopiperazene (**5**) was formed in high yield. In the acetic anhydride–sodium acetate medium, the mixed anhydride–azlactone equilibrium (**2** → **3**, R = Ac) appears rapid and reversible. In the presence of benzaldehyde, the azlactone condensation proceeds to give **4** irreversibly, while in the absence of benzaldehyde a slower intramolecular acylation of the amide nitrogen occurs to give **5**. Trace amounts of **5** can be found in the preparation of **4**. Treatment of acetyldiketopiperazine **5** with a variety of nucleophiles affords monobenzylidene diketopiperazine **6** in high yield. The structure was confirmed by hydrolysis to phenylpyruvoylglycine **7** and condensation with benzaldehyde to afford the dibenzylidene derivative **8** (Scheme I).[1]

SCHEME I



Experimental Section

Acetyldehydrophenylalanylglycine (2, R = H).—Dipeptide **2** was prepared according to the procedure of Fruton and Bergman.[4] From 6.0 g (0.032 mol) of 2-methyl-4-benzal-5-oxazolone (**1**),[5] 7.0 g (83%) of acetyldehydrophenylalanylglycine (**2**, R = H) was obtained which melted at 189–192° (lit.[4] mp 194–195°): $\nu_{max}^{CHCl_3/N(Et)_3}$ (cm^{-1}) 1670 (strong), 1630 (strong); $\tau^{CF_3CO_2H}$ (ppm) 2.51 (6 H, multiplet), 5.58 (2 H, multiplet), 7.62 (2.5 H, singlet), 7.88 (0.5 H, singlet).

The two N-methyl peaks may be due to either *cis–trans* isomerization about the double bond or restricted rotation about one of the amide bonds.

N-Acetyl-6-benzylidene-2,5-diketopiperazine (5).—A solution of 6.0 g (0.023 mol) of acetyldehydrophenylalanylglycine in 15 ml of acetic anhydride was warmed on a steam bath for 9 hr. The acetic anhydride was then removed by distillation leaving a brown solid which melted at 160–170°. After washing well with benzene, 3.82 g (68%) of a pale yellow solid was obtained which melted at 194–198°. Finally recrystallization from chloroform gave a colorless solid which melted at 200–202°: $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3380 (weak), 3020 (weak), 1700 (strong), 1630 (weak), 1420 (medium), 1360 (strong), 1225 (broad, medium); $\tau^{CF_3COH_2}$ (ppm) 2.51 (1 H, singlet), 2.57 (6 H, broad singlet), 5.25 (2 H, singlet), 7.25 (3 H, s). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.4. Found: C, 63.93; H, 4.92; N, 11.42.

3-Benzylidene-2,5-diketopiperazine (6).—A solution of 0.10 g (0.00041 mol) of N-acetyl-6-benzylidene-2,5-diketopiperazine (**5**) and 1.0 g (0.01 mol) of aniline in 1 ml of chloroform was allowed to remain overnight at room temperature. The next day the slurry was filtered to give 0.82 g (99%) of crude product which melted at 274–278°. Recrystallization from acetic acid and

(1) T. Sasaki, *Chem. Ber.*, **54B**, 163 (1921).

(2) R. Brown, C. Kelley, and S. E. Wiberley, *J. Org. Chem.*, **30**, 277 (1965).

(3) See, for example, C. Shin, Y. Chigira, M. Masaki, and M. Ohta, *Tetrahedron Lett.*, 4601 (1967).

(4) J. Fruton and M. Bergman, *J. Biol. Chem.*, **166**, 449 (1946); D. G. Doherty, J. E. Tietzman, and M. Bergman, *ibid.*, **147**, 617 (1943).

(5) R. Herbst and D. Shemin, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p 1.

water gave an analytical sample which melted at 281–282°: ν_{max}^{KBr} (cm^{-1}) 3200 (w), 1680 (s), 1625 (m), 1440 (w), 775 (w); $\tau^{CF_3CO_2H}$ (ppm) 2.98 (5 H, s), 3.05 (1 H, s), 5.92 (2 H, s). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.86. Found: C, 65.18; H, 4.97; N, 13.87.

Hydrolysis of 3-Benzylidene-2,5-diketopiperazine (6).—A slurry of 0.30 g (0.0015 mol) of 3-benzylidene-2,5-diketopiperazine (5) in 4 ml of 0.5 *N* hydrochloric acid and 2 ml of glacial acetic acid was refluxed for 2 hr. On cooling in a refrigerator overnight, 0.10 g of a precipitate which was identified as starting material formed. After filtration crystals appeared in the filtrate on standing at room temperature and after cooling another filtration gave 0.20 g (60%) of a colorless solid which melted at 164–166° (lit. mp 166–167°). This material was the same by a mixture melting point test as phenylpyruvylglycine (7) prepared by hydrolysis of acetyldehydrophenylalanylglycine (2, R = H).[4]

Registry No.—2 (R = H), 19459-01-9; 5, 19459-02-0; 6, 19459-03-1.

A Simple Technique for Performing Reactions with Organotin Hydrides

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The most useful reactions of organotin hydrides include additions to unsaturated systems and reductions of functional groups such as halides.[1] Preparation of the organotin hydride usually involves reduction of an organotin halide or oxide with a reducing agent such as lithium aluminum hydride. The hydride is then isolated and used immediately or stored until needed in an air-tight container.

It has been recently reported that organotin hydrides can be prepared by the reaction of the appropriate oxides with polymethylsiloxane, eq 1.[2] The reactants

$$(R_3Sn)_2O + [CH_3SiHO]_n \rightarrow\rightarrow\rightarrow 2R_3SnH + [CH_3SiO_{1.5}]_n \quad (1)$$

are simply mixed without solvent and the hydride separated from the cross-linked silicone polymer by distillation. Since the polymer is nonvolatile it appeared to us that a substance which would react with the hydride could be added to the mixture without the necessity for isolating the hydride. Furthermore, silanes do not react readily with unsaturated and reducible functions. This suggested further that the desired reaction of the organotin hydride could be effected by simply mixing the polysiloxane, organotin oxide and substrate, as illustrated in eq 2 for an organic

$$2RX + (R'_3Sn)_2O + [CH_2SiHO]_n \longrightarrow 2RH + 2R'_3SnX + [CH_3SiO_{1.5}]_n \quad (2)$$

halide. A preliminary experiment with *n*-heptyl bromide yielded 70% of *n*-heptane indicating that the method was promising and as effective as the conventional method.[3] Further experiments were then carried out to determine whether yields were generally good with simple halides and whether other reducible functions were reduced in competition with the halides.

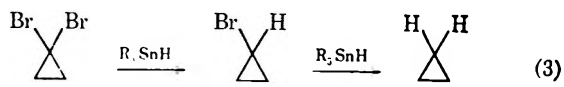
TABLE I

REDUCTION OF GEMINAL DIBROMOCYCLOPROPANES WITH TRI-*n*-BUTYLTIN HYDRIDE GENERATED *in Situ*

Halide	Conditions	% yield of monobromide[a]
1,1-Dibromo-*trans*-2,3-dimethyclycloropropane[b]	0°, 1.5 hr	85
1,1-Dibromo-2,2,3,3-tetramethylcyclopropane[c]	Room temperature, 1.5 hr	73 (78)
7,7-Dibromobicyclo[4.1.0]heptane[d]	50°, 3 hr	79 (82)

[a] Figures in parentheses are from ref 4. [b] P. S. Skell and A. Y. Gardner, *J. Amer. Chem. Soc.*, 78, 3409 (1956). [c] P. S. Skell and A. Y. Gardner, *ibid.*, 78, 5430 (1956). [d] W. von E. Doering and A. K. Hoffman, *ibid.*, 76, 6162 (1954).

One of the more important applications of organotin hydrides in organic synthesis is in the stepwise reduction of geminal polyhalides.[3] This feature has been exploited in the reduction of the adducts of dibromocarbene to simple olefins[4] and to allenes,[5] eq 3.[6] Results of



(3)

the reduction of three dibromocyclopropanes to the corresponding monobromo derivatives are given in Table I, and can be seen to be comparable with those obtained by the conventional procedure.

A survey of the reduction of several aromatic and aliphatic chlorides and bromides was made with the results shown in Table II. Some of the reactions were carried out thermally. Others were initiated photochemically in Pyrex vessels and were found to provide improved yields at lower temperatures. The reactions carried out at 100° or higher were usually accompanied by the formation of a grayish precipitate which was not observed in the photochemical reductions.

It appears that reductions of aromatic bromides by this method are very slow in the presence of a ketone, aldehyde or amino group. Aliphatic carbonyl compounds with α halogens have been shown to be reduced in good yield.[3] Decomposition of organotin hydrides catalyzed by amines is a well-documented process.[1a] When the reduction of *p*-bromo-N,N-dimethylaniline was carried out thermally, the amount of decomposition appeared to be quite large, as reflected in the low yield of reduction product. Although the yield of product was larger in the case of the photochemically induced reduction, the reaction was quite slow.

It is interesting to note that *m*-chlorotoluene was not reduced at all even after irradiation for 5 days, while aliphatic chlorides were reduced in good yield under these conditions. In contrast to this, *o*-bromotoluene

(1) For recent reviews, see (a) H. G. Kuivila in "Advances in Organometallic Chemistry," Vol. I, F. G. A. Stone and R. West, Ed., Academic Press, New York, N. Y., 1964, p 47; (b) W. P. Neumann, *Angew. Chem.*, **76**, 849 (1964); (c) W. P. Neumann, "Die Organishe Chemie Des Zinns," Enke Verlag, Stuttgart, West Germany, 1967; (d) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 293 (1968).

(2) K. Hayashi, J. Iyoda, and I. Shiihara, *J. Organometal. Chem.*, **10**, 81 (1967).

(3) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963).

(4) D. Seyferth, H. Yamazaki, and D. L. Alleston, *ibid.*, **28**, 703 (1963).

(5) W. Rahman and H. G. Kuivila, *ibid.*, **31**, 772 (1966).

(6) Other methods which are available for this reduction involve strongly basic conditions to which functional groups such as esters and nitriles are sensitive; see D. Seyferth and D. Prokai, *ibid.*, **31**, 1702 (1966); A. J. Frey and R. H. Moore, *ibid.*, **33**, 1283 (1968).

TABLE II

REDUCTION OF SOME ORGANIC HALIDES WITH TRI-*n*-BUTYLTIN HYDRIDE GENERATED *in Situ*

Halide	Temp,[a] °C	Time, hr	Product	% yield
n-Bromoheptane	50	1	*n*-Heptane	70
4-Bromovaleronitrile	50	1	Valeronitrile	60
2-Bromoethyl acetate	50	1	Ethyl acetate	63
o-Bromotoluene	110	14	Toluene	93
β-Bromoethylbenzene	110	4	Ethylbenzene	69
2-Chlorooctane	110	16	*n*-Octane	63
p-Bromoanisole	110	4	Anisole	34
	110	16		64
2-Bromopyridine	110	14	Pyridine	91
p-Bromo-N,N-dimethylaniline	110	14	N,N-Dimethylaniline	10
o-Bromotoluene	*hν*	5	Toluene	100
p-Bromo-N,N-dimethylaniline	*hν*	14	N,N-Dimethylaniline	25
2-Chlorooctane	*hν*	7	*n*-Octane	70
	hν	19		100
2-Chloroethyl acetate	*hν*	20	Ethyl acetate	91
3-Chlorobutyronitrile	*hν*	20	Butyronitrile	93
m-Chlorotoluene	*hν*	120	Toluene	0
p-Bromoacetophenone	*hν*	5	Acetophenone	30
p-Bromobenzaldehyde	*hν*	5	No reduction	0
p-Bromobenzenethiol	*hν*	5	No reduction	0

[a] Photoinitiated reaction at 35–40°.

was reduced in quantitative yield after only 5 hr of irradiation. It has been reported that chlorobenzene was reduced to benzene in 64% yield when heated for 21 hr at 80° in the presence of AIBN.[3] Perhaps the lower temperature employed in the photochemical reactions results in more selective reductions.

It is clear that organotin hydride reductions of halides can be carried out in the presence of a variety of functional groups which are sensitive to the basic conditions encountered when other reducing agents are used.

Carbonyl compounds are reduced to alcohols by organotin hydrides,[1a] eq 4. One advantage of this

$$R_2CO = 2SnH \longrightarrow R_2CHOH + Sn\text{-}Sn \qquad (4)$$

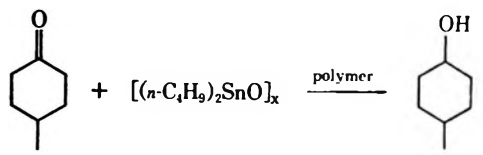
reduction is that hydrolysis is not necessary. Ketones are reduced less readily than halides by tri-*n*-butyltin hydride.[3]

Simple carbonyl compounds are reduced in an exothermic reaction at room temperature by the dihydrides. However, tri-*n*-butyltin hydride required a temperature of 140° for reduction at a convenient rate. Irradiation of a mixture of 4-methylcyclohexanone, silicone polymer and bistri-*n*-butyltin oxide for the 3 days resulted in only 10% reduction of the ketone to a mixture of *cis*- and *trans*-4-methylcyclohexanol.

The hydride exchange reaction between the silicone polymer and organotin oxides has also been used to prepare organotin dihydrides, eq 5. Hydrolysis of

$$\frac{1}{x}(R_2SnO)_x + \frac{2}{n}[MeSiHO]_n \longrightarrow \frac{1}{x}R_2SnH_2 + \frac{2}{n}[MeSiO_{1.5}]_n \qquad (5)$$

di-*n*-butyltin dichloride with sodium hydroxide solution produced di-*n*-butyltin oxide. When the silicone polymer, organotin oxide and ketone were mixed together, an exothermic reaction took place which resulted in extensive decomposition. By slow addition of the ketone and silicone polymer to a slurry of the oxide in toluene, the reaction could be easily controlled. In this manner, 4-methylcyclohexanone was reduced to a mixture of *cis*- and *trans*-4-methylcyclohexanol in 75% yield, eq 6.



(6)

trans/*cis* = 3

Several unsuccessful attempts were made to add organotin hydride, generated *in situ*, to double bonds. Even addition to 1-hexene could not be effected in satisfactory yield after irradiation with the silicone polymer and bistri-*n*-butyltin oxide for 3 days.

Experimental Section

General.—Infrared spectra were determined on a Beckman IR-7 spectrophotometer. Determinations of nmr spectra were carried out with a Varian Model A-60A spectrometer using carbon tetrachloride as solvent and tetramethylsilane as the internal standard. Gas–liquid partition chromatography analysis was carried out on a F & M Model 5750 research gas chromatograph equipped with a dual flame detector. For analysis of starting materials and products of halide reductions, a 6-ft, ⅛-in. Apiezon L on 60–80 Chromosorb W column was used. For analysis of the starting material and products from reduction of 4-methylcyclohexanone, a 15-ft, 0.25-in. 1,2,3-triscyanoethoxypropane on 60–80 Chromosorb P column at 150° was used.

Reduction of 1,1-Dibromo-*trans*-2,3-dimethylcyclopropane.—To a 250-ml round-bottomed one-necked flask, equipped with a powerful magnetic stirrer, pressure-equalizing addition funnel and drying tube, was added 45.6 g (0.2 mol) of dibromide and 18 g (0.3 equiv) of silicone polymer (General Electric Dri-Film 1040). While stirring at 0°, 67.2 g (0.112 equiv) of bistri-*n*-butyltin oxide was added dropwise. After the addition was complete, the reaction mixture was stirred at 0° for 1.5 hr. The flask was then fitted with a condenser and stirring continued at room temperature until the reaction was no longer exothermic or until the mixture set into a gel. The product was distilled through a short column into an efficient Dry Ice trap under reduced pressure, yield 85% based on starting dibromide.

Reduction of 7,7-Dibromobicyclo[4.1.0]heptane.—The above procedure was followed except the reaction mixture was stirred for 3 hr at 50° instead of room temperature.

Thermally Induced Reductions of Halides.—The same procedure was used for all reductions. To a 50-ml flask, equipped with magnetic stirrer, condenser and drying tube, was placed 0.05 mol of halide, 0.075 equiv of silicone polymer (4.6 g) and 0.038 equiv of bistri-*n*-butyltin oxide (22.8 g). The reaction

mixture was stirred for the time at the temperature indicated in Table II. The product was distilled into a Dry Ice trap at reduced pressure (15–20 mm). The infrared spectrum of each product reported was identical with that of an authentic sample.

Photochemically Induced Reduction of Halides.—To a 50-ml Pyrex tube fitted with a glass stopper was added 0.05 mol of halide, 0.075 equiv of polymer (4.6 g), and 0.038 equiv of bistri-*n*-butyltin oxide (22.8 g). The reaction mixture was irradiated in a Rayonet photochemical reactor for the time indicated in Table II. Transfer of the reaction mixture to a 50-ml flask followed by distillation at reduced pressure (15–20 mm) gave pure product. The infrared spectrum of each product reported was identical with that of an authentic sample.

Reduction of 4-Methylcyclohexanone.—To a 100-ml three-necked flask equipped with a Hershberg stirrer, condenser and addition funnel was added 30 g of di-*n*-butyltin oxide (0.12 mol) and 35 ml of toluene. While stirring at 25°, there was added dropwise a mixture of 11.2 g of ketone (0.1 mol) and 18 g of silicone polymer (0.3 equiv). After addition was complete, the reaction mixture was stirred at 25° for 3 hr. Distillation at reduced pressure have a mixture of *cis*- and *trans*-4-methylcyclohexanol: bp 55° (20 mm); yield 75% based on starting ketone.

Registry No.—Tri-*n*-butyltin hydride, 688-73-3; 1,1-dibromo-*trans*-2,3-dimethylcyclopropane, 3591-58-0; 7,7-dibromobicyclo[4.1.0]heptane, 2415-79-4; 4-methylcyclohexanone, 589-92-4.

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Nitrile Oxides. XII. Cycloaliphatic and Aliphatic Stable Nitrile Oxides[1]

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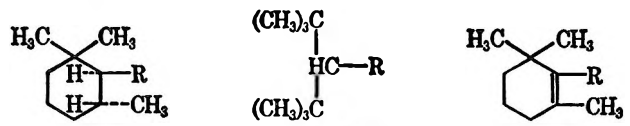
Simple aliphatic nitrile oxides are extremely unstable and isomerize even at 0° in dilute solutions within seconds or, at best, minutes to the corresponding dialkylfurazan oxides (furoxans, 1,2,5-oxadiazole 1-oxides).[2,3] Only recently a few representatives of aliphatic nitrile oxides have been obtained as monomers by working at temperatures of approximately −40°.[4] Trimethylacetonitrile oxide [**1**, $(CH_3)_3C—C{\equiv}N{\rightarrow}O$] is the only member of the series reported so far to be stable enough to be distilled *in vacuo* and to require several days at room temperature to dimerize completely.[2,4,5] In the light of our recent success in completely stabilizing aromatic and heterocyclic nitrile oxides by controlled steric hindrance,[6] the relative stability of **1** may be attributed to the bulky *t*-butyl group. Aromatic and heterocyclic nitrile oxides are adequately protected against dimerization by two methyl groups in *o,o'* position to the CNO group, but the limited lifetime of **1** indicated that a higher degree of steric hindrance than that provided by one *t*-butyl group would be necessary for the stabilization of an aliphatic or cycloaliphatic nitrile oxide, probably because of the greater conformational freedom of these structures.

These speculations were confirmed by the preparation of the strongly hindered nitrile oxides, *trans*-2,2,6-trimethylcyclohexylfulmide (**2**) and di-*t*-butylacetonitrile oxide (**3**). Both compounds proved indefinitely stable at 25°. The parent carbon skeleton structures of **2** and **3** were chosen for their accessibility. The synthesis of both **2** and **3** started with the known aldehydes **4**[7] and **5**,[8] which were converted into the oximes and then dehydrogenated by the recently described improved procedure.[9] The remarkable degree of steric protection provided by the 2,2,6-trimethylcyclohexane moiety was impressively demonstrated by the preparation of 2,2,6-trimethylcyclohexen-1-ylfulmide (**6**) from the corresponding aldehyde **7** (β-cyclocitral). Compound **6** is the first known unsaturated nitrile oxide. Generally, ethylenic double bonds react quite readily with the nitrile oxide function, but their reactivity decreases sharply with increased substitution.[2a,10] No intermolecular reaction of the CNO and the ethylenic group of **6** could be enforced.



2, R = C≡N→O
4, R = CHO
9, R = N=C=O

3, R = C≡N→O
5, R = CHO
8, R = CH_2OH
10, R = N=C=O

6, R = C≡N→O
7, R = CHO
11, R = N=C=O

In spite of the crowded vicinity of the CNO group in **2**, **3**, and **6**, they reacted as easily as unhindered nitrile oxides with a number of typical dipolarophiles and nucleophiles. Heating the nitrile oxides for 5 hr to 125–130° rearranged them neatly to the corresponding isocyanates **9–11** which were characterized by subsequent reaction with aniline to give the corresponding N-phenylureas. Data on the obtained products are listed in Table I.

Experimental Section[11]

trans-2,2,6-Trimethylcyclohexylfulmide (**2**).—*trans*-2,2,6-Trimethylcyclohexane-1-aldehyde (IV) was obtained by the hydrogenation of the ethylene acetal of β-cyclocitral with platinum oxide in acetc acid.[7] The oxime of IV is best prepared by the following method. The aldehyde (5 g) was dissolved in methanol (100 ml) and a solution of hydroxylamine hydrochloride (5 g) and sodium carbonate (3.5 g) in water (15 ml) was added. The reaction mixture was heated to reflux for 5 hr, poured into water (500 ml), and extracted with ether. The ethereal extracts were dried over anhydrous sodium sulfate, the solvent was removed *in vacuo*, and the residue was fractionated. The fraction

(1) Previous communication by C. Grundmann and R. Richter, *Tetrahedron Lett.*, 963 (1968).

(2) (a) C. Grundmann, *Fortschr. Chem. Forsch.*, **7**, 62 (1966); (b) T. Mukaiyama and T. Hoshino, *J. Amer. Chem. Soc.*, **82**, 5339 (1960).

(3) The parent member of this series, fulminic acid, HC≡N→O, is apparently a little more stable in solution, but undiluted will explode at −20° (C. Grundmann in "The Chemistry of the Cyano Group," Z. Rappoport, Ed., Interscience Publishers, Inc., London, in press).

(4) G. Zinner and H. Günther, *Angew. Chem.*, **76**, 440 (1964).

(5) G. Speroni and A. Quilico in "The Chemistry of Heterocyclic Compounds," Vol. XVII, A. Weissberger, Ed., Interscience Publishers, Inc., N. Y., 1962, p 21, Table II.

(6) C. Grundmann and J. M. Dean, *Angew. Chem.*, **76**, 682 (1964); C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965); C. Grundmann and R. Richter, *ibid.*, **32**, 2308 (1967).

(7) L. Colombi, A. Bosshard, A. Schinz, and C. F. Seidel, *Helv. Chim. Acta*, **34**, 265 (1951).

(8) M. S. Newman, A. Arkell, and T. Fukunaga, *J. Amer. Chem. Soc.*, **82**, 2498 (1960).

(9) C. Grundmann and R. Richter, *J. Org. Chem.*, **33**, 476 (1968).

(10) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); C. Grundmann, H. D. Frommeld, K. Flory, and S. K. Datta, *J. Org. Chem.*, **33**, 1464 (1968).

(11) Melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. Molecular weights were determined by the osmometric method; the applied solvent is indicated in parentheses.

TABLE I

ADDITION PRODUCTS FROM THE NITRILE OXIDES 2, 3, AND 6

No.	Registry no.	Reactants	Compound	Yield, %	Mp, °C	Formula[a]
1	19202-80-3	2 + phenylacetylene	3-(2,2,6-Trimethylcyclohexyl)-5-phenylisoxazole	78	90	$C_{18}H_{23}NO$
2	19203-44-2	3 + phenylacetylene	3-Di-*t*-butylmethyl-5-phenylisoxazole	80	108	$C_{18}H_{25}NO$
3	19221-86-4	6 + phenylacetylene	3-(2,2,6-Trimethylcyclohexen-1-yl)-5-phenylisoxazole	82	59	$C_{18}H_{21}NO$
4	19202-81-4	2 + malononitrile	3-(2,2,6-Trimethylcyclohexyl)-4-cyano-5-aminoisoxazole	86	156	$C_{13}H_{19}N_3O$
5	19206-27-0	3 + malononitrile	3-Di-*t*-butylmethyl-4-cyano-5-aminoisoxazole	95	295	$C_{13}H_{21}N_3O$
6	19206-28-1	6 + malononitrile	3-(2,2,6-Trimethylcyclohexen-1-yl)-4-cyano-5-aminoisoxazole	61	138	$C_{13}H_{17}N_3$
7	19202-82-5	2 + aniline	2,2,6-Trimethylcyclohexanoylanilide oxime	77	170	$C_{16}H_{24}N_2O$
8	19206-29-2	3 + aniline	Di-*t*-butylacetanilide oxime	76	135	$C_{15}H_{26}N_2O$
9	19206-30-5	6 + aniline	2,2,6-Trimethylcyclohexen-1-oylanilide oxime	77	159	$C_{16}H_{22}N_2O$
10	19206-31-6	3 + water	Di-*t*-butylacethydroxamic acid	100	154	$C_{10}H_{21}NO_2$
11	19206-32-7	6 + water	2,2,6-Trimethylcyclohexen-1-oyl-hydroxamic acid	76	180	$C_{10}H_{17}NO_2$
12	19202-83-6	9 + aniline	N-(2,2,6-Trimethylcyclohexyl)-N'-phenylurea	100	209	$C_{16}H_{24}N_2O$
13	19206-33-8	10 + aniline	N-(Di-*t*-butylmethyl)-N'-phenylurea	100	236	$C_{16}H_{26}N_2O$
14	19206-34-9	11 + aniline	N-(2,2,6-Trimethylcyclohexen-1-yl)-phenylurea	100	178	$C_{16}H_{22}N_2O$

[a] Supporting combustion data on C, H, and N (±0.3%) were obtained for all the compounds listed.

distilling at 62–64° (0.1 mm) (4 g, 73%) solidified quickly (mp 44°) and was the pure oxime. *Anal.* Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.98; H, 11.34; N, 8.33.

The oxime (0.05 mol) was dehydrogenated to the nitrile oxide with N-bromosuccinimide and sodium methoxide as previously described.[9] After dilution of the reaction mixture with water, it was extracted three times with 50-ml portions of *n*-pentane. The combined solvent extracts were dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* and the residue was fractionated on a 10-cm Vigreux column. The fraction boiling at 31° (0.001 mm) was the pure II (70%). It did not solidify on prolonged storage at −20°: d^{26}_4 0.9739, $n^{26}D$ 1.4690. *Anal.* Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38; mol wt, 167. Found: C, 71.84; H, 10.43; N, 8.32; mol wt, 170 (chloroform).

Di-*t*-butylacetonitrile Oxide (3).—In our first attempts to prepare **3** from the aldehyde **5**, we used samples of **5** as obtained according to the literature,[8] but obtained specimens of the nitrile oxide which did not crystallize and which gave poor analytical results, although the presence of considerable amounts of **3** could be demonstrated by the preparation of the crystalline derivatives 2, 5, 8, and 10 of Table I. According to Newman, *et al.*,[8] the aldehyde is prepared by chromic acid oxidation of a crude 2,2-di-*t*-butylethanol (**8**), containing unknown isomeric alcohols which are apparently carried over through the subsequent steps. Since the aldehyde **5** cannot be separated efficiently from these by-products and neither its oxime nor the nitrile oxide **3** are thermally stable enough to be subjected to a long fractionated distillation, we purified the precursor **8** by filtration of the solid portion of crude **8** at −20° and subsequent recrystallizations from petroleum ether (bp 35–40°) at −20°, until a melting point of 54–55° was attained.

The aldehyde **5** (7 g), obtained from pure **8** by the described procedure, was dissolved in ethanol (250 ml) and refluxed for 18 hr with a solution of hydroxylamine hydrochloride (9 g) and potassium hydroxide (9 g) in water (25 ml). After dilution of the reaction mixture with 250 ml of water, the pH was adjusted to 4 and the major part of the ethanol distilled off. The residue was again diluted with water (250 ml) and extracted with ether. After removal of the solvent, the ethereal extracts left an oil, which, on fractionation, gave di-*t*-butylacetaldoxime boiling at 73–75° (0.35 mm) and soon solidifying (mp 30°), yield 72%. *Anal.* Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.31; H, 12.48; N, 8.27.

Other procedures, recommended in literature for the conversion of aldehydes into oximes, proved unsatisfactory with the highly hindered **5**.

Conversion of the oxime of **5** into the nitrile oxide went smoothly by the procedure described above. The nitrile oxide **3** boiled at 55–56° (0.2 mm) and solidified completely on cooling, mp 24–24.5°, yield 77%. *Anal.* Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28; mol wt, 169. Found: C, 71.04; H, 11.35; N, 8.29; mol wt, 170 (benzene).

2,2,6-Trimethylcyclohexen-1-ylfulmide (6).—The starting material for **6**, the aldehyde **7** (β-cyclocitral), was obtained from commercially available citral by the most recently recommended method,[7] while for the preparation of its oxime an older procedure was found most satisfactory.[12] The pure oxime (mp 84°) was converted as described above in 81% yield into the nitrile oxide **6**, a colorless liquid of unpleasant odor, boiling at 48–49° (0.03 mm). Compound **6** did not solidify on prolonged storage at −20°: d^{31}_4 0.9962, $n^{31}D$ 1.5103. *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48; mol wt, 165. Found: C, 72.73; H, 9.20; N, 8.62; mol wt, 168 (acetone).

Addition Reactions of the Nitrile Oxides.—The isoxazoles 1–3 (Table I) were obtained by mixing the nitrile oxides with a 10% excess of phenylacetylene and allowing the reaction to proceed overnight at 25°. After removal of the excess phenylacetylene *in vacuo*, the solid residue was recrystallized once from aqueous methanol to yield an analytically pure product.

Addition of malononitrile was effected by refluxing for 15 min equal molecular quantities of the compounds (5 mmol) in methanol (5 ml) in presence of sodium methoxide (1 mmol).[13] The compounds 4–6 of Table I separated on dilution with water and were purified by one recrystallization from methanol–water.

The anilide oximes 7–9 of Table I were prepared by heating the nitrile oxide (2 mmol) and aniline (3 mmol) in benzene (2 ml) to reflux for 30 min. Solvent and excess aniline were then removed by vacuum steam distillation, leaving finally a solid residue which was recrystallized once from petroleum ether.

For the hydrolysis to the hydroxamic acid, the previously described procedure for mesitohydroxamic acid was used.[14] After one recrystallization compounds 10 and 11 of Table I were analytically pure.

The crude isocyanates **9–11** (2 mmol), obtained as described above, were mixed with a solution of aniline (2.2 mmol) in benzene (2 ml) and heated on the steam bath for 30 min. On

(12) L. Alessandri, *Atti Accad. Lincei*, [5] **19**, 122 (1910); *Chem. Abstr.*, **5**, 276 (1911).

(13) A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **76**, 146 (1946).

(14) C. Grundmann and H. D. Frommeld, *J. Org. Chem.*, **31**, 157 (1966).

cooling the mixed ureas 12–14 of Table I crystallized out and were purified by one recrystallization from ligroin (bp 60–70°).

Registry No.—2, 19202-78-9; 2 oxime, 19202-79-0; 3, 19203-41-9; 3 oxime, 19203-42-0; 6, 19203-43-1.

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Relative Rate Constants for Hydrogen Abstraction by Methyl Radicals from Substituted Toluenes[1,2]

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Atom abstraction is the most common reaction which radicals undergo, and hydrogen is the most commonly transferred atom.[4a] For this reason, it is important to amass data which can lead to mechanistic insights into the factors influencing this process. Recently, extensive studies have been reported of hydrogen abstraction by the phenyl and *p*-nitrophenyl radicals in solution.[5] There are extensive data on the methyl radical in the gas phase;[6] however, until recently the only data on hydrogen abstraction by methyl radicals in solution were the very limited data of Edwards and Mayo.[7a] Recently, Mayo[7b] himself, as well as other authors, have emphasized the importance of repeating this work. Some data have recently been published by Szwarc[8] and by Berezin and Dobish.[9] In this communication we present data on the Hammett correlation for the reaction of methyl with substituted toluenes. We conclude that methyl is a slightly electrophilic radical; the Hammett equation for abstraction from toluenes by methyl radicals gives a value of ρ^+ of about -0.1. Surprisingly, this is very near the value which correlates data for abstraction by the phenyl radical.[5] We briefly discuss our attempts to obtain relative rate constants for hydrogen abstraction from aliphatic hydrogen donors. For these solvents, the relative values of k_H are solvent dependent.

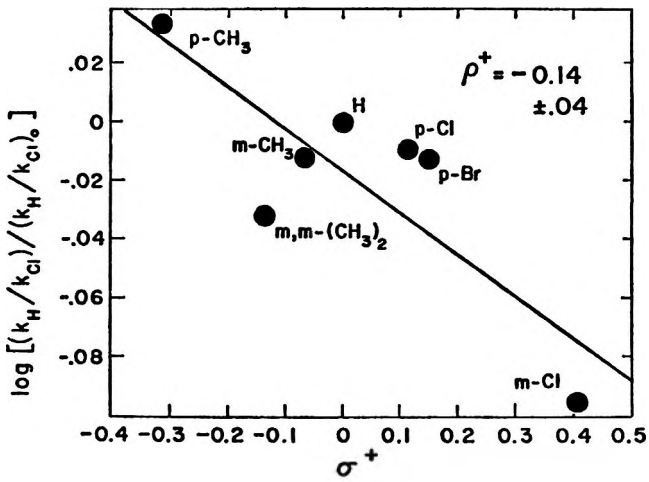

Figure 1.—The Hammett plot for the reaction of methyl radicals with substituted toluenes. The line shown is that given in eq 5 in the text.

We have used the experimental design originated by Edwards and Mayo in which 0.1 *M* solutions of acetyl peroxide are allowed to decompose in a mixed solvent consisting of carbon tetrachloride and a hydrogen donor, and the ratio of CH_4 and CH_3Cl in the products is related to k_H/k_{Cl} (eq 1 and 2). Edwards and Mayo

$$CH_3\cdot + RH \xrightarrow{k_H} CH_4 + R\cdot \quad (1)$$

$$CH_3\cdot + CCl_4 \xrightarrow{k_{Cl}} CH_3Cl + \cdot CCl_3 \quad (2)$$

used a complex gas separation procedure to obtain their analyses. We have used a technique in which 5 to 10 μl of the reaction solution is placed in a capillary tube, which is deaired, and sealed, and placed in a 100° bath, and allowed to react. The capillary is then crushed in the gas stream of an Aerograph Model 202-1 gas chromatograph using a Hewlett–Packard "Solid Sample Analyzer." A $\frac{1}{8}$ in. × 10 ft column of Porapac allows separation and analysis of the following components: CO_2, CH_4, CH_3Cl, C_2H_6, methyl acetate, carbon tetrachloride, and chloroform. The molar response of the gases was determined using both known amounts of the pure gases and standard mixtures made up on a vacuum line.[10]

In agreement with Edwards and Mayo,[7a] we find that some CH_4 is produced even when 0.1 *M* acetyl peroxide is allowed to decompose in pure CCl_4, and a correction must be applied in the mixed solvents for this methane.[5] We have calculated k_H/k_{Cl} values using eq 3 where

$$k_H/k_{Cl} = \frac{CH_4/CO_2 - M_0}{CH_3Cl/CO_2} R_0 \quad (3)$$

$R_0 = X_{CCl_4}/X_{RH}$ (X is the mol fraction[8c]) and $M_0 = (CH_4/CO_2)_0$ is the amount which must be subtracted to correct for the methane which does not arise from reaction 1. Using three values of R_0 and toluene as the hydrogen donor, the value of k_H/k_{Cl} is most nearly constant if M_0 is taken as 3.5% relative to CO_2 as 100.[11]

(1) Reactions of Radicals. 22.

(2) Supported in part by U. S. Public Health Service Grant GM-11908-03.

(3) (a) Postdoctoral Fellow supported by a grant from the Air Force Office of Scientific Research, AFOSR(SRC)-OAR, 1964–1966. (b) National Science Foundation College Teacher Research Participant, 1966–1968.

(4) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., New York, N. Y., 1966: (a) pp 150–175; (b) pp 87–90; (c) p 172; (d) p 164.

(5) (a) R. F. Bridger and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3754 (1963); (b) W. A. Pryor, J. T. Echols, and K. Smith, *ibid.*, **88**, 1189 (1966).

(6) For reviews, see (a) A. F. Trotman-Dickenson, "Free Radicals," Methuen and Co. Ltd., London, 1959; (b) "Gas Kinetics," Butterworth and Co. (Publishers) London, 1955.

(7) (a) F. G. Edwards and F. R. Mayo, *J. Amer. Chem. Soc.*, **72**, 1265 (1950); (b) F. R. Mayo, *ibid.*, **89**, 2654 (1967).

(8) (a) A. E. Eachus, J. A. Meyer, J. Pearson, and M. Szwarc, *ibid.*, **90**, 3646 (1968); (b) J. A. Meyer, V. Stannett, and M. Szwarc, *ibid.*, **83**, 25 (1961); (c) W. J. Cheng and M. Szwarc, *J. Phys. Chem.*, **71**, 2726 (1967); (d) R. P. Buckley, F. Leavitt, and M. Szwarc, *J. Amer. Chem. Soc.*, **78**, 5557 (1956); (e) M. Szwarc, *J. Polym. Sci.*, **16**, 367 (1955).

(9) (a) I. V. Berezin and O. Dobish, *Proc. Acad. Sci., USSR*, **142**, 1 (1962). (b) I. V. Berezin and O. Dobish, *ibid.*, **144**, 382 (1962); V. L. Antonovskii, I. V. Berezin, and L. V. Shevel'kova, *ibid.*, **134**, 887 (1960).

(10) Our analytical results have been confirmed for a number of runs by mass spectrographic analysis.

(11) Edwards and Mayo,[7a] found M_0 to be 0.035 mmol/mol of peroxide decomposed, or approximately 2.7% of the CO_2 yields, by a different method.

TABLE I
REACTION OF METHYL RADICALS WITH ARALKYL HYDROGEN DONORS AND CARBON TETRACHLORIDE MIXTURES AT 100°

Hydrogen donor, RH	X_{CCl_4}/X_{RH}[a]	Moles formed/100 mol of CO_2				n[b]	k_H/k_{Cl}
		CH_4	C_2H_6	CH_3Cl	CH_3OAc		
Toluene	0.44	31.3	4.6	41.6	13.6	8	0.29
Toluene	0.47	28.5	4.0	41.6	13.6	4	0.28
Toluene	0.81	22.3	4.2	51.2	14.3	12	0.30
Toluene	1.61	14.9	4.4	62.2	14.5	6	0.30
Ethylbenzene	0.44	48.9	4.4	26.6	14.8	5	0.74
Ethylbenzene	0.82	38.3	4.2	36.5	14.2	5	0.76
Ethylbenzene	1.62	28.4	4.3	47.9		4	0.82
Cumene	0.47	56.4	4.4	19.2		3	1.29
p-Phenoxytoluene	0.41	21.7	5.2	32.0	42	4	0.23
p-Phenoxytoluene	0.60	17.8	5.3	40.0	44	3	0.21
p-Xylene[c]	0.44	42.0	4.0	26.7	15.9	5	0.63
p-Xylene[c]	0.65	37.0	4.2	34.3	15.6	3	0.63
m-Xylene[c]	0.43	41.2	4.0	27.8	17.6	3	0.58
m-Xylene[c]	0.65	35.1	4.2	36.4	18.7	3	0.56
p-Chlorotoluene	0.41	27.4	4.2	35.3	21	4	0.27
p-Chlorotoluene	0.54	26.0	4.7	40.2		3	0.30
p-Bromotoluene	0.41	25.9	5.2	33.0	21	4	0.27
p-Bromotoluene	0.60	21.9	5.6	36.7	21	3	0.29
m-Chlorotoluene	0.42	24.7	4.4	36.8		3	0.24
m-Chlorotoluene	0.58	20.8	4.1	42.3		2	0.23

[a] Ratio of the mole fraction of CCl_4 to RH in the reaction solution. [b] Number of duplicate runs. [c] The value plotted in Figure 1 has been statistically corrected by dividing by 2.

With ethylbenzene as the hydrogen donor, three values of R_0 gave $M_0 = 4.3\%$ of CO_2. In the calculations in Table I we have used these values of M_0: 0.035 for toluene, 0.043 for ethylbenzene, and an average of 0.039 for the remainder of the solvents. The precise value of M_0 does not affect the value of k_H/k_{Cl} by more than 5%.

We have studied a wide range of hydrogen donors. However, the k_H/k_{Cl} values for substrates which do not possess an aromatic ring are not independent of the solvent ratio. We, therefore, will discuss our data on aromatic solvents first and will return to a consideration of the nonaromatic donors. Table I gives the data and Figure 1 shows the Hammett plot for the reaction of methyl radicals with substituted toluenes. The least-square equations using σ and σ^+ are the following.[12]

$$\log \frac{(k_H/k_{Cl})}{(k_H/k_{Cl})_0} = (-0.121 \pm 0.062)\sigma - (0.010 \pm 0.001) \quad (4)$$

$$\log \frac{(k_H/k_{Cl})}{(k_H/k_{Cl})_0} = (-0.139 \pm 0.045)\sigma^+ - (0.015 \pm 0.009) \quad (5)$$

Figure 1 shows the correlation with σ^+ since this parameter is most often used to correlate radical reactions.[4c] Clearly, methyl radicals have very little polar character, and the value of ρ is too small to either distinguish σ from σ^+ meaningfully or to allow determination of ρ with great precision. Nevertheless, the Hammett correlation is a convenient way to capsulize the polar character of radical species, and in this sense the value $\rho \cong -0.1$ for methyl is quite descriptive. The phenyl radical gives about the same value of ρ;[5] *p*-nitrophenyl, in contrast, is appreciably electrophilic.[5b] Methyl and phenyl radicals also appear quite similar in their reactions with the series toluene/ethylbenzene/cumene. Our data give the relative k_H value *per reactive benzylic hydrogen* for the methyl radical to be 1:3.9:12.9. This agrees closely with Szwarc[8a,b] who reported 1:4.0:12. This pattern[5a] for the phenyl radical is 1:4.6:9.7. The more selective *p*-nitrophenyl radical[5b] gives the pattern 1:6.3:26. The striking similarities in the phenyl and methyl radicals in these reactions are surprising in view of the differing electronegativities of the two groups and of the differing bond dissociation energies of CH_3–H and of C_6H_5–H.[13]

We now wish to discuss our data on aliphatic solvents. We observed that the k_H/k_{Cl} values for alkanes and cycloalkanes are not independent of the solvent ratio R_0. For these solvents, we also observed that amounts of chloroform were produced which were up to ten times greater than the amounts of the $\cdot CCl_3$ radical produced in eq 2. It is clear that some chain process produces chloroform in these solvents, and we suggest eq 6 and 7. This sequence prohibits the use of eq

$$R\cdot + CCl_4 \rightarrow RCl + \cdot CCl_3 \quad (6)$$

$$\cdot CCl_3 + RH \rightarrow HCCl_3 + R\cdot \quad (7)$$

3 to obtain relative k_H values for two reasons. First, so much CCl_4 is used that its concentration does not remain constant during an experiment. Second, the chloroform which is produced is a surprisingly good

(12) (a) The point for *p*-phenoxytoluene has been omitted from the correlation. The σ^+ value for this substituent is uncertain; it has been reported to be −0.57 by G. A. Russell and R. C. Williamson [*J. Amer. Chem. Soc.*, **86**, 2357 (1964)] and −0.899 by C. G. Swain and E. C. Lupton, Jr. [*ibid.*, **90**, 4328 (1968)]. Regardless of which of these values is chosen, however, the correlation requires that the *p*-phenoxy substituent increase the rate constant, whereas actually *p*-phenoxytoluene reacts with methyl radicals more slowly than does toluene. This pattern has been observed before. For example, *p*-phenoxytoluene reacts more slowly than does toluene with phenyl radicals.[5a] It reacts at about the same rate as does toluene and much more slowly than predicted by the Hammett plot, with the *p*-nitrophenyl radical.[5b] It reacts somewhat faster than toluene, but again much more slowly than predicted from the Hammett plot, with the peroxy radical (Russell and Williamson, reference cited above). (b) The application of eq 8 requires that ethane and methyl acetate are produced exclusively in cage reactions which occur independently of the partition of methyl between RH and CCl_4 in free solution.[4b] The data in Table I support this assumption for all the solvents except *p*-phenoxytoluene which has a higher viscosity and appears to be anomalous. (c) The mesitylene point in Figure 1 is from ref 8a. Inclusion of this point hardly affects the value of ρ or the goodness of it. For example, without this point and using σ^+, ρ is (−0.161 ± 0.037) and the intercept is (−0.008 ± 0.008).

(13) The value of $D(CH_3$–H) is 104[14]. The value of $D(C_6H_5$–H) is 112: A. S. Rogers, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **89**, 4578 (1967).

hydrogen donor; much better, in fact, than are most of the RH compounds. By measuring the yields of methane and chloromethane from reaction of acetyl peroxide in mixtures of chloroform and carbon tetrachloride, we obtained these ratios of rate constants: $k_H/k_{Cl} = 160$; $k_H/k_{Cl}' = 53$; $k_{Cl}'/k_{Cl} = 3.2$, where k_H is the rate constant for abstraction of hydrogen from $CHCl_3$, k_{Cl}' is that for abstraction of chlorine from $CHCl_3$, and k_{Cl} is that for abstraction of chlorine from CCl_4. Thus, even fairly short chain lengths for reactions 6 and 7 could produce sufficient $CHCl_3$ to seriously affect the apparent k_H/k_{Cl} value obtained for RH. These conclusions are in accord with the findings of DeTar[15] who studied the hexyl radical using reaction with CCl_4 as the standard. He also found that for aliphatic solvents, $\cdot CCl_3$ reacts with RH to produce $CHCl_3$ and RCl in a reaction with an appreciable chain length.

The difficulty in using CCl_4 as the standard substrate for aliphatic but not for aromatic solvents can be rationalized by a consideration of the heats of reactions 6 and 7. For RH equal to ethane, the heats are -8 and $+2$ kcal/mol, for reactions 6 and 7, respectively; for toluene as RH, the heats are $+5$ and -11.[14] Thus, the chain sequence 6 and 7 is blocked for aromatic donors by the high enthalpy, and consequently high activation energy, of reaction 6. It would appear that this difficulty could be circumvented by using a standard substrate which has a higher bond strength than does CCl_4; unfortunately, this does not appear to be the case. Berezin and Dobish[9b] used the reaction of methyl radicals with tritiated heptane as their standard reaction. However, Table I of their publication[9b] shows that their values of the relative rate constant for hydrogen abstraction also are quite solvent dependent. At present, therefore, there is no satisfactory method for putting the relative rate constants for abstraction of hydrogen from aliphatic and aromatic solvents on the same scale.

This has one important consequence. The relative rate constants measured by Edwards and Mayo are widely quoted and are compared with data for the reaction of methyl radicals in the gas phase. It is often pointed out that the only solvent which appears to give a relative rate constant in solution which does not parallel the gas phase data is cyclohexane.[4d,7b,15,16] This solvent is, in fact, the only solvent studied by Edwards and Mayo which is saturated. It would appear, therefore, that the Edwards and Mayo value of k_H/k_{Cl} for cyclohexane is not reliable; in fact, we find that this value is solvent dependent.

Finally, it is interesting to consider a consequence of the simple mechanism indicated by eq 1 and 2. If eq 1 is the only important methane-producing reaction, and if all the *free* methyl radicals[12b] react either with the hydrogen donor RH or with CCl_4, then one should be able to calculate k_H/k_{Cl} as in eq 8 where M_0 has the same

$$k_H/k_{Cl} = \frac{CH_4/CO_2 - M_0}{[CH_4/CO_2]_{ps} - CH_4/CO_2} R_0 \qquad (8)$$

meaning as before and $[CH_4/CO_2]_{ps}$ is the relative yield of methane obtained in the pure hydrogen donor as solvent.[17] We find that eq 3 and 8 give essentially the same values of k_H/k_{Cl} for aromatic substrates but give very different values for aliphatic donors. This again indicates the solvent dependence of the relative k_H values in aliphatic solvents. Clearly, it is better to calculate k_H/k_{Cl} values using eq 3, but the agreement between eq 3 and 8 gives confidence that this system does yield a simple partition of free methyl radicals between reaction with RH or CCl_4 in aromatic solvents.

Registry No.—Methyl radical, 2229-07-4; toluene, 108-88-3; ethylbenzene, 100-41-4; cumene, 98-82-8; *p*-phenoxytoluene, 1,706-12-3; *p*-xylene, 106-42-3; *m*-xylene, 108-38-3; *p*-chlorotoluene, 106-43-4; *p*-bromotoluene, 106387; *m*-chlorotoluene, 108418.

Acknowledgment.—We wish to thank Dr. Donald F. Hunt, then at the Massachusetts Institute of Technology and now at the University of Virginia, for the mass spectrographic analyses.

(14) J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966).
(15) D. F. DeTar and D. V. Wells, *J. Amer. Chem. Soc.*, **82**, 5839 (1960).
(16) Reference 6a, p 70.

(17) We have measured the value of CH_4/CO_2 in these pure solvents: toluene, 0.730; *p*-xylene, 0.682; *p*-bromotoluene, 0.495 (also see ref 8e). We have used the toluene value for toluene, ethylbenzene, and cumene, the xylene value for both xylenes, and the bromobenzene value for all other solvents in eq 8.

Additions of Sulfenyl Chlorides to Acetylenes. XII.[1a] Addition to *t*-Butylacetylene[1b]

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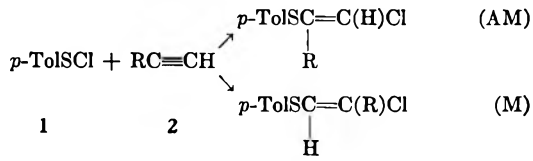
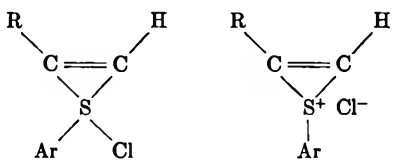
Both Markovnikov (M) and anti-Markovnikov (AM) orientations have been observed in the addition of *p*-toluensulfenyl chloride to acetylenes[2] depending on the nature of the acetylene and on the solvent (with



R = alkyl, 100% AM in all solvents;[3,4] with R = phenyl, 100% AM in ethyl acetate, 29% AM and 71% M in acetic acid). The effects are such that the phenyl substitution at the acetylenic carbons and good hydrogen bonding solvents[5] favor a shift from AM to M addition.

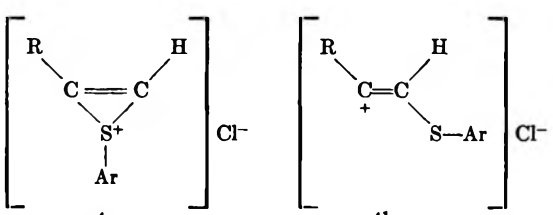
(1) (a) Part XI: L. Di Nunno and G. Scorrano, *Ric. Sci.*, **38**, 343 (1968). (b) This work has been supported by a grant from the Consiglio Nazionale delle Ricerche, Roma. (c) To whom all correspondence should be addressed at the Istituto di Chimica Organica, Via Marzolo, 1, Padova, Italy.
(2) V. Calò, G. Modena, and G. Scorrano, *J. Chem. Soc., C*, 1339 (1968).
(3) Small amounts of M-type adducts have been observed in the addition to alkylacetylenes of *o*-nitrobenzensulfenyl chloride[2] and dimethylaminosulfenyl chloride.[4]
(4) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **33**, 2111 (1968).
(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell Publishers, London, 1953; K. B. Wiberg "Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1964, Chapter 3; A. J. Parker, *Quart. Rev.* (London), 163 (1962); R. Alexander and A. J. Parker, *J. Amer. Chem. Soc.*, **89**, 5549 (1967); M. A. P. Dankleff, R. Curci, J. O. Edwards, and H. Y. Pyun, *ibid.*, **90**, 3209 (1968).

These results have been explained[2] in terms of a common intermediate which leads *via* internal collapse to the AM products, or *via* dissociation into chloride and organic ions to the M products. Following such hypothesis, the intermediate complex formed on reaction of the sulfenyl chloride with the acetylene may be tentatively represented as either a covalent species **3a** or a tight ion pair **3b**. Other resonances or equilibrium structures resembling **3a** and **3b** could also be formulated. The intermediate complex would then collapse to the products by a transition state characterized by little charge separation, yielding the AM adducts.[6] Alternatively **3**, under the influence of a



3a **3b**

good solvent for Cl^- and the stabilizing effect of R on the cation, may dissociate into a loose ion pair or into free ions (represented as **4a** and **4b**)[7] before collapsing to the final product. This product should have the M structure as expected for a two step polar addition. In other words, the transition state leading to the M adducts would be characterized by a much larger degree of charge separation than the one leading to the AM adducts.

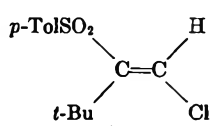
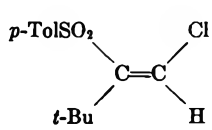
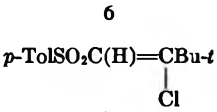


4a **4b**

We wish to report the results of the addition of **1** to *t*-butylacetylene in ethyl acetate and in acetic acid and to relate them to the above problem.

TABLE I

RELATIVE YIELDS OF ISOLATED OXIDATION PRODUCTS IN THE ADDITION OF *p*-TOLUENSULFENYL CHLORIDE TO *t*-BUTYLACETYLENE

	Ethyl acetate	Acetic acid
 **5**	96	38
 **6**	4	7
 **7**	0	5

(6) The collapse to AM adducts of **3a** or **3b** is not well understood. The formation of AM products is an experimental fact and might be due to an appropriate balance of short distance interactions of the groups present in the intermediate complex.

(7) It is not possible at this stage to say whether the cation is better represented by **4a**, and **4b**, or by an equilibrium among them.

The additions have been carried out as previously described.[2,8] After the usual work-up of the solution, the oily residue was distilled at reduced pressure (yield 90%) and oxidized with peroxybenzoic acid in chloroform. The sulfones were separated by column chromatography on silica gel. The oxidation as well as the chromatographic separation gave almost quantitative yields. The results are collected in Table I.[9] The structures of sulfones **5** and **6** have been assigned on the basis of the nmr spectra[2,10] ($CDCl_3$ solutions = CH; **5**, τ 2.24; **6**, τ 3.31) and from the known stereochemistry of reactions of this kind.[2,4,10-16] The stereochemistry of **7** has not yet been defined; by analogy with the results found in similar reactions[2,4,10-16] it should be the *trans* isomer ($ArSO_2$ to Cl).

As pointed out in a previous paper,[10] the presence of the *cis* isomer does not affect the discussion on orientation, since it is due to a successive *trans–cis* isomerization.

As the results above reported show, the preferred orientation of the addition to *t*-butylacetylene is once again the anti-Markovnikov one, but, at variance with the reaction of *n*-butyl- and ethylacetylene,[2,8] a small but significant amount of M adduct is formed in the present case.

In terms of the mechanism proposed for these reactions, it should mean that the *t*-butyl group is favoring the ionization of the intermediate complex **3** more than the other alkyl groups. This could be justified on the basis of the greater +I effect of *t*-butyl[17] in respect to *n*-alkyl. These results would indicate that the stabilizing effect of R on **4a** has to be preferentially inductive in character as observed in the formally similar case of the cyclopropenyl cations.[18] It could be argued, however, that the intervention of a hyperconjugative effect might have caused an opposite shift on the orientation; in our opinion a detailed analysis of the various factors involved in the system under investigation may not be straightforward at this stage.

Experimental Section[19]

Adducts of *t*-Butylacetylene to *p*-Toluenesulfenyl Chloride (1).—The reactions were run in ethyl acetate and acetic acid by adding dropwise to *t*-butylacetylene (0.11 mol in 200 ml of solvent) a solution of **1** (0.1 mol in 50 ml). The solutions were maintained at room temperature until the sulfenyl chloride color was essentially absent. The ethyl acetate solution was washed (water, dilute $NaHCO_3$, water), dried (Na_2SO_4), concentrated

(8) A. Dondoni, G. Modena, and G. Scorrano, *Boll. Sci. Fac. Chim. Ind. Bologna*, **22**, 26 (1964).

(9) When this work was completed we learned from G. Viehe (Union Carbide European Research Associates, Bruxelles, Belgium) that the reaction of concentrated benzene solutions of benzenesulfenyl chloride with *t*-butylacetylene yields a products mixture which composition parallels our results in acetic acid solvent (Halocarbon Chemistry Conference, Wayland, Mass., May 6–7, 1968, and personal communication).

(10) V. Caló, G. Modena, and G. Scorrano, *J. Chem. Soc., C*, 1339 (1968).

(11) F. Montanari, *Gazz. Chim. Ital.*, **86**, 735 (1956).

(12) W. E. Truce and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2748 (1965).

(13) L. Maioli, G. Modena, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna*, **18**, 58 (1960).

(14) L. Benati, M. Tiecco, and A. Tundo, *ibid.*, **21**, 177 (1963).

(15) N. Kharasch and C. N. Yiannios, *J. Org. Chem.*, **29**, 1190 (1964).

(16) V. Caló and G. Scorrano, *Gazz. Chim. Ital.*, **98**, 545 (1968).

(17) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newmann, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956.

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(19) All melting points are uncorrected. The nmr spectra were measured on a Varian A-60 instrument and the shifts are from tetramethylsilane as an internal standard.

and distilled under reduced pressure (1 mm) giving 20.5 g (90%) of the sulfides. The oxidation by peroxybenzoic acid in chloroform gave, in almost quantitative yields, a mixture of ethylenic sulfones from which compounds **5** and **6** can be isolated by column chromatography on silica gel (eluents petroleum ether (bp 30–60°)–ethyl ether 2:1). The chromatographic separation was almost quantitative (over-all yields on sulfides >90%).

The acetic acid solution was poured in iced water and extracted with ether. The ethereal extract has been worked up as the ethyl acetate solution giving a mixture of the three sulfones **5**, **6** and **7** (see Table I).

Identification of Sulfones 5, 6, and 7.—The three sulfones, recrystallized from petroleum ether, gave satisfactory analyses for 1:1 adducts in the oxidized form [*Anal.* Calcd for $C_{13}H_{17}ClO_2S$: Cl, 12.99; S, 11.75. Found. (**5**, mp 84–85°): Cl, 13.00; S, 11.68. (**6**, mp 88–89°) Cl, 13.12; S, 11.71. (**7**, mp 83–84°) Cl, 13.15; S, 11.90]. Hydrogenation of **5** and **6** over 5% palladium–charcoal in ethanol (3.5 atm for 4 hr at room temperature) yielded the same (1,2,2-trimethyl)propyl *p*-tolyl sulfone (**8**). Hydrogenation of **7** yielded (3,3-dimethyl)butyl *p*-tolyl sulfone (**9**).

(1,2,2-Trimethyl)propyl *p*-tolyl sulfone (8) has been synthesized by oxidation of the corresponding sulfide **10** with peroxybenzoic acid in chloroform, mp 67–68° from methanol. *Anal.* Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.96; H, 8.39; S, 13.20.

(3,3-Dimethyl)butyl *p*-tolyl sulfone (9) was obtained by oxidation of the corresponding sulfide **11**, mp 97–98° from methanol. *Anal.* Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.82; H, 8.39; S, 13.28.

(1,2,2-Trimethyl)propyl *p*-tolyl sulfide (10) was obtained by reaction of *p*-bromobenzensulfonic acid (1,2,2-trimethyl)propyl ester[20] with sodium *p*-toluenethiolate in ethanol, bp 118–120° (1 mm). *Anal.* Calcd for $C_{13}H_{20}S$: C, 74.93; H, 9.68; S, 15.41. Found: C, 74.09; H, 9.44; S, 15.30.

(3,3-Dimethyl)butyl *p*-tolyl sulfide (11), obtained by reaction of 1-bromo-3,3-dimethylbutane with sodium *p*-toluenethiolate in ethanol, had bp 104–106° (1 mm). *Anal.* Calcd for $C_{13}H_{20}S$: C, 74.93; H, 9.68; S, 15.41. Found: C, 75.16; H, 9.59; S, 15.10.

Registry No.—*t*-Butylacetylene, 917-92-0; **5**, 19519-80-3; **6**, 19519-81-4; **7**, 19519-66-5; **8**, 19519-67-6; **9**, 19519-68-7; **10**, 19519-69-8; **11**, 19519-70-1.

Acknowledgments.—We thank Professor F. Taddei, Istituto di Chimica Organica e di Chimica Industriale, Bologna, for the nmr spectra.

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Organosulfur Derivatives of Azulene. III. Di-1-azulyl Sulfide, Sulfoxide, and Sulfone[1a]

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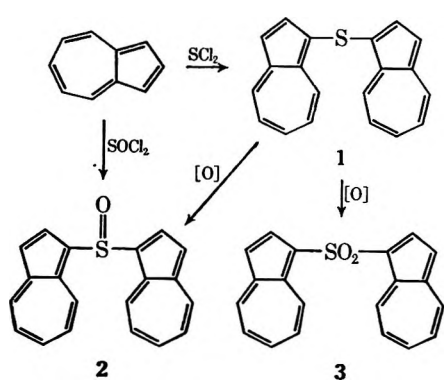
Earlier papers in this series have described the preparation and properties of some methyl and phenyl 1-azulyl sulfides[2] and the corresponding sulfoxides and sulfones.[3] This paper is concerned with the symmetrical derivatives di-1-azulyl sulfide (**1**), di-1-azulyl sulfoxide (**2**), and di-1-azulyl sulfone (**3**).

It is known that aromatics react with sulfur dichloride to form symmetrical diaryl sulfides[4] and with thionyl chloride to form symmetrical diaryl sulfoxides.[5] Azulenes react with benzenesulfenyl chloride to give phenyl 1-azulyl sulfides[2,6] and with methanesulfinyl and benzenesulfinyl chlorides to give methyl and phenyl 1-azulyl sulfoxides.[3] Also, it was reported[7] that the reaction of the sodium salt of 1-azulenesulfonic acid with thionyl chloride gave azulene-1-sulfonyl-3-sulfinyl dichloride. Therefore, it was expected that di-1-azulyl sulfide (**1**) and di-1-azulyl sulfoxide (**2**) should result from the reaction of azulene with sulfur dichloride and thionyl chloride, respectively.

Azulene reacted vigorously with sulfur dichloride in anhydrous ether at −78° to give an 18% yield of the blue, crystalline di-1-azulyl sulfide (**1**). The sulfide (**1**) was characterized by its elemental analysis, its nmr spectrum, which was characteristic of a 1-substituted azulene, and its visible spectrum with λ_{max} 598 mμ. Much unreacted azulene was recovered from this reaction as well as a considerable amount of polymeric green solid. Variations in reaction conditions such as different solvents (tetrahydrofuran, chloroform, or acetonitrile), different temperatures (−45 or −111°), or the inclusion of pyridine did not increase the yield of the sulfide (**1**).

A 21% yield of di-1-azulyl sulfoxide (**2**) was obtained from the reaction of azulene with thionyl chloride in acetonitrile at −45°. The sulfoxide (**2**), a purple, crystalline solid, had λ_{max} 557 mμ and a band at 9.75 μ (S=O) in its infrared (ir) spectrum. The sulfide (**1**) was isolated in very low yield from one of the reactions between azulene and thionyl chloride.[8] When the reaction was carried out at −70° in anhydrous ether, another product, a red solid which eluted before the sulfoxide (**2**), was isolated in low (*ca.* 4%) yield. This red solid was later identified as di-1-azulyl sulfone (**3**) (Scheme I). An attempt to form the sulfone (**3**)

SCHEME I



(1) (a) Supported in part by Grant GP-3885 from the National Science Foundation. (b) National Science Foundation Undergraduate Research Participant, 1967.

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by treating azulene with sulfuryl chloride was unsuccessful, yielding unreacted azulene and a small amount of green oil which probably contained 1-chloro- and 1,3-dichloroazulene. When the sulfide was oxidized by sodium metaperiodate in refluxing methanol for 1 hr, the sulfoxide **2** was obtained in good yield (78%) along with a small amount (5%) of the sulfone **3**. A similar oxidation of **1** for 24 hr afforded di-1-azulyl sulfone (**3**) in good (81%) yield. The sulfone was characterized by its elemental analysis, its λ_{max} at 541 mμ, the bands in its ir spectrum at 7.72 and 8.93 μ, and its nmr spectrum.

A few attempts to prepare tri-1-azulylsulfonium chloride were carried out. It has been reported[9] that triarylsulfonium chlorides result from the reaction of the arene with thionyl chloride and aluminum chloride. Azulene was allowed to react with thionyl chloride and anhydrous stannic chloride in acetonitrile at −45°. A small amount of purple solid was obtained from the dichloromethane extract by twice precipitating it by addition to anhydrous ether. This purple solid, which was suspected to be tri-1-azulylsulfonium chloride, was rather unstable, and we were not able to obtain it in pure form. On heating, it decomposed, turning black, at about 150°.

The shift of the visible band of azulene due to methyl- and phenylthio,[2] methyl- and phenylsulfinyl,[3] and methyl- and phenylsulfonyl[3] groups substituted at the 1 position has been reported and discussed. It is known that electron-withdrawing substituent groups at the 1 position of azulene cause hypsochromic shifts,[10] and the observed shifts of −9 mμ for a phenylthio group, −32 mμ for a phenylsulfinyl group, and −47 mμ for a phenylsulfonyl group are consistent with their relative electron-withdrawing character. In comparison, the spectral shifts (Table I) for the sulfide **1**

TABLE I

PRINCIPAL VISIBLE ABSORPTION MAXIMA AND SPECTRAL SHIFTS OF DI-1-AZULYL SULFIDE, SULFOXIDE, AND SULFONE

Compound	λ_{max}, mμ	$\Delta\lambda_{max}$, mμ
$(1\text{-Az})_2S$ (**1**)	598[a]	+18[c]
$(1\text{-Az})_2SO$ (**2**)	557[b]	−20[b]
$(1\text{-Az})_2SO_2$ (**3**)	541[b]	−36[b]

[a] Cyclohexane solution. [b] Chloroform solution.

(+18 mμ), the sulfoxide **2** (−20 mμ), and the sulfone **3** (−36 mμ) are all more bathochromic than the corresponding phenyl derivatives. Since azulene is electron rich at the 1 position, one would expect a 1-azulyl group to donate electron density to an attached sulfur atom and that a 1-azulylthio, 1-azulenesulfinyl, or 1-azulenesulfonyl group would be less electron withdrawing than the corresponding substituent group which has a phenyl in place of the 1-azulyl moiety.

Experimental Section[11]

Di-1-azulyl Sulfide (1).—To a stirred solution of 640 mg (5.00 mmol) of azulene in approximately 50 ml of anhydrous ether, kept at −78° under an argon atmosphere was added a solution of 0.19 ml (310 mg, 3.0 mmol) of sulfur dichloride in 10 ml of anhydrous ether dropwise over a period of 2 hr. The reaction mixture was poured into ice water and the layers were separated. The aqueous layer was extracted several times with ether, leaving much insoluble green solid behind. Solvent was removed from the combined blue-green ethereal extracts, and the residue was chromatographed over acid-washed alumina. A large blue band which contained unreacted azulene (222 mg) was eluted with petroleum ether, and the darker blue band was eluted with 1:1 petroleum ether–dichloromethane. A large green band followed. The blue-green oily residue from the second band was recrystallized from petroleum ether containing traces of dichloromethane to give 130 mg (18% gross, 28% net yield) of dark blue crystals of di-1-azulyl sulfide (**1**): mp 87–88°; uv max (cyclohexane) 238 mμ (log ε 4.56), 278 (4.77), shoulder at 293 (4.66), 337 (3.93), and 371 (4.07); visible max (cyclohexane) 598 mμ (log ε 2.73) 622 (2.73), and shoulder at 680 (2.52); nmr ($CDCl_3$) τ 1.23 (d, J = 9 Hz, H-8), 1.82 (d, J = 9 Hz, H-4), 2.27 (d, J = 4 Hz, H-2), 2.75 (d, J = 4 Hz, H-3), and 2.4–3.1 (m, H-5, H-6, H-7).

Anal. Calcd for $C_{20}H_{14}S$: C, 83.87; H, 4.93. Found: C, 83.75; H, 4.99.

Di-1-azulyl Sulfoxide (2). A. By Oxidation of 1.—A mixture of 170 mg (0.596 mmol) of di-1-azulyl sulfide, 0.70 ml of 1 *M* aqueous sodium metaperiodate, and 25 ml of methanol was refluxed until tlc (silica gel G, dichloromethane) showed that most of sulfide (front-running blue spot) had reacted and that di-1-azulyl sulfone (intermediate red spot) was being produced (*ca.* 1 hr). Water was added and the mixture was extracted with ether and then with dichloromethane. The organic extracts were combined and dried ($MgSO_4$), and the solvent was removed. The residue was chromatographed over acid-washed alumina; the small blue band which contained 14 mg of unreacted sulfide was eluted with 2:1 petroleum ether–dichloromethane. A small red band which yielded 10 mg (5%) of di-1-azulyl sulfone (**3**), mp 188–189°, was eluted with dichloromethane, and the large purple band was eluted with 1:1 ether–acetone. The residue from the purple eluate was recrystallized from a petroleum ether–dichloromethane mixture to give 140 mg (78%) of di-1-azulyl sulfoxide (**2**): purple crystals; mp 94–95°; uv max ($CHCl_3$) 282 mμ (log ε 4.78), shoulder at 298 (4.40), 336 (4.14), and 373 (4.20) visible max 557 mμ (log ε 2.91); ir ($CHCl_3$) 9.81 μ (S=O); nmr ($CDCl_3$) τ 1.05 (d, J = 9 Hz, H-8), 1.65 (d, J = 9 Hz, H-4), 2.07 (d, J = 4 Hz, H-2), 2.70 (d, J = 4 Hz, H-3) and 2.3–2.7 (m, H-5, H-6 and H-7).

Anal. Calcd for $C_{20}H_{14}OS$: C, 79.44; H, 4.67. Found: C, 79.14; H, 4.55.

B. From Azulene and Thionyl Chloride.—A solution of 0.188 ml (180 mg, 1.5 mmol) of freshly distilled thionyl chloride in 8 ml of dry acetonitrile was added dropwise over a period of 15 min to a stirred, cooled (−45°) mixture of 387 mg (3.02 mmol) of azulene and 25 ml of acetonitrile kept under a dry nitrogen atmosphere. The temperature of the reaction mixture was allowed to rise to −40°, 0.10 ml of pyridine was added, and this mixture was poured into water. The purple mixture was extracted with dichloromethane. Solvent was removed from the organic extract, and the residue was chromatographed over acid-washed alumina. Dichloromethane eluted a large green band which had a small blue front. Some small brown, yellow, and pink bands were eluted before the large purple band (1:1 ether–acetone). The purple eluate yielded 95 mg (21%) of **2** as a purple, crystalline solid, mp 94.5–95.5°. An ir spectrum of this product (chloroform solution) was identical with the ir spectrum of the product above.

Di-1-Azulyl Sulfone (3).—A mixture of 193 mg (0.675 mmol) di-1-azulyl sulfide, 1.5 ml of aqueous 1 *M* sodium metaperiodate, and 25 ml of methanol was refluxed for 24 hr. The reaction mixture was treated in a manner similar to that (method A) above. Chromatography gave a small blue band, eluted with 1:4 dichloromethane–chloroform, which contained 20 mg of unreacted sulfide and a large red band, eluted with dichloromethane.

(9) S. Smiles and R. L. Rossignol, *J. Chem. Soc.*, **89**, 698 (1906).

(10) (a) E. Heilbronner in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, New York, N. Y., 1959, Chapter V; (b) A. G. Anderson, Jr., and B. M. Steckler, *J. Amer. Chem. Soc.*, **81**, 4941 (1959).

(11) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded using a Beckman IR-5; ultraviolet and visible spectra were taken on a Cary 14. Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as the internal marker. Coupling constants were taken directly from the spectra and are apparent values. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., or by Berkeley Analytical Laboratories, Berkeley, Calif.

The red eluate yielded 175 mg (81%) if di-1-azulyl sulfone (**3**): red crystals; mp 187–188°; uv max ($CHCl_3$) 276 mμ (log ε 4.67), 296 (4.57), 306 (4.53), 366 (4.09), and 381 (4.10); visible max 541 mμ (log ε 2.95) and a shoulder at 625 (2.45); ir ($CHCl_3$) 7.72 and 8.93 μ (SO_2); nmr τ 0.55 (d, J = 10 Hz, H-8), 1.58 (d, J = 10 Hz, H-4), 1.62 (d, J = 4 Hz, H-2), 2.72 (d, J = 4 Hz, H-3) and 2.0–2.7 (m, H-5, H-6, and H-7).

Anal. Calcd for $C_{20}H_{14}SO_2$: C, 75.44; H, 4.43; S, 10.07. Found: C, 75.41; H, 4.42; S, 9.79.

Registry No.—**1**, 19254-87-6; **2**, 19254-88-7; **3**, 19254-89-8.

The Reduction of Nitroso Compounds with Diborane

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Received October 22, 1968

In continuation of our studies of the reduction of unsaturated nitrogen functions with diborane,[1] we are now reporting the results with aromatic nitroso compounds, *gem*-nitronitroso, *gem*-chloronitroso, and *gem*-nitrooximino compounds.

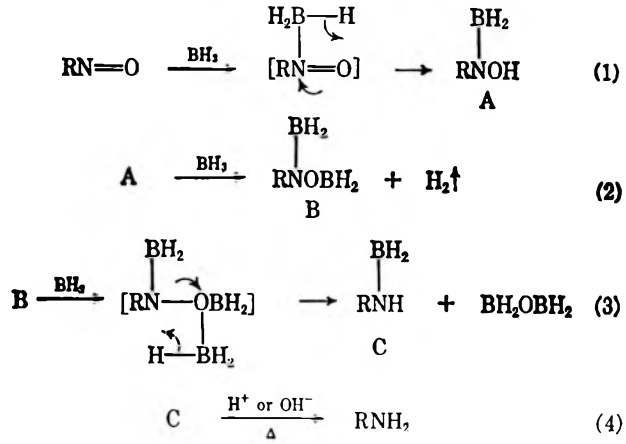
The reduction of aromatic nitroso compounds catalytically or with atomic hydrogen to amines is well documented in the literature.[2] Treatment of *p*-nitrosophenol with sodium borohydride led to *p*-aminophenol (42%);[3] however, nitrosobenzene itself was reduced to azoxybenzene in 73% yield.[3]

As shown by representative examples in Table I, the reduction of aromatic nitroso compounds with diborane at 25° afforded the corresponding amines in good yields. It is of interest to point out that while *p*-nitroso-N,N-dimethylaniline was reduced to 1-amino-4-dimethylaminobenzene in 64% yield, the product of reduction with lithium aluminum hydride was 4,4′-azobis(N,N-dimethylaniline) (80%).[4]

In general the reactions were found to be highly exothermic, and 1 equiv of hydrogen was evolved immediately after the addition of diborane, although no acidic hydrogen was present in the starting material. Hydrogen evolution was also observed by Boyer and Ellzey[3] when *o*-dinitrosobenzene was treated with sodium borohydride.

By employing nitrosobenzene (**1**) as a model compound, it was found that the yield of amine was, over a wide range, independent of the amount of hydride ion per mol of **1**.[5]

On the basis of quantitative measurements of hydride consumption (3 equiv of hydride ion were consumed in the reduction, 1 equiv of which was evolved as hydrogen *prior* to hydrolysis) it is proposed that the reduction of aromatic nitroso compounds with diborane involves essentially four steps (eq 1–4).

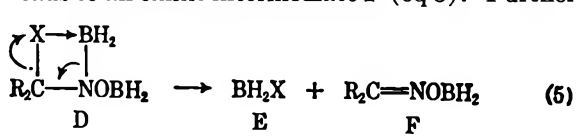


Although intermediates A, B, and C are represented as monomeric, it is quite possible that they are polymeric in nature. The electrophilic attack of diborane on nitrogen in step 1 explains the formation of a hydroxyl group in intermediate A by a four-centered hydride transfer. In step 2, the electrophilic attack on the hydroxyl proton[6] is supported by the fact that hydrogen was evolved during the reaction *prior* to hydrolysis. The possibility of the formation of a hydroxylamine intermediate such as B is based on our findings that phenylhydroxylamine was readily reduced by diborane to aniline (65%) at 25°.[7] The remaining steps 3 and 4 are similar to those proposed for the reduction of oxime ethers with diborane.[1]

A recent report by Exner,[8] that 1,1-nitronitrosocyclohexane (**2**) was converted into cyclohexanone oxime (79%) at 15° on treatment with lithium aluminum hydride, prompted us to investigate the reaction of *gem*-nitronitroso compounds with diborane. It was found that the reaction of **2** with diborane at 25° gave the hydroxylamine, N-cyclohexylhydroxylamine, in 71% yield. As shown in Table II similar results were obtained with 2,2-nitronitrosopropane (**3**), 1,1-chloronitrosocyclohexane (**4**), and 1-nitropropanal oxime (**5**).

It was established that in these reactions the nitro and chloro groups were eliminated in the reduction, for the hydrolysates of the reaction mixtures gave positive tests for these ions.

Our observations that, as in the case of aromatic nitroso compounds, hydrogen was evolved prior to hydrolysis and that the same amount of hydride was consumed makes it very likely that steps 1 and 2 also apply to the reduction of compounds **2–5**. However, the important difference lies in the elimination step which leads to an oxime intermediate F (eq 5). Further



reaction of F with diborane and subsequent hydrolysis would lead to the hydroxylamine.[9]

(1) For previous publications, see H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).

(2) P. A. S. Smith, "The Chemistry of Open Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, p 375.

(3) J. H. Boyer and S. E. Ellzey, Jr., *J. Amer. Chem. Soc.*, **82**, 2525 (1960).

(4) H. I. Schlesinger and A. E. Finholt, U. S. Patent 2,576,311 (1951); *Chem. Abstr.*, **46**, 2716 (1952).

(5) The reduction of **1** with 3.5 and 8.0 equiv of hydride ion gave aniline in yields of 73.8 and 74.2%, respectively.

(6) A. B. Burg and H. I. Schlesinger, *J. Amer. Chem. Soc.*, **55**, 4020 (1933).

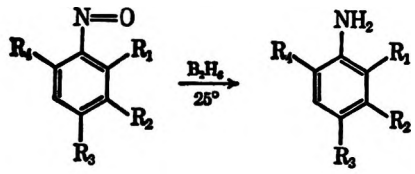
(7) It was previously found that the reduction of aliphatic hydroxylamines to amines with diborane required a temperature range of about 105–110°.[1]

(8) O. Exner, *Chem. Listy*, **51**, 2055 (1957).

(9) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965).

TABLE I

DIBORANE REDUCTION OF AROMATIC NITROSO COMPOUNDS TO AMINES[a,b]



Amine[c]							
R_1	R_2	R_3	R_4	Registry no.	Mp or bp (mm), °C	$n^{20}D$	Yield, %
H	H	H	H	586-96-9	75 (14)	1.5858	79.2
CH_3	H	H	CH_3	19519-71-2	96–98 (15)	1.5593	84.6
H	CH_3	H	CH_3	17075-25-1	99–100 (14)	1.5587	80.5
CH_3	H	H	H	611-23-4	84–86 (15)	1.5695	89.8
Cl	H	H	H	932-33-2	40–41 (15)	1.5869	73.2
H	H	Cl	H	932-98-9	71–72		71.3
Br	H	H	H	19519-75-6	39–40 (0.1)	1.5793	62.4
H	H	$N(CH_3)_2$	H	138-89-6	51–52		63.7

[a] Reactions were carried out for 20 hr at 25°. [b] Hydride consumption measurements indicated that approximately 3 equiv of hydride ion per mole of nitroso compound was consumed, 1 equiv of which was evolved as hydrogen *prior* to hydrolysis. [c] These compounds were identified by their physical data which were in agreement with those reported in the literature.

TABLE II

DIBORANE REDUCTION OF *gem*-NITRONITROSO AND *gem*-CHLORONITROSO COMPOUNDS[a,b]

Compounds	Hydroxylamine[c]	Mp, °C	Yield, %
2,2-Nitronitrosopropane	N-Isopropylhydroxylamine	84–86	65.2
1,1-Nitronitrosocyclohexane	N-Cyclohexylhydroxylamine	140–142	71.0
1-Nitropropanal Oxime	N-Propylhydroxylamine	42–43	71.3
1,1-Chloronitrosocyclohexane	N-Cyclohexylhydroxylamine	140–142	61.7

[a] Reactions were carried out for 20 hr at 25°. [b] Hydride consumption measurements indicated that approximately 3 equiv of hydride ion had been consumed per mole of nitroso compound, 1 equiv of which was evolved as hydrogen *prior* to hydrolysis. [c] These compounds were identified by their physical data which were in agreement with those reported in the literature.

The formation of BH_2X is supported by the findings of Binger and Koster,[10] and Brown, *et al.*,[11] who have reported that the reaction of 1-chloropropene with diborane afforded a mixture consisting of 1- and 2-propanol arising from the hydroboration of propene after the elimination of BH_2Cl. Recently, Pasto[12] has proposed that elimination could occur with any heteroatom having one or more pairs of nonbonded electrons.

Experimental Section

All apparatus, reagents and equipment are similar to those previously described.[1,9] All of the nitroso compounds were prepared by methods described in the literature.

Reaction of Diborane with Aromatic Nitroso Compounds.—The following experiment is typical of the procedure employed. To 2.83 g (20.0 mmol) of *p*-chloronitrosobenzene in 30 ml of THF at 0° was introduced by means of a hypodermic syringe 91.0 mequiv of hydride ion, at such a rate that the temperature did not exceed 10°. Continuing the reaction for 20 hr at ambient temperatures, cautiously adding 4 ml of water at 0°, followed by 10 ml of 20% potassium hydroxide, refluxing the reaction mixture 1 hr, extracting with pentane for 24 hr, and removing the solvent *in vacuo* gave after recrystallization from hexane 1.82 g (71.3%) of ***p*-chloroaniline**: mp 71–72°;[13] ir (KBr) 3534 and 3436 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 3.70 (s, 2, NH_2), 6.70, and 7.30 (q, 4, aromatic H).

Similarly, treating 2.83 g (20.0 mmol) of *p*-chloronitrosobenzene with 91.0 mequiv of hydride ion and keeping the reaction mixture 20 hr at ambient temperatures resulted in the evolution of 20.22 mmol of hydrogen.

Hydrolyzing the reaction mixture at 0° by the cautious addition of 4 ml of water followed by 10 ml of 20% potassium hydroxide, and refluxing for 1 hr gave an additional 27.35 mmol of hydrogen. The total amount of hydrogen evolved was 47.57 mmol, indicating that 2.17 equiv of hydride ion per mole of nitroso compound was consumed in the reduction; in addition 1.02 equiv of hydride ion was used up as hydrogen *prior* to hydrolysis.

Reaction of Diborane with 1,1-Nitronitrosocyclohexane.—The following experimental procedure employed is typical of the reduce *gem*-nitronitroso, *gem*-chloronitroso, and *gem*-nitrooximino compounds. To 3.14 g (19.9 mmol) of 1,1-nitronitrosocyclohexane[8] in 30 ml of THF at 0° was introduced by means of a hypodermic syringe 91.0 mequiv of hydride ion, at such a rate that the temperature did not exceed 10°. Continuing the reaction for 20 hr at ambient temperatures, cautiously adding 4 ml of water at 0°, and then 10 ml of 20% potassium hydroxide was followed by refluxing the reaction mixture for 1 hr. Extracting with pentane for 24 hr, and removing the solvent *in vacuo* gave after recrystallizing from pentane 1.32 g (57.6%) of **N-cyclohexylhydroxylamine**: mp 140–141;[14] ir (Nujol) 3280 and 3125 cm^{-1} (NHOH); nmr ($CDCl_3$) δ 1.30 [m, 6, $(CH_2)_3$], 1.80 [m, 4, $(CH_2)_2CHNHOH$], 2.90 (m, 1, CHNHOH), and 6.08 (s, 2, NHOH).

Similarly treating 3.14 g (19.9 mmol) of 1,1-nitronitrosocyclohexane with 91.0 mequiv of hydride ion and keeping the reaction mixture 20 hr at ambient temperatures resulted in the evolution of 20.70 mmol of hydrogen.

Hydrolyzing the reaction mixture at 0° by the cautious addition of 4 ml of water followed by 10 ml of 20% potassium hydroxide, and refluxing for 1 hr gave an additional 26.70 mmol of hydrogen. The total amount of hydrogen evolved was 47.40 mmol, indicating that 2.17 equiv of hydride ion per mole of nitroso compound was consumed in the reduction; in addition 1.05 equiv of hydride ion was used up as hydrogen *prior* to hydrolysis.

Reaction of Diborane with Phenylhydroxylamine.—The same procedure was followed as in the reduction of aromatic nitroso compounds. From 2.0 g (18.4 mmol) of phenylhydroxylamine[15]

(10) P. Binger and R. Koster, *Tetrahedron Lett.*, 156 (1961).

(11) (a) H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, **86**, 1791 (1964); (b) H. C. Brown and E. Knights, *ibid.*, **90**, 4439 (1968).

(12) D. J. Pasto and J. L. Miesel, *ibid.*, **85**, 2118 (1963).

(13) F. Beilstein and Ap. Kurbatow, *Ann.*, **176**, 27 (1875).

(14) G. Vavon and A. L. Berton, *Bull. Soc. Chim. Fr.*, **37**, 301 (1925).

(15) E. Bamberger, *Chem. Ber.*, **27**, 1548 (1894).

and 102 mequiv of hydride ion there was obtained crude aniline which was converted into the phenylthiourea derivative in 64.5% yield by treatment with phenyl isothiocyanate:[16] mp 155–156°;[17] nmr ($CDCl_3$) δ 7.53 (s, 10, aromatic H) and 8.40 (s, 2, NH).

Similarly treating 1.90 g (17.4 mmol) of phenylhydroxylamine with 120 mequiv of hydride ion and keeping the reaction mixture 20 hr at ambient temperatures resulted in the evolution of 33.74 mmol of hydrogen.

Hydrolyzing the reaction mixture at 0° by the cautious addition of 4 ml of water followed by 10 ml of 20% hydrochloric acid and refluxing for 1 hr gave an additional 68.10 mmol of hydrogen. The total amount of hydrogen evolved was 101.84 mmol, indicating that 1.04 equiv of hydride ion per mole of hydroxylamine was consumed in the reduction.

Registry No.—Diborane, 16970-81-3; 2,2-nitronitrosopropane, 5275-46-7; 1,1-nitronitrosocyclohexane, 14296-14-1; 1-nitropropanal oxime, 19519-78-9; 1,1-chloronitrosocyclophexane, 695-64-7.

Acknowledgment.—We wish to extend our appreciation to the Office of Naval Research for financial support of this work.

(16) N. D. Cheronis and J. B. Entrikin, "Identification of Organic Compounds," Interscience Publishers, New York, N. Y., 1963.
(17) H. Fry, *J. Amer. Chem. Soc.*, **35**, 1539 (1913).

New Synthesis of 1,2-Phenanthrenequinone

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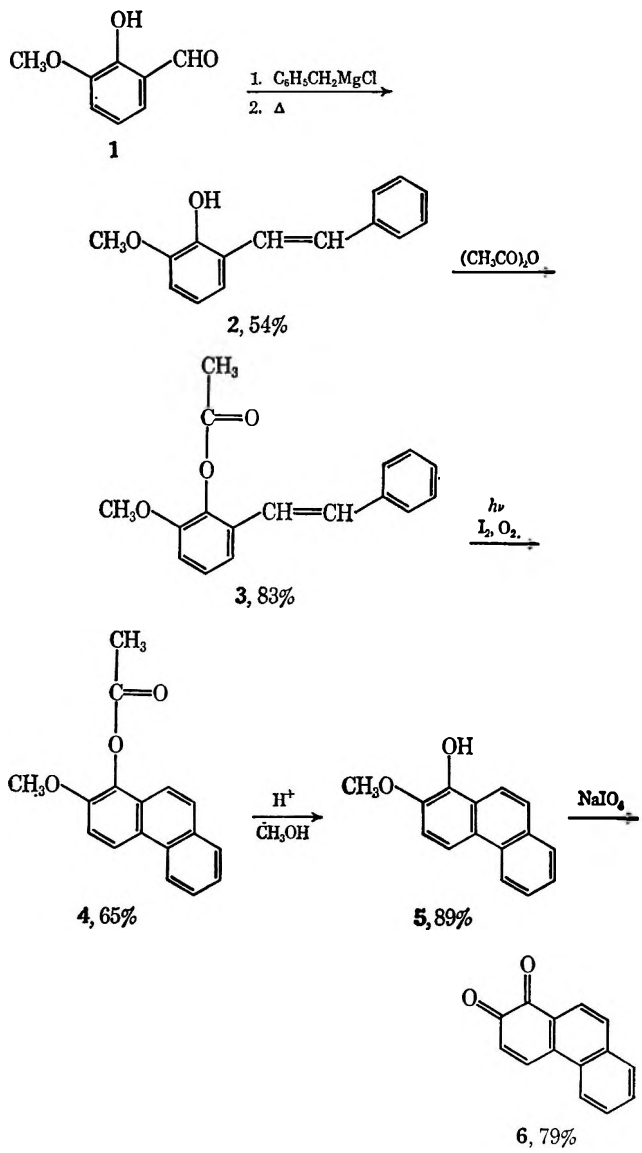
The synthesis of 1,2-phenanthrenequinone described by Fieser[1] in 1929 involves the sulfonation of phenanthrene, separation of phenanthrene-2-sulfonic acid *via* its barium salt, and alkali fusion to give 2-phenanthrol. Coupling with diazotized sulfanilic acid followed by reduction leads to 1-amino-2-phenanthrol which upon oxidation with chromic acid yields 1,2-phenanthrenequinone. According to a more recent procedure, 2-phenanthrol can be converted directly into 1,2-phenanthrenequinone by oxidation with potassium nitrosodisulfonate, but no yield has been reported.[2] The optimal yield of 2-phenanthrol from phenanthrene, however, appears to vary between 13 and 20%.[3,4]

We have now found that 1,2-phenanthrenequinone can easily be prepared from *o*-vanillin according to a reaction sequence outlined in Scheme I. The previously described reaction of benzyl magnesium chloride with *o*-vanillin (**1**) followed by dehydration gives 2-hydroxy-3-methoxystilbene (**2**).[5] Photolysis of its acetate **3** leads to 1-acetoxy-2-methoxyphenanthrene (**4**). Acid catalyzed hydrolysis gives 1-hydroxy-2-methoxyphenanthrene (**5**) which upon oxidation with sodium periodate[6] yields 1,2-phenanthrenequinone (**6**) in a high state of purity. It was characterized by its reduction to 1,2-dihydroxyphenanthrene, which in turn was converted into the diacetate.

SCHEME I
THE SYNTHESIS OF 1,2-PHENANTHRENEQUINONE FROM *o*-VANILLIN



Interestingly, the synthesis of 1-hydroxy-2-methoxyphenanthrene (**5**) has been accomplished a few years ago by the following classical route.[7] Elbs persulfate oxidation of 2-phenanthrol led to 2-hydroxy-1-phenanthryl sulfate. Methylation with diazomethane followed by acid-catalyzed hydrolysis gave **5** in an over-all yield of about 2.8%. According to the new procedure, the over-all yield of **5** based on *o*-vanillin, however, is approximately 25%. The preparative usefulness of the photochemical route to phenanthrols is thus apparent.

Experimental Section

Melting points were taken on a hot-stage microscope and are not corrected. All analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

The photolysis was carried out in an immersion well apparatus.[8]

(1) L. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 1896 (1929).
(2) B. Lukowczyk, *J. Prakt. Chem.*, **8**, 372 (1959).
(3) L. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 2460 (1929).
(4) W. O. Foye, M. Weitzenhoff, and A. M. Stranz, *J. Amer. Pharm. Assoc., Sci. Ed.*, **41**, 312, (1952).
(5) E. Adler and K. Lundquist, *Acta Chem. Scand.*, **17**, 13 (1963).
(6) E. Adler, I. Falkehag, and B. Smith, *ibid.*, **16**, 529 (1962).
(7) P. Sims, *Biochem. J.*, **84**, 558 (1962).
(8) H. D. Becker, *J. Org. Chem.*, **32**, 2115 (1967).

The preparation of 2-hydroxy-3-methoxystilbene **2** is described here since neither experimental details nor any yields have been reported previously.

2-Hydroxy-3-methoxystilbene (2).—A solution of *o*-vanillin (12.5 g) in ether (500 ml) was added slowly to a stirred ether solution (100 ml) of benzyl magnesium chloride (from 7 g of Mg). The resulting suspension was refluxed for 4 hr and then acidified with a mixture of acetic acid (30 ml) and water (100 ml). The ether layer was separated, and the aqueous layer was extracted three times with 100 ml of ether. Drying of the ether solution over sodium sulfate and evaporation of the solvent gave an oil which was subjected to distillation at about 1-mm pressure and a bath temperature of 120° to remove the by-product bibenzyl. The oily residue was then mixed with potassium hydrogen sulfate (1 g) and heated for 30 min to 160–170°. Vacuum distillation at about 0.5-mm pressure and a bath temperature of 180–200° gave a colorless to light yellow distillate that crystallized in the receiver. It was triturated with pentane and filtered to give 10 g (54%) of colorless crystals, mp 86–87° (lit.[5] 86–87°).

2-Acetoxy-3-methoxystilbene (3).—A solution of 2-hydroxy-3-methoxystilbene **2** (6.4 g, 28.3 mmol) in acetic anhydride (40 ml) and pyridine (1 ml) was heated for 5 min to 100° and then kept at room temperature overnight. Decomposition of the acetic anhydride with methanol and evaporation of the solvent gave a colorless crystalline residue which was recrystallized from boiling methanol. The yield was 6.3 g (83%), mp 112–113°.

Anal. Calcd for $C_{17}H_{16}O_3$ (268.30): C, 76.10; H, 6.01. Found: C, 76.00; H, 5.99; mol wt (benzene), 261.

1-Acetoxy-2-methoxyphenanthrene (4).—A solution of 2-acetoxy-3-methoxystilbene **3** (1.34 g, 5 mmol) and iodine (50 mg) in benzene (400 ml) was irradiated (Corex filter, 450-W Hanovia, oxygen) for 70 min. Vacuum evaporation gave a crystalline residue which was recrystallized from a chloroform–methanol mixture. The yield was 720 mg (54%), mp 192–193° (lit.[7] mp 185°).

Anal. Calcd for $C_{17}H_{14}O_3$ (266.28): C, 76.67; H, 5.30. Found: C, 76.92; H, 5.19; mol wt (in benzene), 258.

The irradiation was also carried out in a quartz apparatus in cyclohexane solution. The yield thus could be increased to 65%; however, the immersion well had to be cleaned repeatedly since the product tended to crystallize at the immersion well, thus impairing the light absorption.

1-Hydroxy-2-methoxyphenanthrene (5).—A solution of 1-acetoxy-2-methoxyphenanthrene **4** (665 mg, 2.5 mmol) in a mixture of chloroform (30 ml) and methanol (30 ml) containing concentrated hydrochloric acid (4 ml) was refluxed for 2 hr. Vacuum evaporation of the solvent gave a crystalline residue which was recrystallized from petroleum ether (bp 30–60°) or aqueous methanol. The yield was 500 mg (89%), mp 120–121° (lit.[7] mp 113°).

Anal. Calcd for $C_{15}H_{12}O_2$ (224.25): C, 80.33; H, 5.39. Found: C, 80.14; H, 5.35; mol wt (in benzene), 209.

1,2-Phenanthrenequinone (6).—A warm solution (50°) of sodium metaperiodate (2.5 g, 11.7 mmol) in 50% aqueous acetic acid (40 ml) was added to a stirred solution of 1-hydroxy-2-methoxyphenanthrene **5** (1.12 g, 5 mmol) in acetic acid (100 ml). 1,2-Phenanthrenequinone precipitated in form of beautiful red needle-shaped crystals. Stirring was continued for 30 min. The reaction mixture was then diluted with water (50 ml) and filtered to give 825 mg (79%) of 1,2-phenanthrenequinone, mp 215° dec (lit.[1] mp 216°). Recrystallization from aqueous acetic acid did not raise the melting point.

Anal. Calcd for $C_{14}H_8O_2$ (208.20): C, 80.76; H, 3.87. Found: C, 80.44; H, 3.91.

1,2-Dihydroxyphenanthrene.—A solution of sodium dithionite (2 g) in water (50 ml) was added to a stirred suspension of 1,2-phenanthrenequinone (300 mg) in chloroform (50 ml). After 1 hr of stirring the chloroform was removed from the colorless reaction mixture by evaporation *in vacuo*. Filtration gave 300 mg (99%) of silver gray crystals, melting between 174 and 178° (with darkening). Sublimation at 0.1-mm pressure (bath temperature 120–150°) gave a colorless crystalline sublimate, melting at 178–180° (with darkening) (lit.[9] mp 178°).

Anal. Calcd for $C_{14}H_{10}O_2$ (210.22): C, 79.98; H, 4.79. Found: C, 79.82; H, 4.96.

1,2-Diacetoxyphenanthrene.—1,2-Dihydroxyphenanthrene was acetylated with acetic anhydride in the presence of pyridine. The diacetate was recrystallized from aqueous methanol to give needle-shaped crystals, mp 153–154° (lit.[10] mp 147°).

Anal. Calcd for $C_{18}H_{14}O_4$ (294.29): C, 73.46; H, 4.80. Found: C, 73.38; H, 4.77.

Registry No.—**3**, 19551-00-9; **4**, 19551-02-1; **5**, 19551-03-2; **6**, 573-12-6; 1,2-dihydroxyphenanthrene, 19551-04-3; 1,2-diacetoxyphenanthrene, 19551-05-4.

Acknowledgment.—Part of this work was carried out during the author's stay 1966–1967 at the Department of Chemistry, Chalmers University of Technology, Gothenburg, Sweden. The author is very much indebted to Professor E. Adler for his kind hospitality.

(9) L. F. Fieser and M. A. Peters, *J. Amer. Chem. Soc.*, **53**, 792 (1931).

(10) E. Mosettig and A. Burger, *ibid.*, **55**, 2981 (1933).

Oxidative Trimerization of 2,4-Diphenylphenol

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The oxidation of 2,4-disubstituted phenols with common one-electron oxidants generally leads to 2,2′-dihydroxydiphenyl compounds which often undergo further oxidation.[1] For example, oxidation of 2,4-di-*t*-butylphenol gives 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl which is rapidly converted into a spiroquinol ether by an intramoleclar oxidative coupling reaction.[2] The oxidation of 2,4-diphenylphenol apparently has not been reported previously.

We have now found that 2,4-diphenylphenol (**1**) (see Scheme I) is easily oxidized with alkaline potassium ferricyanide to give the yellow crystalline dioxepin **2** which was isolated in 54% yield. The dioxepin structure is supported by elemental analysis, molecular weight determination, and the following data and chemical transformations.

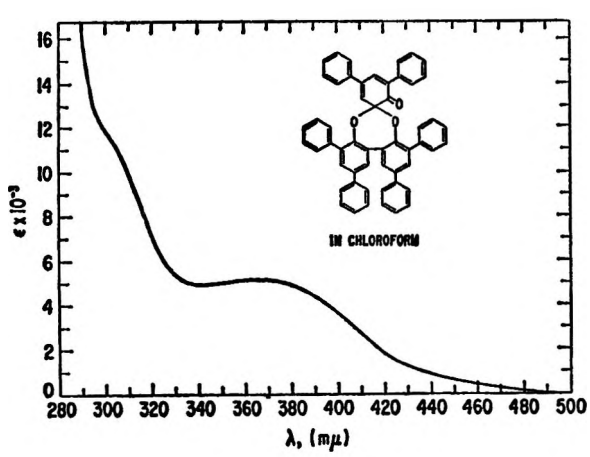
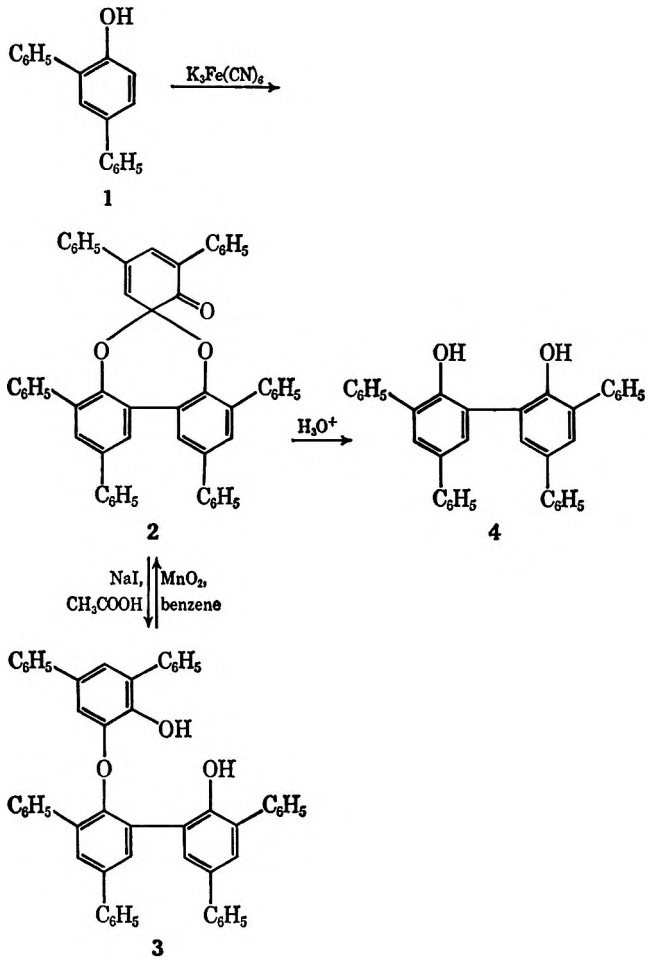


Figure 1.

(1) For a recent review, see H. Musso in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1957, p 1.

(2) E. Müller, R. Mayer, B. Narr, A. Rieker, and K. Scheffler, *Ann.*, **645**, 25 (1961).

SCHEME I



The ultraviolet and visible spectrum of **2** (see Figure 1) is indicative of the 2,4-cyclohexadienone system.[3] The infrared spectrum shows no absorption in the hydroxyl region but exhibits a carbonyl band at 1693 cm^{-1} (in KBr). Upon treatment with sodium iodide in acetic acid the trimer is reduced to give a quantitative yield of the colorless crystalline bisphenol **3** which was characterized by its diacetate. Oxidation of bisphenol **3** with active manganese dioxide[4] in benzene results in an intramolecular coupling reaction regenerating dioxepin **2** in excellent yield. The quinone ketal structure and the diphenyl linkage in the trimeric oxidation product of 2,4-diphenylphenol is confirmed by the acid-catalyzed hydrolysis which leads to 2,2′-dihydroxy-3,3′,5,5′-tetraphenylbiphenyl (**4**). No attempt has been made to isolate and characterize any products deriving from the 3,5-diphenyl-*o*-benzoquinone, the second fragment of the hydrolysis reaction.

The formation of **5** can be interpreted in terms of oxidative C–C coupling of **1** to give **4** which then undergoes intermolecular oxidative C–O coupling with **1** to give **3**, the direct precursor of dioxepin **2**.

Dioxepin formation has been observed recently in the oxidation of alkoxyphenols.[5,6] Although numerous 2,4-dialkylphenols have been studied previously, only the dehydrogenation of 2-methyl-4-*t*-butylphenol with either silver[7] oxide or $CuCl_2$ in the presence of pyridine[8] has been reported to give a dioxepin. In that case, the dioxepin formation was considered to be a deviation in phenol oxidation.[7] The isolation of **2** suggests that other examples of deviation may be found as the interest in phenol oxidation continues.

Experimental Section

Melting points were determined on a hot-stage microscope. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Molecular weights were determined by thermoelectric measurement.

2,4,8,10,4′,6′-Hexaphenyldibenzo[*d*,*f*][1,3]dioxepin-6-spiro-2′-cyclohexa-3′,5′-dien-2-one (2).—A solution of potassium ferricyanide (33 g) and potassium hydroxide (6 g) in water (300 ml) was added over a 5-min period to a stirred solution of 2,4-diphenylphenol (12.3 g) in benzene (500 ml) under nitrogen. A colorless precipitate formed, but dissolved again as stirring was continued. After 15 min the green benzene layer was separated, washed with water and dried over sodium sulfate. Evaporation of the benzene *in vacuo* gave a green oily residue which crystallized upon treatment with acetone. Filtration gave 6.6 g (54%) of yellow crystals, mp 255–258°.

Anal. Calcd for $C_{54}H_{36}O_3$: C, 88.50; H, 4.95; mol wt, 732.78. Found: C, 88.37; H, 4.89; mol wt, 732 (M^+).

From the acetone filtrate no other products but polymeric methanol insoluble material could be isolated. Slow addition of 2,4-diphenylphenol to the alkaline potassium ferricyanide solution decreased the yield of the trimer considerably and increased the yield of polymeric material.

Reduction of Dioxepin 2 with Sodium Iodide (3).—A mixture of **2** (1.22 g, 1.55 mmol) in chloroform (50 ml) and sodium iodide (3 g) in acetic acid (120 ml) was refluxed for 30 min. The chloroform was then evaporated *in vacuo* and the liberated iodine was reduced by dropwise addition of 0.1 *N* sodium thiosulfate solution. The colorless crystalline precipitate thus obtained was dried overnight *in vacuo* at 60°: yield 1.20 g (98%); mp 159–162°. The substance was dissolved in hot acetic acid (75 ml) and filtered through cellulose powder in order to remove a trace of insoluble material. Addition of a little water to the hot filtrate gave a colorless crystalline precipitate having the same melting point as the crude reduction product. The substance was dried overnight *in vacuo* at 110°.

Anal. Calcd for $C_{54}H_{38}O_3$: C, 88.25; H, 5.21; mol wt, 734.90. Found: C, 87.99; H, 5.05; mol wt, 734 (M^+).

The nmr spectrum of **3** (in $CDCl_3$) indicates two different hydroxy groups by singlets at τ 4.7 and 4.2 ppm.

Oxidation of Reduction Product 3.—A suspension of active MnO_2 (2.5 g) in a solution of reduction product **3** (250 mg) in benzene (50 ml) was shaken for 2 hr. Evaporation of the filtrate *in vacuo* gave a glassy yellow residue which crystallized upon trituration with little acetone: yield 230 mg (92%); mp 252–255°; mmp with authentic **2** gave no depression.

Acetylation of Reduction Product 3.—Reduction product **3** (488 mg, 0.66 mmol) was acetylated with hot acetic anhydride in the presence of pyridine. The diacetate was recrystallized from a boiling chloroform–methanol mixture to give 480 mg of colorless crystals, mp 212–213°.

Anal. Calcd for $C_{58}H_{42}O_5$ (818.98): C, 85.06; H, 5.17. Found: C, 84.74; H, 5.19.

The nmr spectrum of the diacetate (in $CDCl_3$) indicates two different acetyl groups by singlets at τ 8.2 and 8.3 ppm.

Acid-Catalyzed Hydrolysis of Dioxepin 2 (4).—A solution of **2** (732 mg, 1 mmol) in a mixture of chloroform (20 ml), methanol (10 ml), and concentrated hydrochloric acid (2 ml) was refluxed for 18 hr. Most of the chloroform was then removed by distillation. The residual light yellow solution gave a colorless crystalline precipitate when most of the solvent had evaporated at room temperature: yield 210 mg (43%); mp 188–190°. Recrystallization from a boiling chloroform–methanol mixture raised the melting point to 189–192°.

(3) For a recent review, see A. J. Waring, *Advan. Alicyclic Chem.*, **1**, 129 (1966).

(4) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. N. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(5) D. F. Bowman, F. R. Hewgill, and B. R. Kennedy, *J. Chem. Soc., C*, 2274 (1966); see also other papers of that series by F. R. Hewgill and coworkers.

(6) J. C. Pew and W. J. Connors, unpublished results cited by J. M. Harkin in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Batterysb, Ed., Marcel Dekker, Inc., New York, N. Y., 1957, p 243.

(7) D. F. Bowman and F. R. Hewgill, *Chem. Commun.*, 471 (1968).

(8) W. W. Karpow and M. L. Khydekel, *Zh. Org. Khim.*, **4**, 861 (1968).

Anal. Calcd for $C_{36}H_{26}O_2$: C, 88.13; H, 5.34; mol wt, 490.57. Found: C, 87.92; H, 5.47; mol wt (in dioxane), 495.

Registry No.—**1**, 6093-03-4; **2**, 19550-96-0; **3**, 19550-98-2; **3** (diacetate), 19550-99-3; **4**, 19550-97-1.

Acknowledgment.—The author is very much indebted to Drs. A. S. Hay and J. R. Ladd for providing the 2,4-diphenylphenol.

Decabromopentacyclo-[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one

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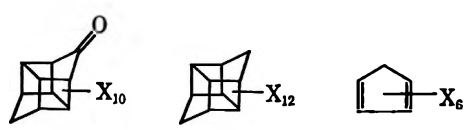
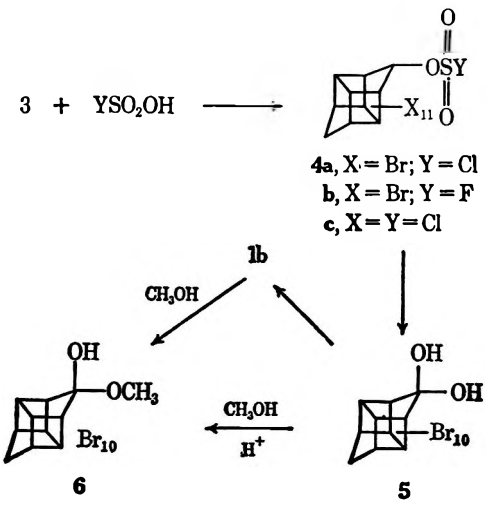
Despite many investigations of the chemistry of decachloropentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one (**1a**) and its derivatives,[2,3] the synthesis of the analogous bromine compound has not been reported in the literature, although the synthesis of the parent bromocarbon, dodecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**2b**), has been described.[4,5] Recent interest in the synthesis and reactions of hexabromocyclopentadiene[6] (**3b**) prompts us to report our results on the reaction of **3b** with fluoro- and chlorosulfonic acids. This investigation has led to the successful syntheses of the first derivatives of **2b.**



1 **2** **3**

a, X = Cl
b, X = Br

Hexabromocyclopentadiene (**3b**) and excess fluorosulfonic acid were stirred and heated at 60–80° for about 2 hr. The reaction mixture was cooled to room temperature or less, filtered, and product washed with water, dried, and recrystallized from ether–methanol to give a white solid, mp >310° dec. The elucidation of the structure of the product as the fluorosulfate ester of undecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-ol (**4b**) follows unmistakably from the elemental analyses and spectral data. The mass spectrum had a parent peak at *m/e* 1088 (^{79}Br) and the ^{19}F nmr spectrum showed a singlet at −51.2 ppm from $CFCl_3$ in good agreement with the proposed structure. The infrared spectrum did not show carbon–hydrogen or double bond absorption but the $-SO_2-$ symmetric and antisymmetric stretching modes were present at 1259 and 1438 cm^{-1}, respectively. Recent work on the structural elucidation



4a, X = Br; Y = Cl
b, X = Br; Y = F
c, X = Y = Cl

of the products from the reaction of **3a** with the chlorosulfonic acids provides further support for the strucure of **4b.**[7] With chlorosulfonic acid, **3b** yields the corresponding ester, **4a.** Sulfur trioxide, which will effect the synthesis of **4c** from **3a**,[8] cannot be substituted for fluoro- or chlorosulfonic acid in the reaction with hexabromocyclopentadiene. Apparently, bromide ion is formed in the reaction and oxidized by the sulfur trioxide and complete decomposition of the starting material is observed.

Hydrate **5** of the title compound was prepared from either **4a** or **4b.** From the fluorosulfate ester **4b**, aqueous alkali is required to effect the hydrolysis, whereas chlorosulfate ester **4a** is hydrolyzed readily by dissolution in 10% aqueous acetone.[9,10] Ketone hydrate **5** is readily dehydrated at elevated temperatures and reduced pressure to the title compound **1b.** The dehydration may be followed by the disappearance of the hydroxyl stretching modes in the 3600-cm^{-1} region of the infrared spectrum and by the appearance of the strong carbonyl stretching mode at 1798 cm^{-1}, a reasonable frequency for the caged ketone.[11] Hemiketal **6** was prepared from either dissolution of **1b** in methanol or by recrystallization of **5** from methanol containing a trace of mineral acid.

Experimental Section

Infrared spectra were obtained with a Beckman IR-9 spectrometer. The mass spectra were obtained on a CEC-21-110B (Direct Probe) instrument. The isotope peaks observed match the relative abundances calculated for the naturally occurring isotopes.

Hexabromocyclopentadiene (**3b**) was prepared by the method of Straus.[12] Recrystallization from hexane or methanol yielded a product melting at 86.5–88°.

Fluorosulfonic Acid, Undecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]-decan-5-yl Ester (**4b**).—Hexabromocyclopentadiene (25 g, 0.046

(1) To whom inquiries should be addressed.

(2) K. V. Scherer, Jr., G. A. Ungefug, and R. S. Lunt, III, *J. Amer. Chem. Soc.* **88**, 2859 (1966).

(3) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211 (1967).

(4) R. H. Earle, Jr., Ph.D. Thesis, Purdue University, June 1957.

(5) C. W. Roberts and M. B. Chenoweth, U. S. Patent 3,212,973 (1965).

(6) P. T. Kwitowski and R. West, *J. Amer. Chem. Soc.*, **88**, 4541 (1966); **90**, 4697 (1968).

(7) (a) Y. Okaya and A. Bednowitz, *Acta Cryst.*, **22**, 111 (1967); (b) R. G. Pews, *Can. J. Chem.*, in press.

(8) E. E. Gilbert and S. L. Giolito, U. S. Patents 2,616,825 and 2,616,928 (1952).

(9) The facile hydrolysis of **4a** compared to **4b** is in good agreement with the order of reactivity of toluenesulfonyl halides with nucleophilic reagents. The order of reactivity toward diethylamine in benzene at 25° is I > Br > Cl ≫ F.[10]

(10) L. M. Litvinenko, A. F. Popov, and A. M. Borovenski, *Reaktsii Sposobnost. Organ. Soedin., Gos. Univer.*, **3**, 93 (1966); *Chem. Abstr.*, **66**, 115190 (1966).

(11) The carbonyl stretching mode of the caged ketone **1a** in KBr is 1810 cm^{-1}: G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964).

(12) F. Straus, L. Kollek, and W. Heyn, *Ber.*, **63B**, 1868 (1930).

mol) and fluorosulfonic acid[13] (200 ml) were stirred overnight in 500-ml round-bottomed flask equipped with condenser and drying tube. The reaction mixture was heated to 80° and maintained at that temperature for 2 hr, cooled and poured onto cracked ice with vigorous stirring. The product was filtered, washed with water and then dissolved in methylene chloride. After drying the methylene chloride solution with $MgSO_4$ the solvent was evaporated and the product recrystallized from ether–methanol to give 12 g (48%) of product, mp >310°. At temperatures above 200° the material darkens and continues this color change to ~310°. At this temperature decomposition takes place with the evolution of bromine. Thus the melting point cannot be used as a criterion of purity. The infrared spectrum showed the antisymmetric and symmetric –S=O stretching modes at 1458 and 1259 cm^{-1}, respectively. The molecular weight by mass spectroscopy was found to be 1088 (^{79}Br). The ^{19}F nmr gave a singlet a −51.2 ppm from $CFCl_3$ in good agreement with the proposed structure.

Anal. Calcd for $C_{10}Br_{11}SO_3F$: C, 10.93; H, 0.00; Br, 80.04; S, 2.92; F, 1.73; O, 4.38. Found: C, 11.00; H, <0.30; Br, 80.00; S, 2.95; F, 1.66; 0O, 4.00.

Chlorosulfonic Acid, Undecabromopentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]-decan-5-yl Ester (4a).—Hexabromocyclopentadiene (50 g, 0.0925 mol) and chlorosulfonic acid (250 g) were placed in a 500-ml round-bottom flask equipped with magnetic stirrer, condenser, and drying tube. The reaction mixture was heated with vigorous stirring for 2 hr at 50°. The reaction mixture was cooled to ice bath temperature and the white precipitate that formed during the reaction and cooling process was removed by filtration through a sintered glass filter. After slurrying with carbon tetrachloride, filtering, and drying, 40 g (78%) of the crude chlorosulfate ester was obtained. Attempts to purify the crude chlorosulfate resulted in decomposition as evidenced by the disappearance of the SO_2 stretching vibrations at 1429 and 1205 cm^{-1}, respectively, in the infrared and the formation of –OH stretching bands in the 3300-cm^{-1} region.

Decabromopentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decan-5-one (1b). Procedure A.—The fluorosulfate ester (3.0 g, 0.0027 mol) was dissolved in tetrahydrofuran (30 ml) and 30 ml of 0.4 *N* potassium hydroxide was added to the solution. The reaction mixture was stirred for 20 min, diluted with water (75 ml) and acidified with concentrated hydrochloric acid. The acidified solution was extracted with methylene chloride and the extract dried (Na_2SO_4) and evaporated to give a 70% yield of the crude ketone hydrate. The ketone monohydrate was obtained by the addition of hexane to a benzene acetone (2:1) solution of the crude hydrate. Purified hydrate 5 was vacuum dried at ~125° and 10 mm pressure to give the anhydrous ketone **1b**, mp >330°. The mass spectrum showed a molecular ion peak at *m/e* 926 (calcd for $C_{10}Br_{10}O$, *m/e* 926), ir (split mull) 1798 cm^{-1} (C=O).

Anal.[14] Calcd for $C_{10}Br_{10}O$: C, 12.82; H, 0.00; Br, 85.47. Found: C, 13.30; H, <0.2; Br, 85.1.

Procedure B.—The chlorosulfate ester (10 g) was dissolved in 10% aqueous acetone (10 ml). The dissolution and/or reaction of the ester resulted in a mild exothermic reaction. After cooling to room temperature, the nearly colorless solution was poured onto ice–water and the precipitate filtered and dried. Recrystallization and drying as described above gave pure anhydrous ketone.

Methyl Hemiketal of Decabromopentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]-decan-5-one (6).—Hydrate 5 was recrystallized from anhydrous methanol containing a trace of mineral acid to give product mp >330°: ir (split mull) 2950–2850 and 1450–1435 (CH_3), 3512 cm^{-1} (OH); nmr ($CDCl_3$) δ 3.66 (s, 3, OCH_3), 2.98 (s, 1, OH). The mass spectrum showed a molecular ion peak at *m/e* 958 (calcd for $C_{11}H_4Br_{10}O_2$, *m/e* 928).

Anal. Calcd for $C_{11}H_4Br_{10}O_2$: C, 13.64; H, 0.42; Br, 82.64. Found: C, 13.80; H, 0.60; Br, 82.5.

Registry No.—**1b**, 19581-67-0; **4b**, 19581-66-9; **6**, 19613-61-7.

(13) CAUTION: The addition of fluorosulfonic acid to water is a violent reaction. The decomposition must be carried out in a hooded area with adequate facial protection, etc. It should also be noted that skin burns resulting from contact with fluorosulfonic acid are often reluctant to heal!

(14) All attempts to obtain acceptable analyses for **1b** or **5** were unsuccessful, presumably due to the facile hydration and dehydration reactions.

Acknowledgment.—The authors are grateful to Dr. J. Heeschen for the ^{19}F nmr experiment, to Mr. R. Nyquist for determining the infrared spectra, and to Dr. L. Shadoff for the mass spectral data. We are indebted to Mr. L. Swim and his associates for the elemental analyses reported herein.

A Calculation of the Optical Activity of a Trefoil Knot

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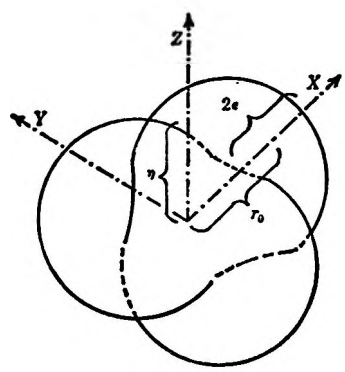
The optical activity of a trefoil, a ring which contains a simple overhand knot, is a property of the structure which distinguishes it from the unknotted ring.[3] To obtain some feeling for the magnitude and sign of rotation expected we have carried out a straightforward Kirkwood calculation[4] of the activity expected for a polymethylene trefoil $(CH_2)_m$.

A particular conformation of the knot of absolute configuration I may be represented by the parametric



I

equations[5]

$$r = r_0 + \epsilon \cos\left(\frac{3}{2}\theta\right)$$

$$z = \eta \sin\left(\frac{3}{2}\theta\right) \qquad (1)$$

with

$$0 \leq \theta \leq 4\pi, \quad 0 < |\epsilon| < r_0, \quad \eta > 0$$

The chain was divided into *n* segments (*n* = 10, 25, or 50) and the fragments were treated as the individually polarizable groups characteristic of the Kirkwood

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(3) H. L. Frisch and E. Wasserman, *J. Amer. Chem. Soc.*, **83**, 3789 (1961).

(4) J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937). Note correction in sign in W. W. Wood, W. Fickett, and J. G. Kirkwood, *ibid.*, **20**, 561 (1952), footnote 2.

(5) We wish to thank Dr. F. H. Stillinger for a discussion on this point.

theory. The positions of these fragments were taken as those of the center of the segments and their orientations as those of the tangents to the curve at the center. With these values the sum[4] given in eq 2 was evaluated,

$$\Sigma_G = \frac{1}{6}\sum_{i,k=1}^{n}\frac{1}{R_{ik}^3}\left[\vec{b}_i\cdot\vec{b}_k - \frac{3(\vec{b}_i\cdot\vec{R}_{ik})\,(\vec{b}_k\cdot\vec{R}_{ik})}{R_{ik}^2}\right] \times \vec{R}_{ik}\cdot(\vec{b}_i\times\vec{b}_k) \quad (2)$$

where b_i is the direction of the unit vector at the center of the ith segment and R_{ik} is the distance between the center of the ith and kth segments. Taking the isotropic and anisotropic polarizability, α and β, of an equivalent length of a linear polymethylene chain[6] as characteristic of those of each of the segments, we then obtain the Kirkwood rotation as[4]

$$[\alpha]_D = 4.96 \times 10^5\left(\frac{n^2+2}{3M}\right)\times\alpha^2\beta^2\Sigma_G \quad (3)$$

where n is the refractive index of the medium and M the molecular weight.

The values of the rotation are largely independent of the number of segments assumed, and we find for m = 66 a rotation $[\alpha]_D$ +2.1 for r_0 = 5.7 Å, ϵ = 2.09 Å, and η = 2.7 Å. While smaller knots are possible, steric interactions prevent the particular atomic arrangement given by eq 1. The small value of $[\alpha]_D$ may be viewed as caused, in part, by the fact that some portions of I are right-handed helices and others are left-handed helices. Extensive cancellation thus results.

The small value arising from the cancellation reduces our confidence in the assignment of absolute configuration. Small deviations of the structure from that of eq 1, by straightening one portion of a curve or by rotating a portion by 90° about its chord, can lead to increases in α by factors of 10 or to decreases and changes in sign. The rotation is likely to be a sensitive function of the environment of the molecule for all but the smallest and tightest knots near C_{50}. Near the lower limit the deviations from eq 1 are sufficiently large that the calculation is of doubtful validity.

(6) C. W. Bann and R. de P. Daubeny, *Trans. Faraday Soc.*, **50**, 1173 (1954).

The Preparation and Redistribution of 4-(2,6-Diphenylphenoxy)-2,6-diphenylphenol

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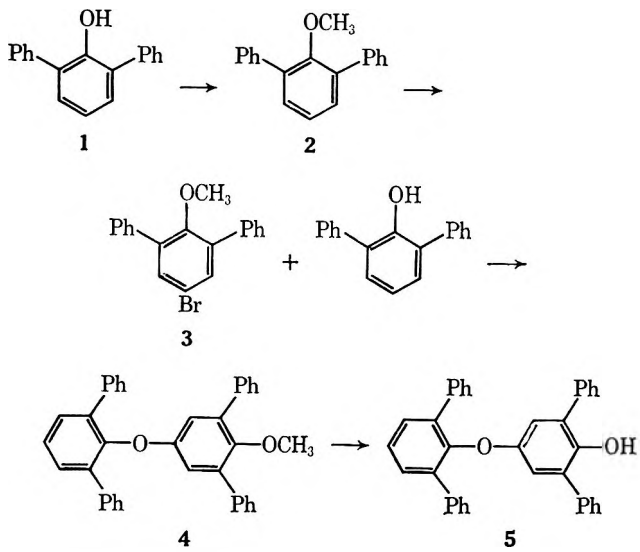
The discovery by Hay[1] that 2,6-diphenylphenol could be oxidatively coupled to form poly(2,6-diphenylphenylene oxide) led into a closer examination of the chemistry of 2,6-diphenylphenol. This molecule appears to be relatively hindered and the relative ease of its oxidative coupling was interesting. The backbone structure of poly(2,6-diphenylphenylene oxide) is identical with that of poly(2,6-dimethylphenylene oxide)[2] and this work was undertaken to see whether other reactions of 2,6-diphenyl-substituted phenols were similar to 2,6-dimethylphenol.

The phenyl-substituted analog of 2,6-xylenol dimer[3] was prepared. This is 4-(2,6-diphenylphenoxy)-2,6-diphenylphenol (5) and was prepared by the following sequence of reactions. The phenol **1** was converted to the methyl ether **2** which was brominated to give 4-bromo-2,6-diphenylanisole **3**. This was coupled with 2,6-diphenylphenol in an Ullmann reaction to give 4-(2,6-diphenylphenoxy)-2,6-diphenylanisole (**4**) which was cleaved to give the phenol dimer **5**.



When the dimer **5** was dissolved in benzene and treated with a radical source such as tri-*t*-butylphenoxyl it underwent redistribution.[3,4] The solution was silylated[5] with bis(trimethylsilyl)acetamide and examined by thin layer chromatography (tlc) or vapor phase chromatography (vpc). The vpc showed three components which were identified as monomer **1**, dimer **5**, and, by analogy, trimer **6**. These materials arise from a redistribution of the dimer radical **5a**.

The same solution was examined on tlc and showed a spectrum of 11 spots in decreasing amounts. The first two were identified as monomer **1** and dimer **5**. The other spots were assigned as being the higher oligomers of 2,6-diphenylphenol. This was further substantiated by degrading a sample of 2,6-diphenylphenol polymer with 2,6-diphenylphenol according to the method of Cooper, Gilbert, and Finkbeiner.[4] The resulting mixture gave the same series of compounds on tlc.

The final proof that the reactions of 2,6-diphenylphenol dimer **5** are identical with those of the 2,6-dimethylphenol dimer is that **5** can be polymerized to poly(2,6-diphenylphenylene oxide) by the use of metal oxides such as lead dioxide.[6] The polymer obtained from this oxidation is identical with polymer obtained from the copper–amine-catalyzed polymerization of 2,6-diphenylphenol.

(1) A. S. Hay, unpublished work.

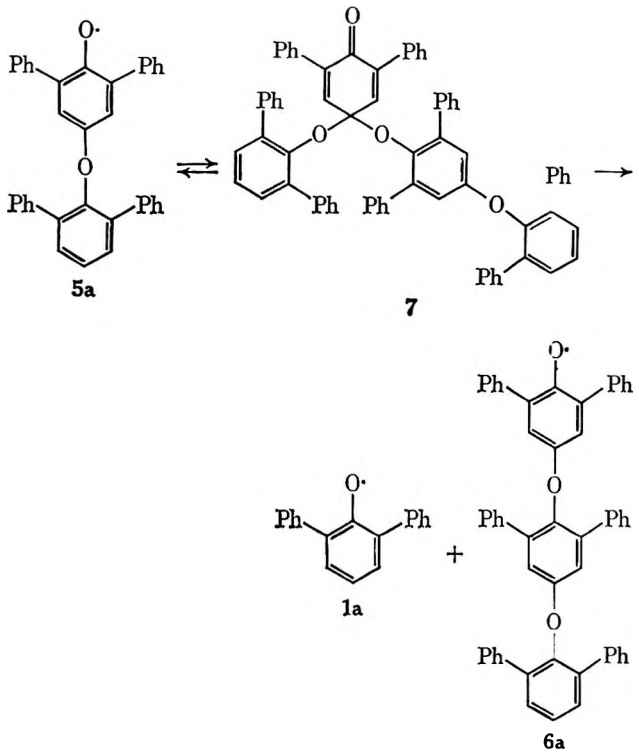
(2) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Amer. Chem. Soc.*, **81**, 6335 (1959).

(3) D. A. Bolon, *J. Org. Chem.*, **32**, 1584 (1967).

(4) G. D. Cooper, A. R. Gilbert, and H. Finkbeiner, Polymer Preprints, Winter Meeting of the American Chemical Society, Phoenix, Ariz., 1966, p 166.

(5) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

(6) H.-D. Becker, U. S. Patent 3,390,425 (1968).



This reaction clearly demonstrates that a hindered phenoxy radical can and does react at the *para* position of another phenoxy radical. The relative ease of the redistribution of **5a** is at some variance with what might be predicted by an examination of molecular models. However, an examination of a model of the quinone ketal **7** shows that one of the pendant phenoxy rings is nearly coplanar with the cyclohexadienone ring and consequently is less hindered than the planar written form of **7** would appear.

Experimental Section

2,6-Diphenylphenol (1).—This material was prepared as described by Plešek.[7]

2,6-Diphenylanisole (2).—To a stirred solution of sodium methoxide (0.75 mol) and 2,6-diphenylphenol (88.6 g, 0.56 mol) in methanol (240 ml) under nitrogen was added slowly dimethyl sulfate (76 ml). The reaction was stirred 6 hr and the methanol was distilled. The residue was treated with water, the organics were taken up in pentane, and any phenolic material was extracted with Claisen alkali.[8] The pentane was evaporated and the residue was distilled yielding a colorless oil (bp 175–177° (2.2 mm), mp 40–41°, $n^{20}D$ 1.6329, 63% yield).

Anal. Calcd for $C_{19}H_{16}O$: C, 88.2; H, 6.2; mol wt, 260. Found: C, 88.0; H, 6.4; mol wt, 256.

4-Bromo-2,6-diphenylanisole (3).—2,6-Diphenylanisole (54 g, 0.02 mol) was brominated (32 g, 0.02 mol) in glacial acetic acid (200 ml). After 4 hr at room temperature, the reaction was refluxed for 2 hr and then poured into sodium bisulfite solution (300 ml, 1%). The brown oil which formed slowly crystallized and was recrystallized from 80% ethanol giving 58.5 g (85%) of white crystals, mp 98–99°.

Anal. Calcd for $C_{19}H_{15}OBr$: C, 67.3; H, 4.4; mol wt, 339. Found: C, 67.3; H, 4.9; mol wt, 334.

4-(2,6-Diphenylphenoxy)-2,6-diphenylanisole (4).—Potassium *t*-butoxide (11.2 g, 0.1 mol) and dimethylformamide (DMF) (20 ml) were combined under nitrogen and a mixture of 2,6-diphenylphenol (24.6 g, 0.1 mol) in hexamethylphosphoric triamide (18 g) was added. This mixture was heated until all of the *t*-butyl alcohol distilled out. The reaction was cooled and 4-bromo-2,6-diphenylanisole (33.9 g, 0.1 mol), DMF (30 ml), and cuprous bromide (2.0 g) were added. The mixture was stirred and heated to reflux while 3 ml of DMF was distilled to remove any traces of *t*-butyl alcohol. The reaction was cooled after 18 hr and a mixture of methanol (600 ml) and concentrated HCl (25 ml) was added. The reaction was filtered and the organic material was extracted with benzene. Residual 2,6-diphenylphenol was removed with Claisen alkali[8] from the benzene which was then dried and distilled. There were three fractions obtained after the benzene: 2,6-diphenylanisole,[9] 4-bromo-2,6-diphenylanisole, and 4-(2,6-diphenylphenoxy)-2,6-diphenylphenol bp 237–260°/(3 mm). This material was recrystallized from 4:1 hexane–toluene giving white crystals, 11 g, 22%, mp 149–150°.

Anal. Calcd for $C_{37}H_{28}O_2$: C, 88.1; H, 5.6; mol wt, 504. Found: C, 87.8; H, 5.4; mol wt, 470.

4-(2,6-Diphenylphenoxy)-2,6-diphenylphenol (5).—Anisole **4** (8.2 g, 0.016 mol) was heated to reflux under nitrogen with pyridine hydrochloride (5.5 g, 0.048 mol) for 18 hr. The residue was poured into water (150 ml). The tan solids were recrystallized from hexane–toluene giving white plates, mp 162–164°, 4.0 g, 50%. A thin layer chromatography showed that the dimer was contaminated with unreacted starting material which was separated by elution chromatography on alumina with hexane–benzene: mp 175–177°.

Anal. Calcd for $C_{36}H_{26}O_2$: C, 88.2; H, 5.3; mol wt, 490. Found: C, 87.8; H, 5.5; mol wt, 470.

Redistribution.—4-(2,6-Diphenylphenoxy)-2,6-diphenylphenol (**5**, 10 mg) in benzene (1 ml) under nitrogen at 25° was treated with the tri-*t*-butylphenoxy radical[10] (10 μl of 0.1 *M* solution). The blue color of the radical was discharged immediately and after a few minutes the orange-red color of the diphenoquinone appeared.[3] The sample was treated with bis(trimethylsilyl)acetamide and the silylated phenols were examined by tlc and vpc. A complete redistribution sequence was observed which corresponded to seeing oligomers up to 11 monomer units long. This sequence was identical with the one obtained from the reaction of 2,6-diphenylphenol, poly(2,6-diphenylphenylene oxide) and an oxidizing agent.[5]

A vpc analysis of the silylated mixture showed three components as their silyl ethers: 2,6-diphenylphenol, 4-(2,6-diphenylphenoxy)-2,6-diphenylphenol, and the trimer **6**. The monomer and dimer were shown to be identical with the known materials by retention times and by infrared spectra.

Polymerization.—Dimer **5** (0.5 g) was stirred in toluene (30 ml) with lead dioxide (5 g) for 24 hr. The colorless solution was filtered. The polymer was isolated by precipitation into methanol: yield 0.42 g, 84%. Intrinsic viscosity in $CHCl_3$, 0.97.

A sample of 2,6-diphenylphenol treated in an identical manner gave a red solution which yielded 0.35 g (70%) of polymer which had an intrinsic viscosity of 0.48.

Registry No.—**2**, 20104-40-9; **3**, 20104-39-6; **4**, 20104-41-0; **5**, 20104-42-1.

(7) J. Plešek, *Chem. Listy*, **50**, 252 (1956), reprinted in *Coll. Czech. Chem. Commun.*, **21**, 375 (1956).

(8) See L. F. Fieser "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 191.

(9) The 2,6-diphenylanisole results from debromination of the bromo compound. In spite of the fact that both the bromoanisole and the phenol are present in the reaction at this point, further addition of cuprous bromide only results in debromination and not in production of more dimer.

(10) C. D. Cook and R. C. Woodworth, *J. Amer. Chem. Soc.*, **75**, 6242 (1953).

Transesterification with an Anion-Exchange Resin

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Received January 8, 1969

Although the modification of esters of edible oils by alcoholysis using anion exchange resins is used commercially,[1] synthetic applications of such base-catalyzed transesterifications are rare.[2]

(1) A. T. Gros and R. O. Feuge, *J. Amer. Oil Chem. Soc.*, **26**, 97, 704 (1949).

(2) C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.*, **44**, 2868 (1952); M. J. Astle and J. E. Zaslowsky, *ibid.*, **44**, 2868 (1952).

TABLE I

PHYSICAL CONSTANTS OF METHYL ESTERS

Compound	Registry no.	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CBz-Gly-GlyOMe	13437-63-3	55–57	$C_{13}H_{16}N_2O_5$	55.71	5.75	10.00	55.62	5.73	10.00
D-Ala-OMe·HCl	14316-64-4	95–96	$C_4H_{10}NO_2Cl$	34.43	7.17	10.04	33.82	6.92	9.87
t-BOC-L-Val-D-AlaOMe	15136-15-9	88–90	$C_{14}H_{26}N_2O_5$	55.61	8.67	9.27	55.37	8.58	9.56
t-BOC-L-Pro-L-LeuOMe	15136-16-0	80–81	$C_{17}H_{30}N_2O_5$	59.62	8.83	8.18	59.51	8.96	8.31

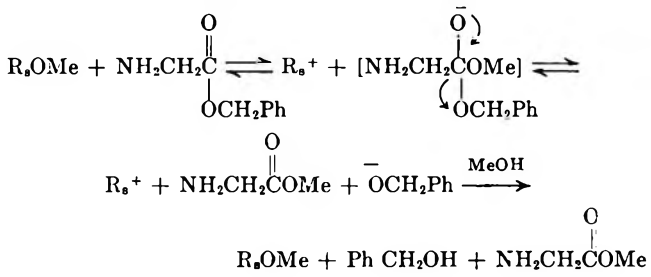
TABLE II

Compound	Registry no.	Mp or bp (mm), °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
N-Acetyl-DL-Ala-OEt	5143-72-6	72 (0.1)	$C_7H_{13}NO_3$	52.81	8.23	8.8	52.80	8.22	8.69
CBz-L-Leu-L-Ala-OEt	19817-68-6	66–67	$C_{19}H_{28}N_2O_5$	62.62	7.74	7.69	62.45	7.65	7.79
CBz-Gly-Gly-L-Ala-OEt	5673-76-7	71–73	$C_{17}H_{23}N_3O_6$	55.88	6.35	11.50	56.42	6.18	11.50
N-Benzoyl-DL-Phe-OEt	19817-70-0	83–85	$C_{18}H_{19}NO_3$	72.70	6.44	4.71	72.69	6.34	4.78
CBz-L-Met-L-Try-OEt	19842-38-7	102–104	$C_{26}H_{31}N_3O_5S$	62.77	6.23	8.45	62.91	6.34	8.51

We now report that amino acid and peptide alkyl ester derivatives as well as fatty acid esters are readily transesterified by treatment with a *strong* anion exchange resin in methanol or ethanol at room temperature. Under the experimental conditions used, the carbobenzoxy, the *t*-butyloxycarbonyl, and the O-, S-, and the imidazole-benzyl protecting groups commonly used in peptide synthesis remain intact but the ω-carboxyl functions of aspartic and glutamic residues are also transesterified. By using sterically pure L-amino acid and LL dipeptide derivatives, it was shown by gas chromatographic analysis of the products[3,4] that the reaction proceeds without detectable racemization (<1% D). Attempts to prepare higher alkyl or benzyl esters from amino acid and fatty acid methyl esters were less successful than the synthesis of ethyl esters. The formation of significant quantities of benzyl esters required refluxing in benzyl alcohol for several hours and chromatographically pure esters could be isolated only in low yields (<50%).

The presence of the resin is essential for the transesterification reaction to proceed. The absence of reactivity of methanolic solutions from which the resin, after contact for several hours, had been removed indicated that transesterification was due to the continuous replenishment of methoxide ions by the resin in the solvent. On the basis of these findings the transesterification reaction may be rationalized as in Scheme I, where R_s^+ is the resin cation. In peptide synthesis where the stability and the selective removal of protecting groups is an important consideration, it may be practically useful to remove a benzyl ester function by transesterification with retention of steric purity.

SCHEME I



Experimental Section[5]

Preparation of Anion Exchange Resin.—BIO-RAD AG I-X8 resin (50 g, (50–100 mesh, chloride form) was converted into the hydroxide form by washing with 500 ml of 1 *N* NaOH, and the excess free hydroxyl ions were removed by washing the resin with deionized water until the pH of the effluent was lower than 8. The resin was dehydrated by continuous washing with anhydrous methanol or ethanol (<0.01% H_2O). The resin suspensions were stored in the refrigerator, and under these conditions kept their activity for 1–2 weeks.

Preparation of Methyl Esters from Benzyl Esters.—Methyl esters were prepared in 80–95% yield by stirring 400–600 mg of the amino acid benzyl ester derivative with 1–2 g of anion exchange resin and 10–15 ml of methanol, at room temperature, for 30–80 min. The progress of the reaction was followed by tlc (isopropyl ether:chloroform:acetic acid 6:3:1) or glpc (5 ft × 1/8 in. column of 5% trifluoropropyl methyl silicone fluid (QF-I) on Aeropack 30). The solutions were filtered, and the solvent was evaporated to yield the corresponding methyl ester. The D-AlaOMe was characterized as the hydrochloride (Table I).

Preparation of Ethyl Esters from Methyl Esters.—Several ethyl esters were prepared in 80–90% yield from methyl esters by a similar transesterification procedure using a resin which had been dehydrated with ethanol. The reactions were carried out in anhydrous ethanol (Table II).

Preparation of Methyl Esters from Ethyl Esters.—Methyl esters were prepared in 80–90% yield from ethyl esters using resins which had been dehydrated with methanol and anhydrous methanol was used as the solvent. The L-Ala-OMe and L-Leu-OMe were characterized as the hydrochlorides (Table III).

Preparation of Benzyl Esters from Methyl Esters.—Benzyl esters were prepared in <50% yield from methyl esters using resin which had been dehydrated with benzyl alcohol. Benzyl alcohol was used as solvent. The reactions were carried out at 80–90° for 24 hr. The DL-Val-OBz was characterized as the *p*-toluenesulfonate (Table IV).

Steric Analysis of Amino Acid and Peptide Derivatives.—The amino acid alkyl esters (Table I and III) were treated with TFA-L-prolyl chloride as described previously.[3] Glpc analysis of the diastereoisomers confirmed the steric homogeneity of the products (<1% of the undesirable dipeptide). Direct glpc of *t*-BOC-L-Pro-L-Leu OMe[4] also showed less than 1% of the LD dipeptide in the isolated product.

Alcoholysis of Amino Acid Esters Containing S, O, and $N^{(im)}$

(3) B. Halpern and J. W. Westley, *Biochem. Biophys. Res. Commun.*, 19, 361 (1965).

(4) J. W. Westley and B. Halpern in "Gas Chromatography 1968," A. B. Littlewood, Ed., Institute of Petroleum, London, 1968.

(5) All melting points and boiling points are uncorrected. Glpc analyses were carried out on a Varian 600D gas chromatograph using a 5 ft × 1/8 in. (5% QFI on Aeropack 30) column with a nitrogen flow of 30 ml/min. All compounds were characterized by mass spectrometry using a Finnigan 1015 quadrupole mass spectrometer.

TABLE III

PHYSICAL CONSTANTS OF METHYL ESTERS

Compound	Registry no.	Mp or bp (mm), °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
L-Ala-OMe HCl	2491-20-5	98–100	$C_4H_{10}NO_2Cl$	34.43	7.17	10.04	34.24	6.90	9.97
L-Leu-OMe HCl	7517-19-3	145–147	$C_7H_{16}NO_2Cl$	46.30	8.82	7.71	46.26	8.86	7.66
Methyl caprate	110-42-9	90–92 (4)	$C_{11}H_{22}O_2$	70.92	11.90		70.72	11.63	
Methyl stearate	112-61-8	40–41	$C_{19}H_{38}O_2$	76.45	12.83		76.72	12.79	

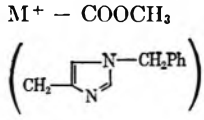
TABLE IV

PHYSICAL CONSTANTS OF BENZYL ESTERS

Compound	Registry no.	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Benzyl stearate	5531-65-7	44–45	$C_{25}H_{42}O_2$	80.15	11.30		80.39	11.44	
DL-Val-OBz *p*-toluene sulfonate	17664-92-5	134–138	$C_{19}H_{25}NO_5S$	60.02	6.59	3.77	60.15	6.64	3.76

TABLE V

CHARACTERISTIC PEAKS IN MASS SPECTRA OF TRANSESTERIFICATION PRODUCTS

Compound	Registry no.	*m/e*	Fragment
S-Bz-L-Cys-OEt (mol wt, 239)	953-18-4	239	M^+
		166	$M^+ - (COOEt)$
		102	$M^+ - (PhCH_2 - SCH_2)$
O-Bz-L-Tyr-OEt (mol wt, 299)	19842-36-5	299	M^+
		226	$M^+ - (COOEt)$
$N^{(im)}$Bz-L-HiS-OMe (mol wt, 259)	19817-75-5	200	$M^+ - COOCH_3$
		171	
t-BOC-L-Asp-β-OMe-Leu-OMe (mol wt, 374)	19817-76-6	374	M^+
		317	$M^+ - (CH_3)_3C$
		315	$M^+ - COOCH_3$
t-BOC-L-Asp-β-OMe-L-Ala-OMe (mol wt, 332)	19817-77-7	332	M^+
		301	$M^+ - OCH_3$
t-BOC-L-Thr-ε-CBz-L-Lys-OMe (mol wt, 495)	19842-37-6	394	$M^+ - (CH_3)_3COC(=O)$
		287	$M^+ - [CBz + (CH_3)_2CO]$

Benzyl, Carbobenzoxy, *t*-Butyloxycarbonyl, and Aspartic Acid β-Benzyl Ester Derivatives.—S-Bz-L-Cys-OMe, O-Bz-L-Tyr-OMe, $N^{(im)}$-Bz-L-His-OMe, *t*-BOC-L-Asp-OBz-L-Leu-OBz, *t*-BOC-L-Asp-L-Ala-OBz, and *t*-BOC-L-Thr-εCbz-L-Lys-OBz were transesterified with ethanol or methanol, respectively. The chromatographically pure product (tlc, isopropyl ether:chloroform:acetic acid 6:3:1) were examined by mass spectrometry. The results (Table V) indicated that only the β-benzyl ester function of aspartic acid had been transesterified under these conditions.

Acknowledgments.—This investigation was supported by National Aeronautics and Space Administration Grant NGR-05-020-004.

$[(C_6H_5)_3P]_3RhCl$

Tris(triphenylphosphine)rhodium(I) chloride

While investigating the properties of phosphine complexes of transition metals, Wilkinson and co-workers found that this red, crystalline, air-stable solid derivative of rhodium has several extremely useful applications. Soluble in non-polar solvents such as benzene and methylene chloride, it reacts rapidly and reversibly with molecular hydrogen, acting as an effective *low temperature, low pressure hydrogenation catalyst* (1). The catalyst is specific for olefins and acetylenes – other groups such as C=O or NO_2 are unaffected. Hydrogenation is stereospecific for *cis*-addition, generally without isomerization of the olefin (1,2).

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$$(Ph_3P)_3RhCl + RCOCl \rightarrow (Ph_3P)_2Rh(CO)Cl + RH$$

(a reaction which becomes catalytic above 180°C) and, under some conditions, as an oxidation catalyst, converting cyclohexene to cyclohexene-1-one and cyclohexene-1-ol (5).

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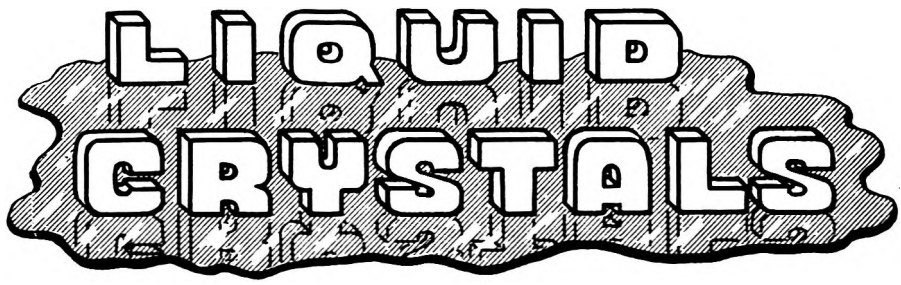

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