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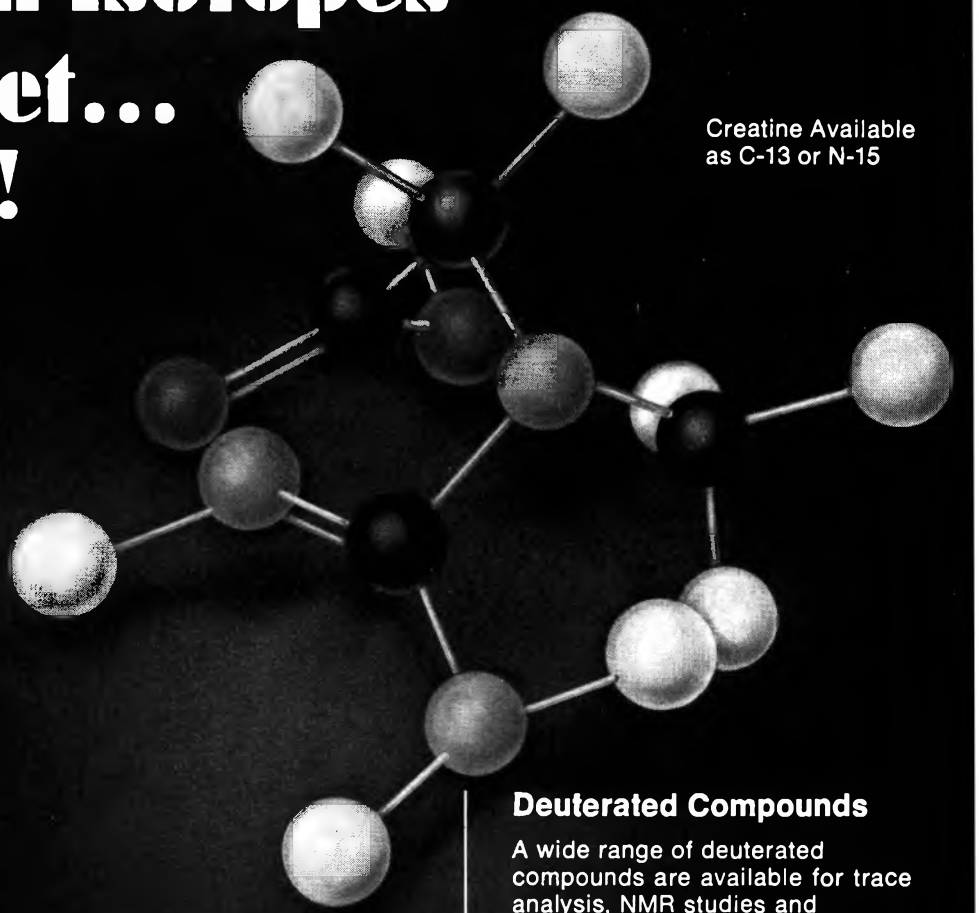

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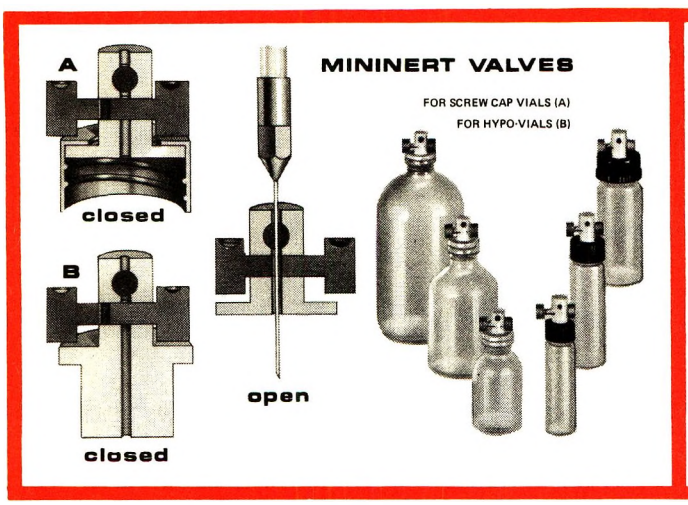

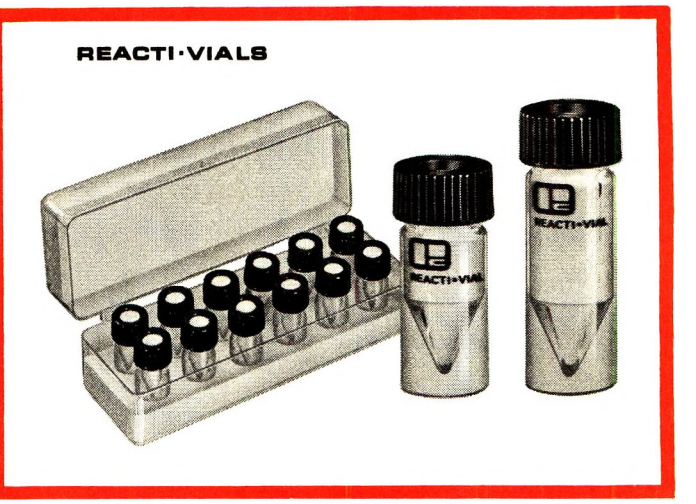

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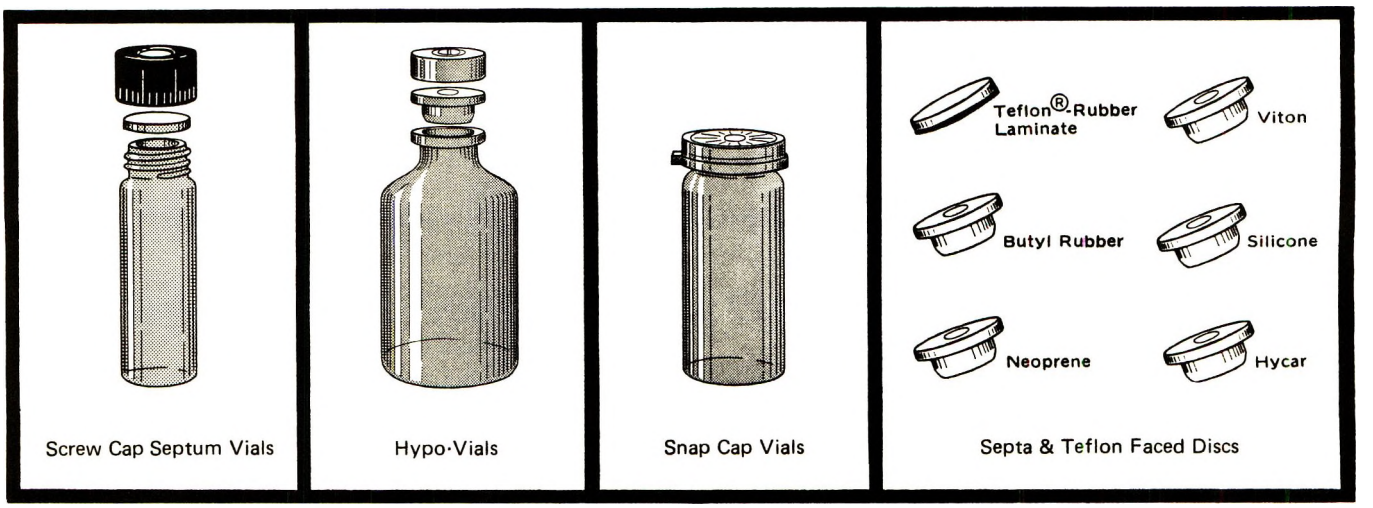

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VOLUME 35, NUMBER 9

SEPTEMBER 1970

IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry[1]

Introduction

This Section of the IUPAC Rules for Nomenclature of Organic Chemistry differs from previous Sections in that it is here necessary to legislate for words that describe concepts as well as for names of compounds.

At the present time, concepts in stereochemistry (that is, chemistry in three-dimensional space) are in the process of rapid expansion, not merely in organic chemistry, but also in biochemistry, inorganic chemistry, and macromolecular chemistry. The aspects of interest for one area of chemistry often differ from those for another, even in respect to the same phenomenon. This rapid evolution and the variety of interests have led to development of specialized vocabularies and definitions that sometimes differ from one group of specialists to another, sometimes even within one area of chemistry.

The Commission on the Nomenclature of Organic Chemistry does not, however, consider it practical to cover all aspects of stereochemistry in this Section E. Instead, it has two objects in view: to prescribe, for basic concepts, terms that may provide a common language in all areas of stereochemistry; and to define the ways in which these terms may, so far as necessary, be incorporated into the names of individual compounds. The Commission recognizes that specialized nomenclatures are required for local fields; in some cases, such as carbohydrates, amino acids, peptides and proteins, and steroids, international rules already exist; for other fields, study is in progress by specialists in Commissions or Subcommittees; and further problems doubtless await identification. The Commission believes that consultations will be needed in many cases between different groups within IUPAC and IUB if the needs of the specialists are to be met without confusion and contradiction between the various groups.

The Rules in this Section deal only with Fundamental Stereochemistry, that is, the main principles. Many of these Rules do little more than codify existing practice, often of long standing; however, others extend old principles to wider fields, and yet others deal with nomenclature that is still subject to controversy.

Rule E-0

The stereochemistry of a compound is denoted by an affix or affixes to the name that does not prescribe the stereochemistry; such affixes, being additional, do not change the name or the numbering of the compound. Thus, enantiomers, diastereoisomers, and *cis–trans* isomers receive names that are distinguished only by means of different stereochemical affixes. The only exceptions are those trivial names that have stereochemical implications (for example, fumaric acid, cholesterol).

Note: In some cases (see Rules E-2.23 and E-3.1) stereochemical relations may be used to decide between alternative numberings that are otherwise permissible.

(1) These Rules are reproduced by the kind permission of IUPAC. These Rules may be called the IUPAC 1968 Tentative Rules, Section E, Fundamental Stereochemistry. They are issued by the Commission[2] on the Nomenclature of Organic Chemistry of the International Union of Pure and Applied Chemistry. Section A, Hydrocarbons, and Section B, Fundamental Heterocyclic Systems, were published in 1957 (2nd edition, 1966); Section C, Characteristic Groups Containing Carbon, Hydrogen, Oxygen, Nitrogen, Halogen, Sulfur, Selenium, and/or Tellurium, was published in 1965. Section D, which is in preparation and is expected to be published soon, will deal with organometallic compounds in general, chains and rings containing heterogeneous atoms, and organic derivatives of phosphorus, arsenic, antimony, bismuth, silicon, and boron. Comments on Section E should be addressed to the Secretary of the Commission.[2] Reprints of these Rules are available from Chemical Abstracts Service, Columbus, Ohio 43210.

(2) Titular members: P. E. Verkade (Chairman), S. P. Klesney (Secretary, 3609 Boston, Midland, Mich. 48640 U. S. A.), L. C. Cross, G. M. Dyson, K. L. Loening, N. Lozac'h, H. S. Nutting, J. Rigaudy, S. Veibel. Associate members: R. S. Cahn, H. Grünewald. Observers: K. Bláha, K. Hirayama, K. A. Jensen, W. Klyne.

E-1. Types of Isomerism

E-1.1.—The following nonstereochemical terms are relevant to the stereochemical nomenclature given in the Rules that follow.

(a) The term structure may be used in connection with any aspect of the organization of matter.

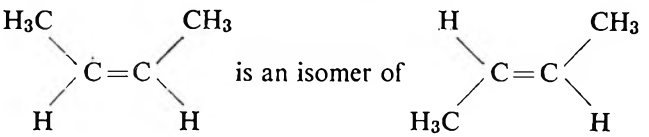
Hence: structural (adjectival)

(b) Compounds that have identical molecular formulas but differ in the nature or sequence of bonding of their atoms or in arrangement of their atoms in space are termed isomers.

Hence: isomeric (adjectival)
isomerism (phenomenological)

Examples:

$H_3C—O—CH_3$ is an isomer of $H_3C—CH_2—OH$



(In this and other Rules a broken line denotes a bond projecting behind the plane of the paper, and a thickened line denotes a bond projecting in front of the plane of the paper. In such cases a line of normal thickness denotes a bond lying in the plane of the paper.)

(c) The constitution of a compound of given molecular formula defines the nature and sequence of bonding of the atoms. Isomers differing in constitution are termed constitutional isomers.

Hence: constitutionally isomeric (adjectival)
constitutional isomerism (phenomenological)

Example:

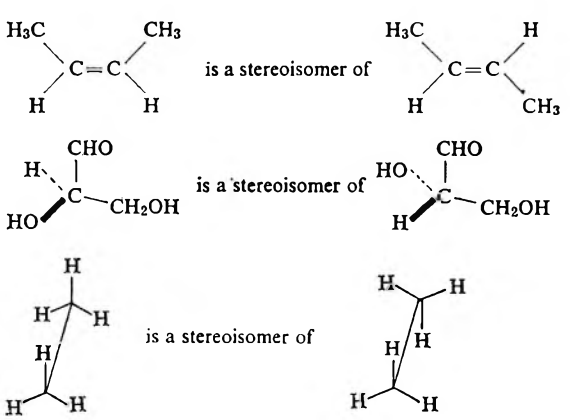
$H_3C—O—CH_3$ is a constitutional isomer of $H_3C—CH_2—OH$

Note: Use of the term "structural" with the above connotation is abandoned as insufficiently specific.

E-1.2.—Isomers are termed stereoisomers when they differ only in the arrangement of their atoms in space.

Hence: stereoisomeric (adjectival)
stereoisomerism (phenomenological)

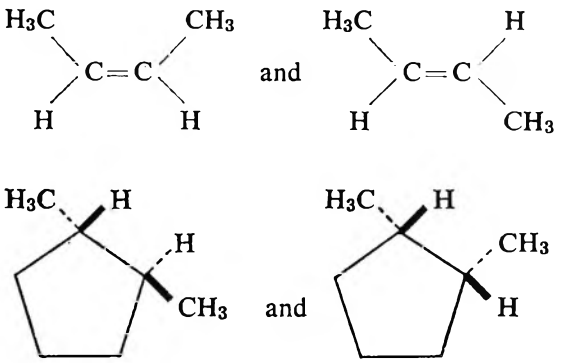
Examples:



E-1.3.—Stereoisomers are termed *cis–trans* isomers when they differ only in the positions of atoms relative to a specified plane in eases where these atoms are, or are considered as if they were, parts of a rigid structure.

Hence: *cis–trans* isomeric (adjectival)
cis–trans isomerism (phenomenological)

Examples:



E-1.4.—Various views are current regarding the precise definition of the term "configuration." (a) Classical interpretation: The configuration of a molecule of defined constitution is the arrangement of its atoms in space without regard to arrangements that differ only as after rotation about one or more single bonds. (b) This definition is now usually limited so that no regard is paid also to rotation about π bonds or bonds of partial order between one and two. (c) A third view limits the definition further so that no regard is paid to rotation about bonds of any order, including double bonds.

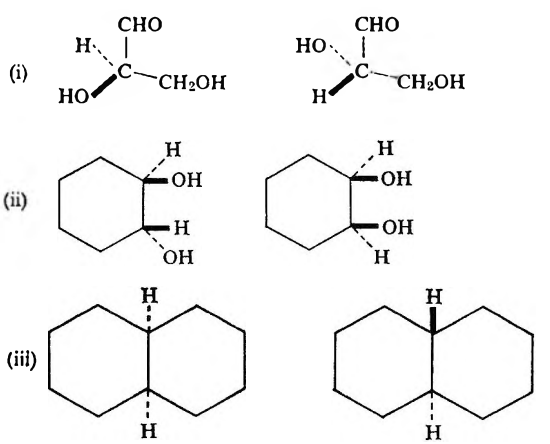
Molecules differing in configuration are termed configurational isomers.

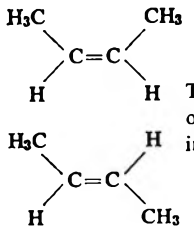
Hence: configurational isomerism

Notes: (1) Contrast conformation (Rule E-1.5). (2) The phrase "differ only as after rotation" is intended to make the definition independent of any difficulty of rotation, in particular independent of steric hindrance to rotation. (3) For a brief discussion of views (a)–(c), see Appendix 1. It is hoped that a definite concensus of opinion will be established before these Rules are made "Definitive".

Examples:

The following pairs of compounds differ in configuration:





(iv) These isomers (iv) are configurational in view (a) or (b) but are conformational (see Rule E-1.5) in view (c)

E-1.5.—Various views are current regarding the precise definition of the term "conformation." (a) Classical interpretation: The conformations of a molecule of defined configuration are the various arrangements of its atoms in space that differ only as after rotation about single bonds. (b) This is usually now extended to include rotation about π bonds or bonds of partial order between one and two. (c) A third view extends the definition further to include also rotation about bonds of any order, including double bonds.

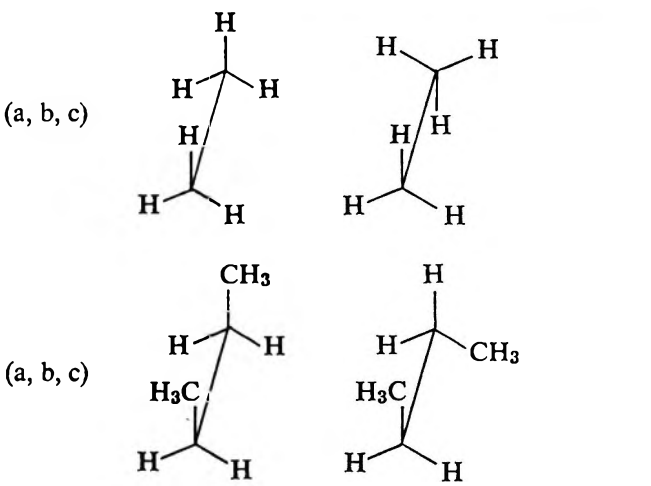
Molecules differing in conformation are termed conformational isomers.

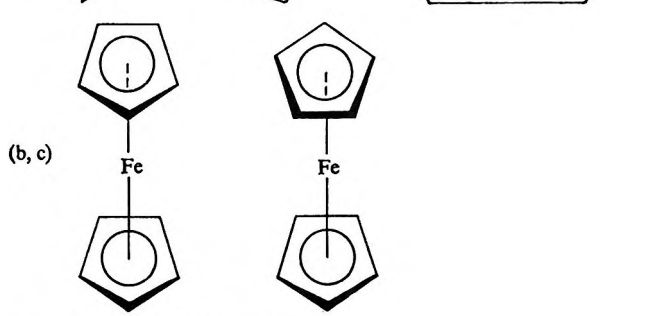
Hence: conformational isomerism

Notes: All the Notes to Rule E-1.4 apply also to E-1.5.

Examples:

Each of the following pairs of formulas represents a compound in the same configuration but in different conformations.





(c) See Example (iv) to Rule E-1.4.

E-1.6.—The terms relative stereochemistry and relative configuration are used with reference to the positions of various atoms in a compound relative to one another, especially, but not only, when the actual positions in space (absolute configuration) are unknown.

E-1.7.—The terms absolute stereochemistry and absolute configuration are used with reference to the known actual positions of the atoms of a molecule in space.[3]

E-2. *cis–trans* Isomerism[4]

Preamble.—The prefixes *cis* and *trans* have long been used for describing the relative positions of atoms or groups attached to nonterminal doubly bonded atoms of a chain or attached to a ring that is considered as planar. This practice has been codified for hydrocarbons by IUPAC (see footnote 4 below). There has, however, not been agreement on how to assign *cis* or *trans* at terminal double bonds of chains or at double bonds joining a chain to a ring. An obvious solution was to use *cis* and *trans* where doubly bonded atoms formed the backbone and were nonterminal and to enlist the sequence-rule preferences to decide other cases; however, since the two methods, when generally applied, do not always produce analogous results, it would then be necessary to use different symbols for the two procedures. A study of this combination showed that both types of symbol would often be required in one name and, moreover, it seemed wrong in principle to use two symbolisms for essentially the same phenomenon. Thus it seemed to the Commission wise to use only the sequence-rule system, since this alone was applicable to all cases. The same decision was taken independently by Chemical Abstracts Service[5] who introduced *Z* and *E* to correspond more conveniently to *seqcis* and *seqtrans* of the sequence rule.

It is recommended in the Rules below that these designations *Z* and *E* based on the sequence rule shall be used in names of compounds, but *Z* and *E* do not always correspond to the classical *cis* and *trans* which show the steric relations of like or similar groups that are often the main point of interest. So the use of *Z* and *E* in names is not intended to hamper the use of *cis* and *trans* in discussions of steric relations of a generic type or of groups of particular interest in a specified case (see Rule E-2.1 and its Examples and Notes, also Rule E-5.11).

It is also not necessary to replace *cis* and *trans* for describing the stereochemistry of substituted monocycles (see Subsection E-3). For cyclic compounds the main problems are usually different from those around double bonds; for instance, steric relations of substituents on rings can often be described either in terms of chirality (see Subsection E-5) or in terms of *cis–trans* relationships, and, further, there is usually no single

(3) Determination of absolute configuration became possible through work by J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, **168**, 271 (1951); *cf.* J. M. Bijvoet, *Proc. Kon. Ned. Akad. Wetensch.*, **52**, 313 (1949).

(4) These Rules supersede the Tentative Rules for olefinic hydrocarbons published in the Comptes rendus of the 16th IUPAC Conference, New York, N. Y., 1951, pp 102–103.

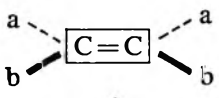
(5) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968); J. E. Blackwood, C. L. Gladys, A. E. Petrarca, W. H. Powell, and J. E. Rush, *J. Chem. Doc.*, **8**, 30 (1968).

relevant plane of reference in a hydrogenated polycycle. These matters are discussed in the Preambles to Subsections E-3 and E-4.

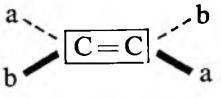
E-2.1. Definition of *cis–trans*.—Atoms or groups are termed *cis* or *trans* to one another when they lie respectively on the same or on opposite sides of a reference plane identifiable as common among stereoisomers. The compounds in which such relations occur are termed *cis–trans* isomers. For compounds containing only doubly bonded atoms the reference plane contains the doubly bonded atoms and is perpendicular to the plane containing these atoms and those directly attached to them. For cyclic compounds the reference plane is that in which the ring skeleton lies or to which it approximates. When qualifying another word or a locant, *cis* or *trans* is followed by a hyphen. When added to a structural formula, *cis* may be abbreviated to *c*, and *trans* to *t* (see also Rule E-3.3).

Examples:

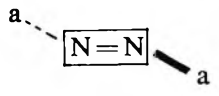
[Rectangles here denote the reference planes and are considered to lie in the plane of the paper.]



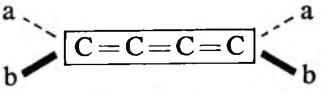
cis



trans



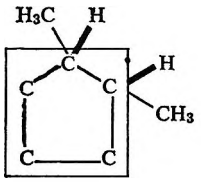
trans



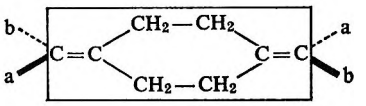
cis

The groups or atoms a,a are the pair selected for designation but are not necessarily identical; b,b are also not necessarily identical but must be different from a,a.

cis or *trans* according as a or b is taken as basis of comparison

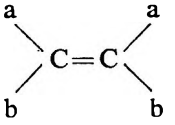


cis



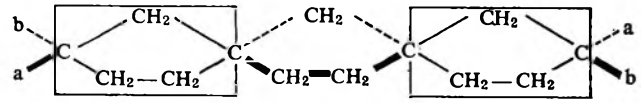
trans

Notes: The formulas above are drawn with the reference plane in the plane of the paper, but for doubly bonded compounds it is customary to draw the formulas so that this plane is perpendicular to that of the paper; atoms attached directly to the doubly bonded atoms then lie in the plane of the paper and the formulas appear as, for instance



cis

Cyclic structures, however, are customarily drawn with the ring atoms in the plane of the paper, as above. However, care is needed for complex cases, such as



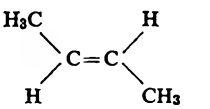
The central five-membered ring lies (approximately) in a plane perpendicular to the plane of the paper. The two a groups are *trans* to one another; so are the b groups; the outer cyclopentane rings are *cis* to one another with respect to the plane of the central ring. *cis* or *trans* (or *Z* or *E*; see Rule E-2.21) may also be used in cases involving a partial bond order when a limiting structure is of sufficient importance to impose rigidity around the bond of partial order. An example is

trans (or *E*)

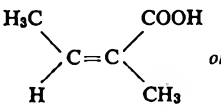
E-2.2. *cis–trans* **Isomerism around Double Bonds**

E-2.21.—In names of compounds steric relations around one or more double bonds are designated by affixes *Z* and/or *E*, assigned as follows. The sequence-rule-preferred[6] atom or group attached to one of a doubly bonded pair of atoms is compared with the sequence-rule-preferred atom or group attached to the other of that doubly bonded pair of atoms; if the selected pair are on the same side of the reference plane (see Rule 2.1) an italic capital letter *Z* prefix is used; if the selected pair are on opposite sides an italic capital letter *E* prefix is used.[7] These prefixes, placed in parentheses and followed by a hyphen, normally precede the whole name; if the molecule contains several double bonds, then each prefix is immediately preceded by the lower or less primed locant of the relevant double bond.

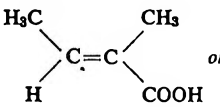
Examples:



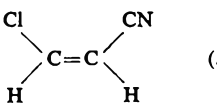
(*E*)-2-Butene



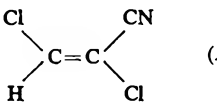
(*Z*)-2-Methyl-2-butenoic acid[8] *or* (*Z*)-2-Methylisocrotonic acid (see Exceptions below)



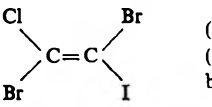
(*E*)-2-Methyl-2-butenoic acid[9] *or* (*E*)-2-Methylcrotonic acid (see Exceptions below)



(*Z*)-3-Chloroacrylonitrile



(*E*)-2,3-Dichloroacrylonitrile



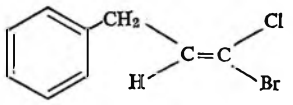
(*Z*)-1,2-Dibromo-1-chloro-2-iodoethylene (By the sequence rule, Br is preferred to Cl, but I to Br)

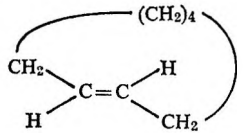
(6) For sequence-rule preferences see Appendix 2.

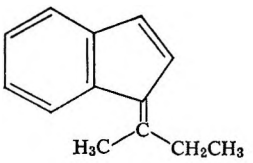
(7) These prefixes may be rationalized as from the German *zusammen* (together) and *entgegen* (opposite).

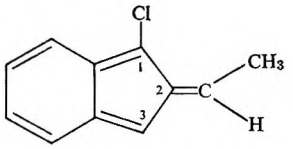
(8) The name angelic acid is abandoned because it has been associated with the designation *trans* with reference to the methyl groups.

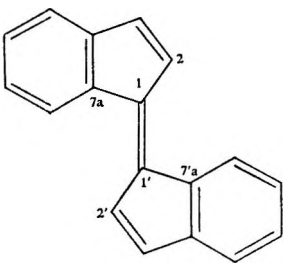
(9) The name tiglic acid is abandoned because it has been associated with the designation *cis* with reference to the methyl groups.

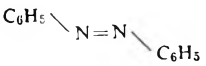

(*E*)-(3-Bromo-3-chloroallyl)benzene


(*E*)-Cyclooctene


(*E*)-1-*sec*-Butylideneindene

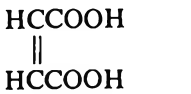

(*Z*)-1-Chloro-2-ethylidene-2*H*-indene

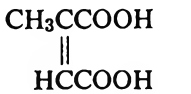

(*E*)-1,1′-Biindenylidene


(*E*)-Azobenzene

Exceptions to Rule E-2.21.—The following are examples of accepted trivial names in which the stereochemistry is prescribed by the name and is not cited by a prefix.


Fumaric acid


Maleic acid

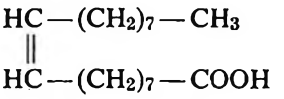

Citraconic acid[10]

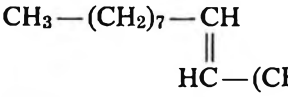

Mesaconic acid[10]


Crotonic acid

(10) Systematic names are recommended for derivatives of these compounds formed by substitution on carbon.


Isocrotonic acid


Oleic acid

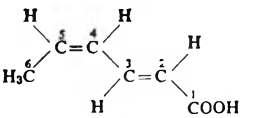

Elaidic acid

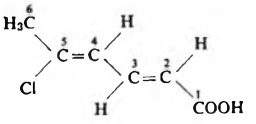
E-2.22 (Alternative to Part of E-2.21).—(a) When more than one series of locants starting from unity is required to designate the double bonds in a molecule, or when the name consists of two words, the *Z* and *E* prefixes together with their appropriate locants may be placed before that part of the name where ambiguity is most effectively removed.

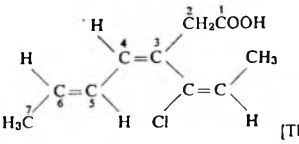
(b) [Alternative to (a)] When several *Z* or *E* prefixes are required they are arranged in order as follows: of the four atoms or groups attached to each doubly bonded pair of atoms, that one preferred by the sequence rule is selected; the single atoms or groups thus selected are then arranged in their sequence rule order (determined in respect of their position in the whole molecule), and the prefixes *Z* and/or *E* for the respective double bonds are placed in that order, but *without* their locants.

Note: In method (a) the final choice is left to an author or editor because of the variety of cases met and because the problems are not always the same in different languages. The presence of the locants usually eases translation from the name to a formula, but this method (a) may involve the logical difficulty explained for the third example below. Method (b) always gives a single unambiguous order and is not subject to the logical difficulty just mentioned, but translation from the name to the formula is harder than for method (a). Method (a) may be more suitable for cursive text, and method (b) for compendia. If method (b) is used it should be used whenever more than one double bond is involved, but method (a) is to be used only under the special conditions detailed in the rule.

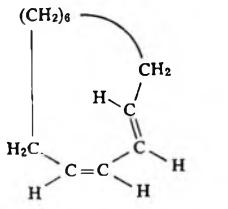
Examples:


(a) (2*E*,4*Z*)-2,4-Hexadienoic acid
(b) (*E*,*Z*)-2,4-Hexadienoic acid


(a) (2*E*,4*Z*)-5-Chloro-2,4-hexadienoic acid
(b) (*Z*,*E*)-5-Chloro-2,4-hexadienoic acid

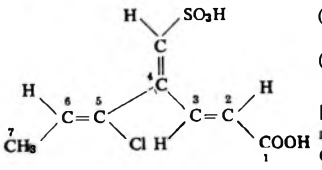

(a) 3-[(*E*)-1-Chloropropenyl]-(3*Z*,5*E*)-3,5-heptadienoic acid
(b) (*E*,*Z*,*E*)-3-(1-Chloropropenyl)-3,5-heptadienoic acid

[The last example shows the disadvantages of both methods. In method (a) there is a fault of logic, namely, the 3*Z*,5*E* are not the property of the unsubstituted heptadienoic acid chain, but the 3*Z* arises only because of the side chain that is cited before the 3*Z*,5*E*. In method (b) it is some trouble to assign the *E*,*Z*,*E* to the correct double bonds.]



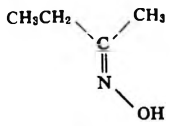
(a) (1*Z*,3*E*)-1,3-Cyclododecadiene
(b) (*Z*,*E*)-1,3-Cyclododecadiene

[The lower locant is assigned to the *Z* double bond.]

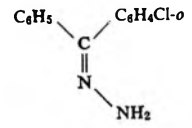


(a) 5-Chloro-4-(*E*-sulfomethylene)-(2*E*,5*Z*)-2,5-heptadienoic acid
(b) (*Z*,*E*,*E*)-5-Chloro-4-(sulfomethylene)-2,5-heptadienoic acid

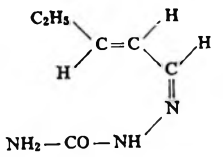
[In application of the sequence rule, the relation of the SO_3H to CCl (rather than to C-3), and of the CH_3 to Cl, are decisive.]



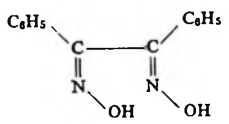
(a) Butanone (*E*)-oxime[11]
(b) (*E*)-Butanone oxime



(a) 2-Chlorobenzophenone (*Z*)-hydrazone
(b) (*Z*)-2-Chlorobenzophenone hydrazone



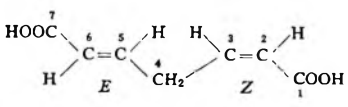
(a) (*E*)-2-Pentenal (*Z*)-semicarbazone
(b) (*Z*,*E*)-2-Pentenal semicarbazone



(a) Benzil (*Z*,*E*)-dioxime
(b) (*Z*,*E*)-Benzil dioxime

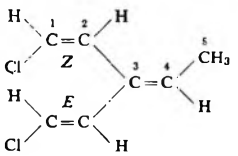
E-2.23.—When Rule C-13.1 or E-2.22(b) permits alternatives, preference for lower locants and for inclusion in the principal chain is allotted as follows, in the order stated, so far as necessary: *Z* over *E* groups; *cis* over *trans* cyclic groups; *R* over *S* groups (also *r* over *s*, etc., as in the sequence rule); if the nature of these groups is not decisive, then the lower locant for such a preferred group at the first point of difference.

Examples:



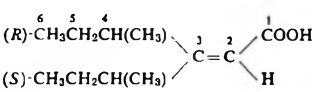
(a) (2*Z*,5*E*)-2,5-Heptadienedioic acid
(b) (*E*,*Z*)-2,5-Heptadienedioic acid

[The lower numbers are assigned to the *Z* double bond.]



(a) 1-Chloro-3-[2-chloro-(*E*)-vinyl]-(1*Z*,3*Z*)-1,3-pentadiene
(b) (*E*,*Z*,*Z*)-1-Chloro-3-(2-chlorovinyl)-1,3-pentadiene

[According to Rule C-13.1 the principal chain must include the C=C—CH_3 group because this gives lower numbers to the double bonds (1,3 rather than 1,4); then the Cl-containing *Z* group is chosen for the remainder of the principal chain in accord with Rule E-2.23.]



(a,b) (*Z*)-(4*R*)-3-[(*S*)-*sec*-Butyl]-4-methyl-2-hexenoic acid

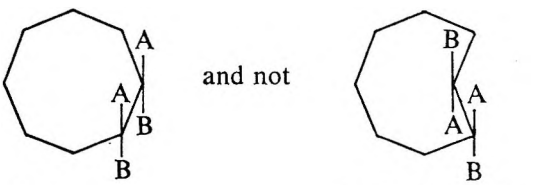
[The principal chain is chosen to include the (*R*)-group, and the prefix *Z* refers to the (*R*)-group.]

(11) The terms *syn*, *anti*, and *amphi* are abandoned for such compounds.

E-3. Relative Stereochemistry of Substituents in Monocyclic Compounds[12]

Preamble.—*cis* and *trans* prefixes are commonly used to designate the positions of substituents on rings relative to one another; when the ring is, or is considered to be, rigidly planar or approximately so and is placed horizontally, these prefixes define which groups are above and which below the (approximate) plane of the ring. This differentiation is often important, so this classical terminology is retained in Subsection E-3; since the difficulties inherent in end groups do not arise for cyclic compounds, it is unnecessary to resort to the less immediately informative *E*/*Z* symbolism.

When the *cis*–*trans* designation of substituents is applied, rings are considered in their most extended form; reentrant angles are not permitted; for example

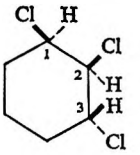


cis apparently *trans*

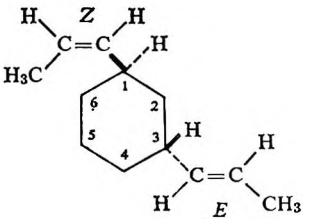
The absolute stereochemistry of optically active or racemic derivatives of monocyclic compounds is described by the sequence-rule procedure (see Rule E-5.9 and Appendix 2). The relative stereochemistry may be described by a modification of sequence-rule symbolism as set out in Rule E-5.10. If either of these procedures is adopted, it is then superfluous to use also *cis* or *trans* in the names of individual compounds.

E-3.1.—When alternative numberings of the ring are permissible according to the Rules of Section C, that numbering is chosen which gives a *cis* attachment at the first point of difference; if that is not decisive, the criteria of Rule E-2.23 are applied. *cis* and *trans* may be abbreviated to *c* and *t*, respectively, in names of compounds when more than one such designation is required.

Examples:



1,*c*-2,*t*-3-Trichlorocyclohexane

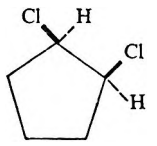


1-(*Z*)-Propenyl-*trans*-3-(*E*)-propenylcyclohexane

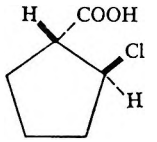
E-3.2.—When one substituent and one hydrogen atom are attached at each of two positions of a monocycle, the steric relations of the two substituents are expressed as *cis* or *trans*, followed by a hyphen and placed before the name of the compound.

(12) Formulas in Examples to this Rule denote relative (not absolute) configurations.

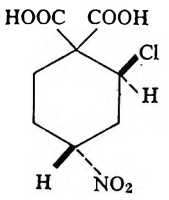
Examples:



cis-1,2-Dichlorocyclopentane



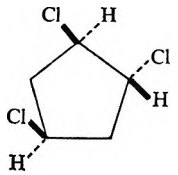
trans-2-Chloro-1-cyclopentanecarboxylic acid



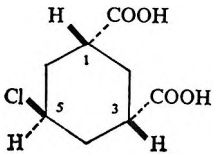
trans-2-Chloro-4-nitro-1,1-cyclohexanedicarboxylic acid

E-3.3.—When one substituent and one hydrogen atom are attached at each of more than two positions of a monocycle, the steric relations of the substituents are expressed by adding *r* (for *reference* substituent), followed by a hyphen, before the locant of the lowest numbered of these substituents and *c* or *t* (as appropriate), followed by a hyphen, before the locants of the other substituents to express their relation to the reference substituent.

Examples:



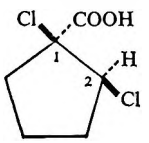
r-1,*t*-2,*c*-4-Trichlorocyclopentane (not *r*-1, *t*-2, *t*-4 which would follow from the alternative direction of numbering; see Rule E-3.1)



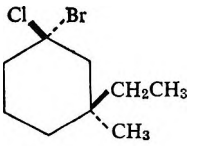
t-5-Chloro-*r*-1,*c*-3-cyclohexanedicarboxylic acid

E-3.4.—When two different substituents are attached at the same position of a monocycle, then the lowest numbered substituent named as suffix is selected for designation as reference group in accordance with Rule E-3.2 or E-3.3; or, if none of the substituents is named as suffix, then of the lowest numbered pair that one preferred by the sequence rule is selected as reference group; and the relation of the sequence-rule preferred group at each other position, relative to the reference group, is cited as *c* or *t* (as appropriate).

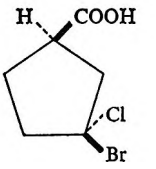
Examples:



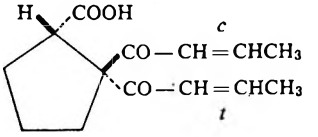
1,*t*-2-Dichloro-*r*-1-cyclopentanecarboxylic acid



r-1-Bromo-1-chloro-*t*-3-ethyl-3-methylcyclohexane (alphabetical order of prefixes)



c-3-Bromo-3-chloro-*r*-1-cyclopentanecarboxylic acid



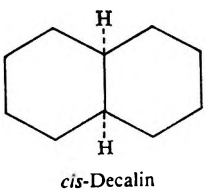
2-Crotonoyl-*t*-2-isocrotonoyl-*r*-1-cyclopentanecarboxylic acid

E-4. Fused Rings

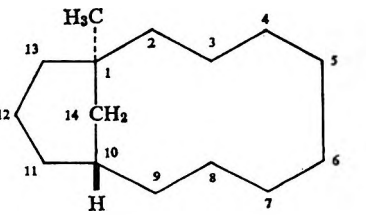
Preamble.—In simple cases the relative stereochemistry of substituted fused-ring systems can be designated by the methods used for monocycles. For the absolute stereochemistry of optically active and racemic compounds the sequence-rule procedure can be used in all cases (see Rule E-5.9 and Appendix 2), and for related relative stereochemistry the procedure of Rule E-5.10 can be applied. Sequence-rule methods are, however, not descriptive of geometrical shape for other than quite simple cases. There is as yet no generally acceptable system for designating in an immediately interpretable manner the stereochemistry of polycyclic bridged ring compounds (for instance, the *endo–exo* nomenclature, which should solve one set of problems, has been used in different ways). These and related problems (*e.g.*, cyclophanes, catenanes) will be considered in a later document.

E-4.1.—Steric relations at saturated bridgeheads common to two rings are denoted by *cis* or *trans*, followed by a hyphen and placed before the name of the ring system, according to the relative positions of the exocyclic atoms or groups attached to the bridgeheads. Such rings are said to be *cis* fused or *trans* fused.

Examples:



cis-Decalin



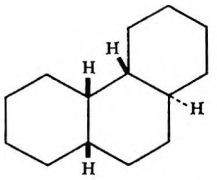
1-Methyl-*trans*-bicyclo[8.3.1]tetradecane

E-4.2.—Steric relations at more than one pair of saturated bridgeheads in a polycyclic compound are denoted by *cis* or *trans*, each followed by a hyphen and, when necessary, the corresponding locant of the lower numbered bridgehead and a second hyphen, all placed before the name of the ring system. Steric relations between the nearest atoms[13] of *cis*- or *trans*-bridgehead

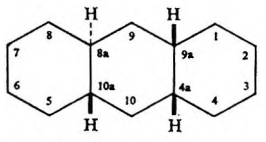
(13) The term "nearest atoms" denotes those linked together through the smallest number of atoms, irrespective of actual separation in space. For instance, in the second Example to this Rule, the atom 4a is "nearer" to 10a than to 8a.

pairs may be described by affixes *cisoid* or *transoid*, followed by a hyphen and, when necessary, the corresponding locants and a second hyphen, the whole placed between the designations of the *cis*- or *trans*-ring junctions concerned. When a choice remains among nearest atoms, the pair containing the lower numbered atom is selected. *cis* and *trans* are not abbreviated in such cases. In complex cases, however, designation may be more simply effected by the sequence-rule procedure (see Appendix 2).

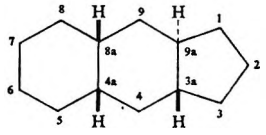
Examples:



cis-cisoid-trans-Perhydrophenanthrene



cis-cisoid-4a,10a-*trans*-Perhydroanthracene or *rel*-(4a*R*,8a*S*,9a*S*,10a*S*)-Perhydroanthracene[14]



trans-3a-*cisoid*-3a,4a-*cis*-4a-Perhydrobenz[*f*]indene or *rel*-(3a*R*,4a*S*,8a*R*,9a*R*)-Perhydrobenz[*f*]indene

E-5. Chirality

E-5.1.—The property of nonidentity of an object with its mirror image is termed chirality. An object, such as a molecule in a given configuration or conformation, is termed chiral when it is not identical with its mirror image; it is termed achiral when it is identical with its mirror image.

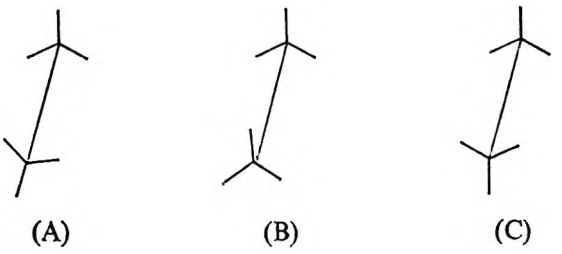
Notes: (1) Chirality is equivalent to handedness, the term being derived from the Greek Χειρ = hand.

(2) All chiral molecules are molecules of optically active compounds, and molecules of all optically active compounds are chiral. There is a 1:1 correspondence between chirality and optical activity.

(3) In organic chemistry the discussion of chirality usually concerns the individual molecule or, more strictly, a model of the individual molecule. The chirality of an assembly of molecules may differ from that of the component molecules, as in a chiral quartz crystal or in an achiral crystal containing equal numbers of dextrorotatory and levorotatory tartaric acid molecules.

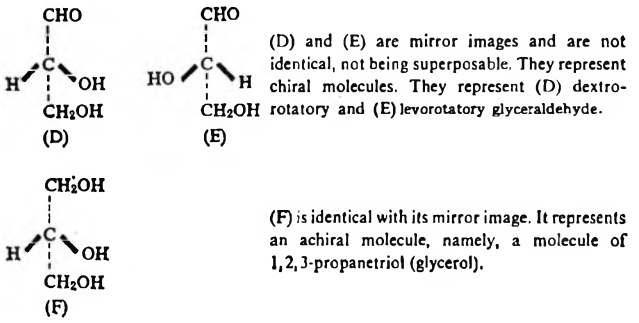
(4) The chirality of a molecule can be discussed only if the configuration or conformation of the molecule is specifically defined or is considered as defined by common usage. In such discussions structures are treated as if they were (at least temporarily) rigid. For instance, ethane is configurationally achiral although many of its conformations, such as (A), are chiral; in fact, a configuration of a mobile molecule is chiral only if all its possible conformations are chiral; and conformations of ethane such as (B) and (C) are achiral.

(14) For the designation *rel*, see Rule E-5.10.



(A) (B) (C)

Examples:



(D) and (E) are mirror images and are not identical, not being superposable. They represent chiral molecules. They represent (D) dextrorotatory and (E) levorotatory glyceraldehyde.

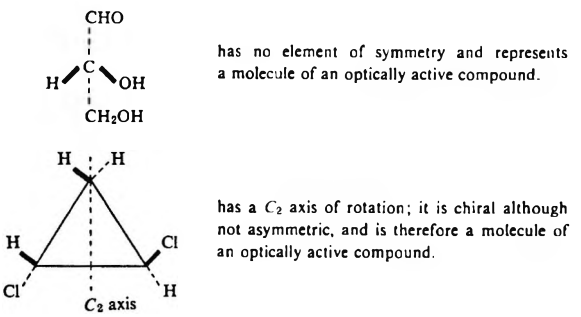
(F) is identical with its mirror image. It represents an achiral molecule, namely, a molecule of 1,2,3-propanetriol (glycerol).

E-5.2.—The term asymmetry denotes absence of any symmetry. An object, such as a molecule in a given configuration or conformation, is termed asymmetric if it has no element of symmetry.

Notes: (1) All asymmetric molecules are chiral, and all compounds composed of them are therefore optically active; however, not all chiral molecules are asymmetric since some molecules having axes of rotation are chiral.

(2) Notes (3) and (4) to Rule E-5.1 apply also in discussions of asymmetry.

Examples:



has no element of symmetry and represents a molecule of an optically active compound.

has a C_2 axis of rotation; it is chiral although not asymmetric, and is therefore a molecule of an optically active compound.

E-5.3.—(a) An asymmetric atom is one that is tetrahedrally bonded to four different atoms or groups, none of the groups being the mirror image of any of the others.

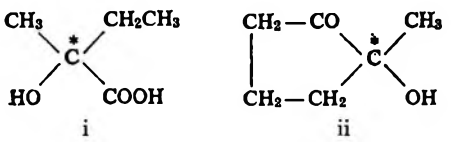
(b) An asymmetric atom may be said to be at a chiral center since it lies at the center of a chiral tetrahedral structure. In a general sense, the term "chiral center" is not restricted to tetrahedral structures; the structure may, for instance, be based on an octahedron or tetragonal pyramid.

(c) When the atom by which a group is attached to the remainder of a molecule lies at a chiral center, the group may be termed a chiral group.

Notes: (1) The term "asymmetric", as applied to a carbon atom in rule E-5.3 (a), was chosen by van't Hoff because there is no plane of symmetry through a tetrahedron whose corners are occupied by four atoms or groups that differ in scalar properties. For dif-

ferences of vector sense between the attached groups, see Rule E-5.8.

(2) In Subsection E-5 the word "group" is used to denote the series of atoms attached to one bond. For instance, in i the groups attached to C* are $-CH_3$, $-OH$, $-CH_2CH_3$, and $-COOH$; in ii they are $-CH_3$, $-OH$, $-COCH_2CH_2CH_2$, and $-CH_2CH_2CH_2CO$.



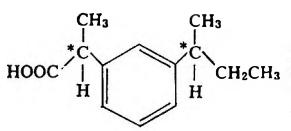
i ii

(3) For the chiral axis and chiral plane (which are less common than the chiral center), see Appendix 2.

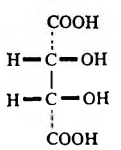
(4) There may be more than one chiral center in a molecule and these centers may be identical, or structurally different, or structurally identical but of opposite chirality; however, the presence of an equal number of structurally identical chiral groups of opposite chirality, and no other chiral group, leads to an achiral molecule. These statements apply also to chiral axes and chiral planes. Identification of the sites and natures of the various factors involved is essential if the overall chirality of a molecule is to be understood.

(5) Although the term "chiral group" is convenient for use in discussions it should be remembered that chirality attaches to molecules and not to groups or atoms. For instance, although the *sec*-butyl group may be termed chiral in dextrorotatory 2-*sec*-butylnaphthalene, it is not chiral in the achiral compound $(CH_3CH_2)(CH_3)CH-CH_3$.

Examples:



In this chiral compound there are two asymmetric carbon atoms, marked C*, each lying at a chiral centre. These atoms form part of different chiral groups, namely, $-CH(CH_3)COOH$ and $-CH(CH_3)CH_2CH_3$.



In this molecule (*meso*-tartaric acid) the two central carbon atoms are asymmetric atoms and each is part of a chiral group $-CH(OH)COOH$. These groups, however, although structurally identical, are of opposite chirality, so that the molecule is achiral.

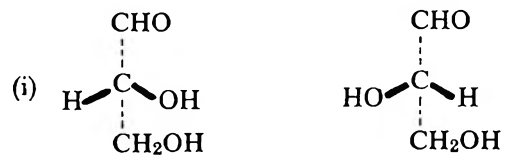
E-5.4.—Molecules that are mirror images of one another are termed enantiomers and may be said to be enantiomeric. Chiral groups that are mirror images of one another are termed enantiomeric groups.

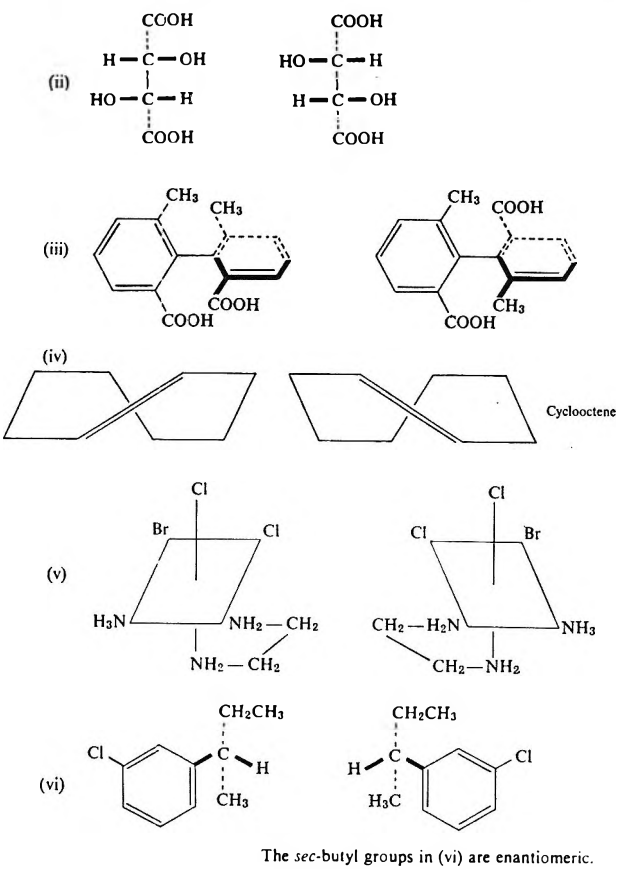
Hence: enantiomerism (phenomenological)

Note: Although the adjective enantiomeric may be applied to groups, enantiomerism strictly applies only to molecules [see Note (5) to Rule E-5.3].

Examples:

The following pairs of molecules are enantiomeric.





The *sec*-butyl groups in (vi) are enantiomeric.

E-5.5.—When equal amounts of enantiomeric molecules are present together, the product is termed racemic, independently of whether it is crystalline, liquid, or gaseous. A homogeneous solid phase composed of equimolar amounts of enantiomeric molecules is termed a racemic compound. A mixture of equimolar amounts of enantiomeric molecules present as separate solid phases is termed a racemic mixture. Any homogeneous solid containing equimolar amounts of enantiomeric molecules is termed a racemate.

Examples:

The mixture of two kinds of crystal (mirror-image forms) that separate below 28° from an aqueous solution containing equal amounts of dextrorotatory and levorotatory sodium ammonium tartrate is a racemic mixture.

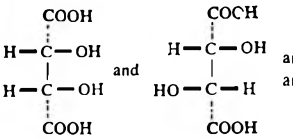
The symmetrical crystals that separate from such a solution above 28°, each containing equal amounts of the two salts, provide a racemic compound.

E-5.6.—Stereoisomers that are not enantiomeric are termed diastereoisomers.

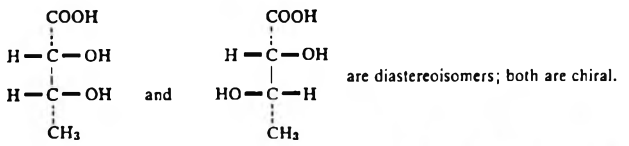
Hence: diastereoisomeric (adjectival)
diastereoisomerism (phenomenological)

Note: Diastereoisomers may be chiral or achiral.

Examples:

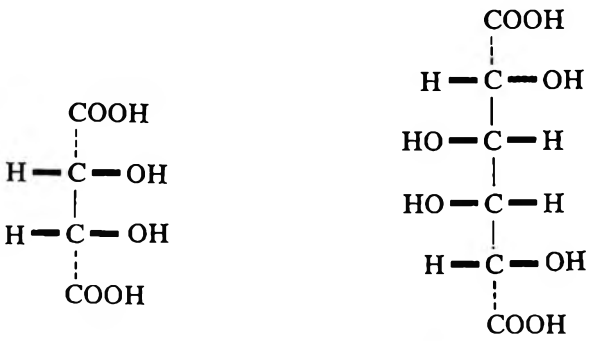


are diastereoisomers; the former is achiral, and the latter is chiral.



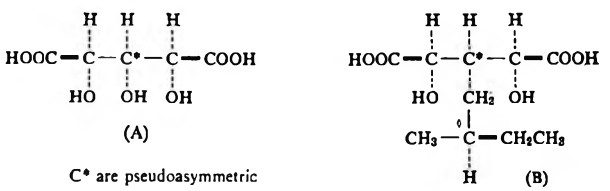
E-5.7.—A compound whose individual molecules contain equal numbers of enantiomeric groups, identically linked, but no other chiral group, is termed a *meso* compound.

Example:



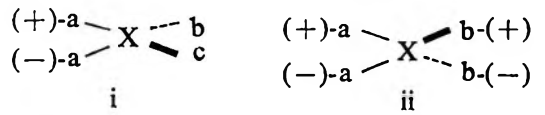
E-5.8.—An atom is termed pseudoasymmetric when bonded tetrahedrally to one pair of enantiomeric groups (+)-a and (−)-a and also to two atoms or groups b and c that are different from group a, different from each other, and not enantiomeric with each other.

Examples:



Notes: (1) The orientation, in space, of the atoms around a pseudoasymmetric atom is not reversed on reflection; for a chiral atom (see Note to Rule E-5.3) this orientation is always reversed.

(2) Molecules containing pseudoasymmetric atoms may be achiral or chiral. If ligands b and c are both achiral, the molecule is achiral as in the first example to this Rule. If either or both of the nonenantiomeric ligands b and c are chiral, the molecule is chiral, as in the second example to this Rule, that is the molecule is not identical with its mirror image. A molecule (i) is also chiral if b and c are enantiomeric, that is, if the molecule



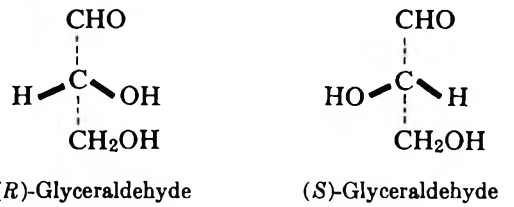
can be symbolized as ii, but then, by definition, it does not contain a pseudoasymmetric atom.

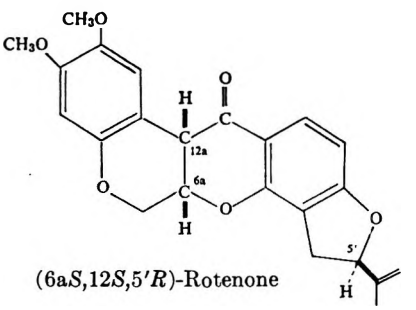
(3) Compounds differing at a pseudoasymmetric atom belong to the larger class of diastereoisomers.

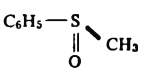
(4) In example (A), interchange of H and OH on C* gives a different achiral compound, which is an achiral diastereoisomer of (A) (see Rule E-5.6). In example (B), diastereoisomers are produced by inversion at C* or ^{0}C, giving in all four diastereoisomers, all chiral because of the $-CH(CH_3)CH_2CH_3$ group.

E-5.9.—Names of chiral compounds whose absolute configuration is known are differentiated by preffixes *R*, *S*, etc., assigned by the sequence-rule procedure (see Appendix 2), preceded when necessary by the appropriate locants.

Examples:







E-5.10.—(a) Names of compounds containing chiral centers, of which the relative but not the absolute configuration is known, are differentiated by prefixes *R**, *S** (spoken R star, S star), preceded when necessary by the appropriate locants, these prefixes being assigned by the sequence-rule procedure (see Appendix 2) on the arbitrary assumption that the prefix first cited is *R*.

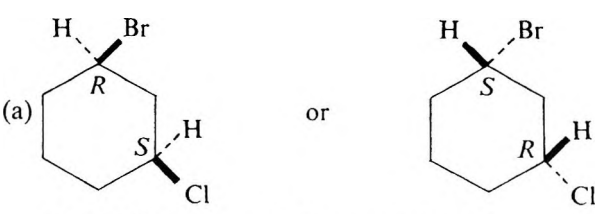
(b) In complex cases the stars may be omitted and, instead, the whole name is prefixed by *rel* (for *relative*).

(c) When only relative configuration is known, enantiomers are distinguished by a prefix (+) or (−), referring to the direction of rotation of plane-polarized light passing through them (wavelength, temperature, solvent, and/or concentration should also be specified, particularly when known to affect the sign).

(d) When a substituent of known absolute chirality is introduced into a compound of which only the relative configuration is known, then starred symbols *R**, *S** are used and not the prefix *rel*.

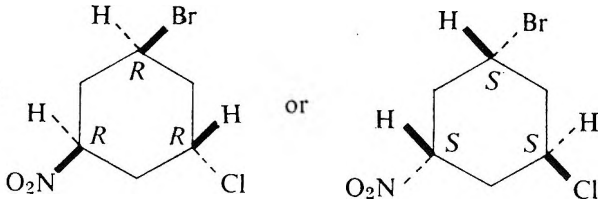
Note: This Rule does not form part of the procedure formulated in the sequence-rule papers by Cahn, Ingold, and Prelog (see Appendix 2).

Examples:



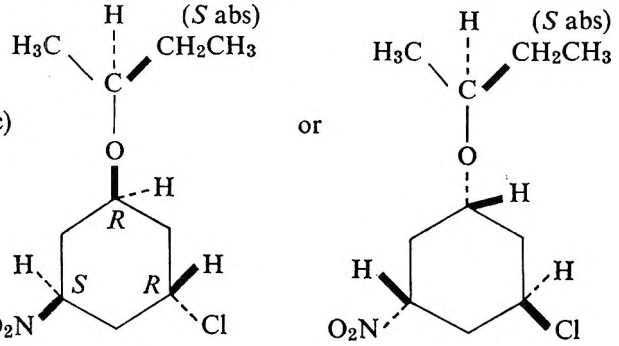
(1*R**,3*S**)-1-Bromo-3-chlorocyclohexane

(b)



rel-(1*R*,3*R*,5*R*)-1-Bromo-3-chloro-5-nitrocyclohexane

(c)



(1*R**,3*R**,5*S**)-[(1*S*)-*sec*-Butoxy]-3-chloro-5-nitrocyclohexane

E-5.11.—When it is desired to express relative or absolute configuration with respect to a class of compounds, specialized local systems may be used. The sequence rule may, however, be used additionally for positions not amenable to treatment by the local system.

Examples:

gluco, *arabino*, etc., combined when necessary with D or L, for carbohydrates and their derivatives [see IUPAC/IUB Tentative Rules for Carbohydrate Nomenclature, in press; see also *J. Org. Chem.*, **28**, 281 (1963)].

D, L for amino acids and peptides [see Comptes rendus of the 16th IUPAC Conference, New York, N. Y., 1951, pp 107–108; also published in *Chem. Eng. News*, **30**, 4522 (1952)].

D, L, and a series of other prefixes and trivial names for cyclitols and their derivatives [see IUPAC/IUB Tentative Rules for the Nomenclature of Cyclitols, 1967, IUPAC Information Bulletin, No. 32 (Aug 1968), pp 51–80; also published in *J. Biol. Chem.*, **243**, 5809 (1968)].

α, β, and a series of trivial names for steroids and related compounds [see IUPAC/IUB Revised Tentative Rules for the Nomenclature of Steroids, 1967, IUPAC Information Bulletin, No. 33 (Dec 1968), pp 23–67; also published in *J. Org. Chem.*, **34**, 1517 (1969)].

The α, β system for steroids can be extended to other classes of compounds such as terpenes and alkaloids when their absolute configurations are known; it can also be combined with stars or the use of the prefix *rel* when only the relative configurations are known.

In spite of the Rules of Subsection E-2, *cis* and *trans* are used when the arrangement of the atoms constituting an unsaturated backbone is the most important factor, as, for instance, in polymer chemistry and for carotenoids. When a series of double bonds of the same stereochemistry occurs in a backbone, the prefix all-*cis* or all-*trans* may be used.

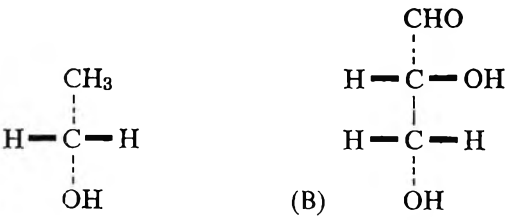
E-5.12.—(a) An achiral object having at least one pair of features that can be distinguished only by reference to a chiral object or to a chiral reference frame is said to be prochiral, and the property of having such a pair of features is termed prochirality. A consequence is that, if one of the paired features of a prochiral object is considered to differ from the other, the resultant object is chiral.

(b) In a molecule an achiral center or atom is said to be prochiral if it would be held to be chiral when two attached atoms or groups, that taken in isolation are indistinguishable, are considered to differ.

Notes: (1) For a tetrahedrally bonded atom this requires a structure Xaabc (where none of the groups a, b, or c is the enantiomer of another).

(2) For a fuller exploration of this concept, which is of particular importance to biochemists and spectroscopists, and for its extension to axes, planes, and unsaturated compounds, see K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966).

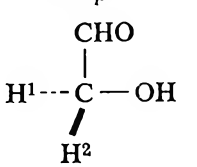
Examples:



In both examples (A) and (B) the methylene carbon atom is prochiral; in both cases it would be held to be at a chiral center if one of the methylene hydrogen atoms were considered to differ from the other. An actual replacement of one of these protium atoms by, say, deuterium would produce an actual chiral center at the methylene carbon atom; as a result compound (A) would become chiral, and compound (B) would be converted into one of two diastereoisomers.

E-5.13.—Of the identical pair of atoms or groups in a prochiral compound, that one which leads to an (*R*) compound when considered to be preferred to the other by the sequence rule (without change in priority with respect to other ligands) is termed *pro-R*, and the other is termed *pro-S*.

Example:

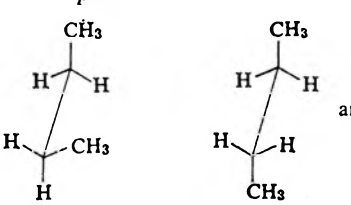


H^1 is *pro-R*. H^2 is *pro-S*.

E-6. Conformations

E-6.1.—A molecule in a conformation into which its atoms return spontaneously after small displacements is termed a conformer.

Examples:



are different conformers.

E-6.2.—(a) When, in a six-membered saturated ring compound, atoms in relative positions 1, 2, 4, and 5 lie in one plane, the molecule is described as in the

chair or boat conformation according as the other two atoms lie, respectively, on opposite sides or on the same side of that plane.

Examples:

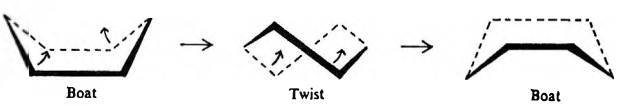
Note: These and similar representations are idealized, minor divergences being neglected.

(b) A molecule of a monounsaturated six-membered ring compound is described as being in the half-chair or half-boat conformation according as the atoms not directly bound to the doubly bonded atoms lie, respectively, on opposite sides or on the same side of the plane containing the other four (adjacent) atoms.

Examples:

(c) A median conformation through which one boat form passes during conversion into the other boat form is termed a twist conformation. Similar twist conformations are involved in conversion of a chair into a boat form or *vice versa*.

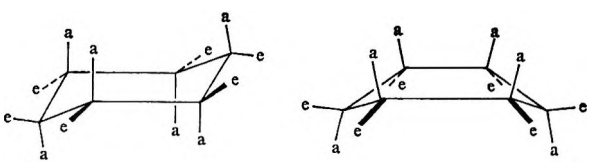
Examples:



E-6.3.—(a) Bonds to a tetrahedral atom in a six-membered ring are termed equatorial or axial according as they or their projections make a small or a large angle, respectively, with the plane containing a majority of the ring atoms.[15] Atoms or groups attached to such bonds are also said to be equatorial or axial, respectively.

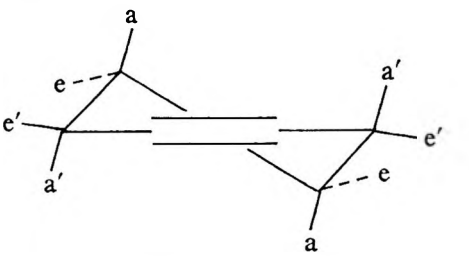
Notes: (1) See, however, pseudoequatorial and pseudoaxial [Rule 6.3(b)]. (2) The terms equatorial and axial may be abbreviated to e and a when attached to formulas; these abbreviations may also be used in names of compounds and are there placed in parentheses after the appropriate locants, for example, 1(e)-bromo-4(a)-chlorocyclohexane.

Examples:



(b) Bonds from atoms directly attached to the doubly bonded atoms in a monounsaturated six-membered ring are termed pseudoequatorial or pseudoaxial according as the angles that they make with the plane containing the majority of the ring atoms approximate those made by, respectively, equatorial or axial bonds from a saturated six-membered ring. Pseudoequatorial and pseudoaxial may be abbreviated to e′ and a′, respectively, when attached to formulas; these abbreviations may also be used in names, then being placed in parentheses after the appropriate locants.

Example:



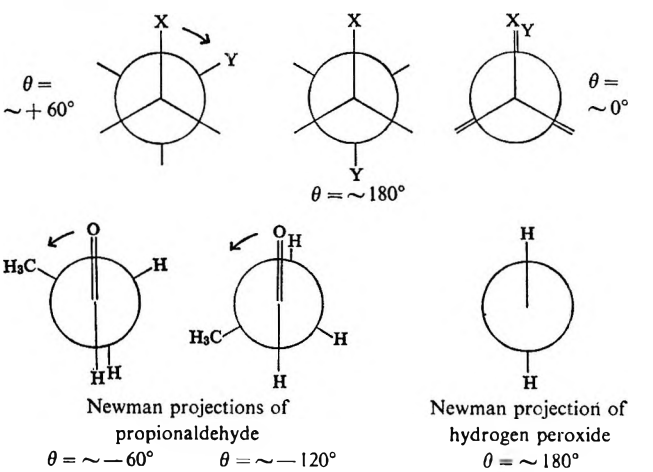
E-6.4.—Torsion angle: In an assembly of attached atoms X–A–B–Y, where neither X nor Y is collinear with A and B, the smaller angle subtended by the bonds X–A and Y–B in a plane projection obtained by viewing the assembly along the axis A–B is termed the torsion angle (denoted by the Greek lower case letter theta θ or omega ω). The torsion angle is considered positive or negative according as the bond to the front atom X or Y requires rotation to the right or left, respectively, in order that its direction may coincide with that of the bond to the rear selected atom Y or X. The multiplicity of the bonding of the various atoms is irrelevant. A torsion angle also exists if the axis for rotation is formed by a collinear set of more than two atoms directly attached to each other.

Notes: (1) It is immaterial whether the projection be viewed from the front or the rear.

(2) For the use of torsion angles in describing molecules see Rule E-6.6

Examples:

(For construction of Newman projections, as here, see Rule E-7.2.)

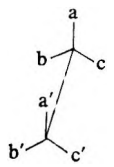


E-6.5.—If two atoms or groups attached at opposite ends of a bond appear one directly behind the other when the molecule is viewed along this bond, these atoms or groups are described as eclipsed, and that portion of the molecule is described as being in the eclipsed conformation. If not eclipsed, the atoms or

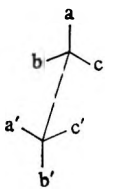
(15) The terms axial, equatorial, pseudoaxial and pseudoequatorial [see Rule E-6.3(b)] may be used also in connection with other than six-membered rings if, but only if, their interpretation is then still beyond dispute.

groups and the conformation may be described as staggered.

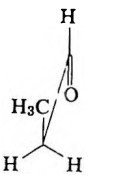
Examples:



Eclipsed conformation.
The pairs a/a', b/b', and c/c' are eclipsed.



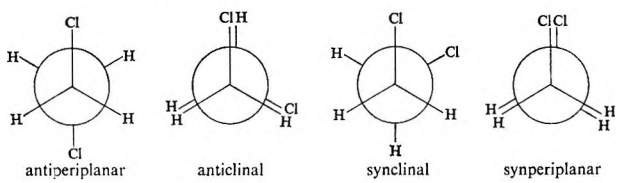
Staggered conformation.
All the attached groups are staggered.



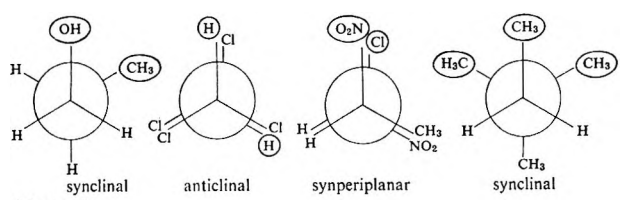
Projection of CH_3CH_2CHO.
The CH_3 and the H of the CHO are eclipsed.
The O and the H's of CH_2 in CH_2CH_3 are staggered.

E-6.6.—Conformations are described as synperiplanar (*sp*), synclinal (*sc*), anticlinal (*ac*), or antiperiplanar (*ap*) according as the torsion angle is within ±30° of 0°, ±60°, ±120°, or ±180°, respectively; the letters in parentheses are the corresponding abbreviations. Atoms or groups are selected from each set to define the torsion angle according to the following criteria: (1) if all the atoms or groups of a set are different, that one of each set that is preferred by the sequence rule; (2) if one of a set is unique, that one; or (3) if all of a set are identical, that one which provides the smallest torsion angle.

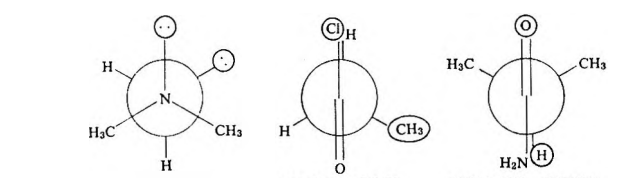
Examples:



In the above conformations, all CH_2Cl–CH_2Cl, the two Cl atoms decide the torsion angle.



Criterion for:				
rear atom	2	2	1	3
front atom	2	2	1	2

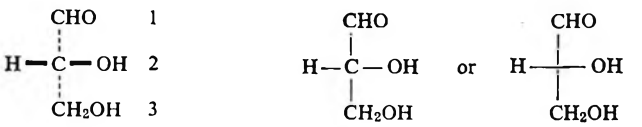


Criterion for:			
rear atom	2	2	2
front atom	2	1	1

E-7. Stereoformulas

E-7.1.—In a Fischer projection the atoms or groups attached to a tetrahedral center are projected on to the plane of the paper from such an orientation that atoms or groups appearing above or below the central atom lie behind the plane of the paper and those appearing to left and right of the central atom lie in front of the plane of the paper, and that the principal chain appears vertical with the lowest numbered chain member at the top.

Examples:

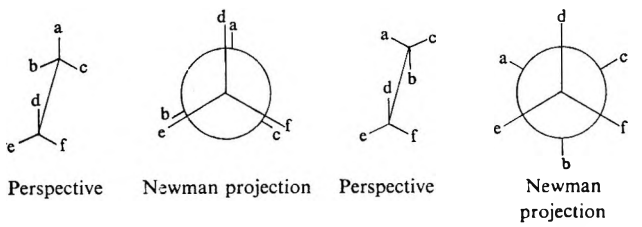


Notes: (1) The first of the two types of Fischer projection should be used whenever convenient.

(2) If a Fischer projection formula is rotated through 180° in the plane of the paper, the upward and downward bonds from the central atom still project behind the plane of the paper, and the sideways bonds project in front of that plane. If, however, the formula is rotated through 90° in the plane of the paper, the upward and downward bonds now project in front of the plane of the paper and the sideways bonds project behind that plane.

E-7.2.—To prepare a Newman projection a molecule is viewed along the bond between two atoms; a circle is used to represent these atoms, with lines from outside the circle toward its center to represent bonds to other atoms; the lines that represent bonds to the nearer and the further atom end at, respectively, the center and the circumference of the circle. When two such bonds would be coincident in the projection, they are drawn at a small angle to each other.[17]

Examples:



E-7.3. General Note.—Formulas that display stereochemistry should be prepared with extra care so as to be unambiguous and, whenever possible, self-explanatory. It is inadvisable to try to lay down rules that will cover every case, but the following points should be borne in mind.

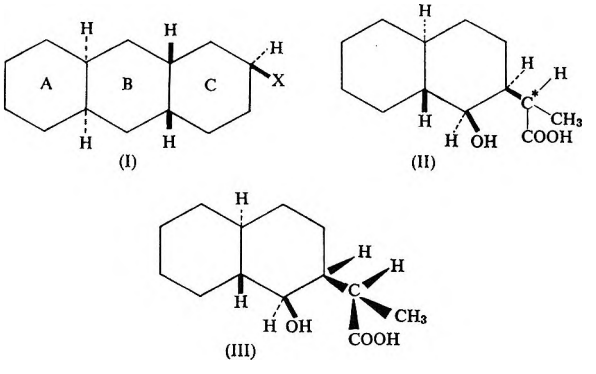
(16) The lone pair of electrons (represented by two dots) on the nitrogen atoms are the unique substituents that decide the description of the conformation (these are the "phantom atoms" of the sequence-rule symbolism).

(17) *Cf.* M. S. Newman, *Rec. Chem. Progr.*, **13**, 111 (1952); *J. Chem. Educ.*, **33**, 344 (1955); "Steric Effects in Organic Chemistry," John Wiley & Sons Inc., New York, N. Y., 1956, p 5–6.

A thickened line (▬) denotes a bond projecting from the plane of the paper toward an observer, a broken line (- - -) denotes a bond projecting away from an observer, and, when this convention is used, a full line of normal thickness (——) denotes a bond lying in the plane of the paper. A wavy line (〰) may be used to denote a bond whose direction cannot be specified or, if it is explained in the text, a bond whose direction it is not desired to specify in the formula. Dotted lines (· · · · · ·) should preferably not be used to denote stereochemistry, and never when they are used in the same paper to denote mesomerism, intermediate states, etc. Wedges should not be used as complement to broken lines (but see below). Single large dots have sometimes been used to denote atoms or groups attached at bridgehead positions and lying above the plane of the paper, with open circles to denote them lying below the plane of the paper, but this practice is strongly deprecated.

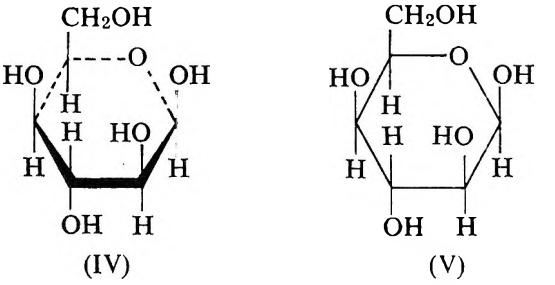
Hydrogen or other atoms or groups attached at sterically designated positions should never be omitted.

In chemical formulas, rings are usually drawn with lines of normal thickness, that is, as if they lay wholly in the plane of the paper even though this may be known not to be the case. In a formula such as (I) it is then clear that the H atoms attached at the A/B ring junction lie further from the observer than these bridgehead atoms, that the H atoms attached at the B/C ring junction lie nearer to the observer than those bridgehead atoms, and that X lies nearer to the observer than the neighboring atom of ring C.

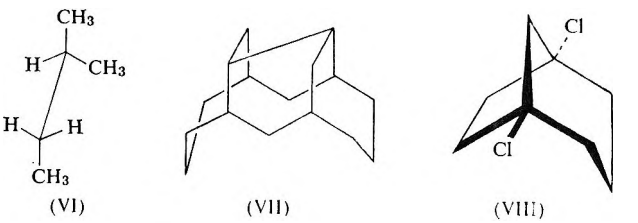


However, ambiguity can then sometimes arise, particularly when it is necessary to show stereochemistry within a group such as X attached to the rings that are drawn planar. For instance, in formula (II), the atoms O and C*, lying above the plane of the paper, are attached to ring B by thick bonds, but then, when showing the stereochemistry at C*, one finds that the bond *from* C* *to* ring B projects away from the observer and so should be a broken line. Such difficulties can be overcome by using wedges in place of lines, the broader end of the wedge being considered nearer to the observer, as in (III).

In some fields, notably for carbohydrates, rings are conveniently drawn as if they lay perpendicular to the plane of the paper, as represented in (IV); however, conventional formulas such as (V), with the lower bonds considered as the nearer to the observer, are so well established that it is rarely necessary to elaborate this to form (IV).



By a similar convention, in drawings such as (VI) and (VII), the lower sets of bonds are considered to be nearer than the upper to the observer. In (VII), note the gaps in the rear lines to indicate that the bonds crossing them pass in front (and thus obscure sections of the rear bonds). In some cases, when atoms have to be shown as lying in several planes, the various conventions may be combined, as in (VIII). In all cases the overriding aim should be clarity.



Appendix 1. Configuration and Conformation

See Rules E-1.4 and E-1.5.

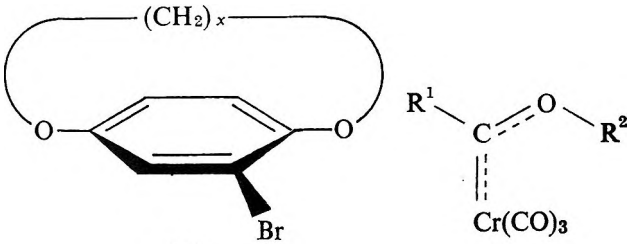
Various definitions have been propounded to differentiate configurations from conformations.

The original usage was to consider as conformations those arrangements of the atoms of a molecule in space that can be interconverted by rotation(s) around a single bond, and as configurations those other arrangements whose interconversion by rotation requires bonds to be broken and then re-formed differently. Interconversion of different configurations will then be associated with substantial energies of activation, and the various species will be separable, but interconversion of different conformations will normally be associated with less activation energy, and the various species, if separable, will normally be more readily interconvertible. These differences in activation energy and stability are often large.

Nevertheless, rigid differentiation on such grounds meets formidable difficulties. Differentiation by energy criteria would require an arbitrary cut in a continuous series of values. Differentiation by stability of isolated species requires arbitrary assumptions about conditions and half-lives. Differentiation on the basis of rotation around single bonds meets difficulties connected both with the concept of rotation and with the selection of single bonds as requisites, and these need more detailed discussion here.

Enantiomeric biaryls are nowadays usually considered to differ in conformation, any difficulty in rotation about the 1,1′ bond due to steric hindrance between the neighboring groups being considered to be overcome by bond bending and/or bond stretching, even though the movements required must closely approach bond breaking if these substituents are very

large. Similar doubts about the possibility of rotation occur with a molecule such as (A), where rotation of the benzene ring around the oxygen-to-ring single bonds affords easy interconversion if x is large but appears to be physically impossible if x is small; and no critical size of x can be reasonably established. For reasons such as this, Rules E-1.4 and E-1.5 are so worded as to be independent of whether rotation appears physically feasible or not (see Note 2 to those Rules).



(A) (B)

The second difficulty arises in the many cases where rotation is around a bond of fractional order between one and two, as in the helicenes, crowded aromatic molecules, metallocenes, amides, thioamides, and carbene–metal coordination compounds (such as B). The term conformation is customarily used in these cases and that appears a reasonable extension of the original conception, though it will be wise to specify the usage if the reader might be in doubt.

When interpreted in these ways, Rules E-1.4 and E-1.5 reflect the most frequent usage of the present day and provide clear distinctions in most situations. Nevertheless, difficulties remain and a number of other usages have been introduced.

It appears to some workers that, once it is admitted that change of conformation may involve rotation about bonds of fractional order between one and two, it is then illogical to exclude rotation about classical double bonds because interconversion of open-chain *cis–trans* isomers depends on no fundamentally new principle and is often relatively easy, as for certain alkene derivatives such as stilbenes and for azo compounds, by irradiation. This extension is indeed not excluded by Rules E-1.4 and E-1.5, but if it is applied that fact should be explicitly stated.

A further interpretation is to regard a stereoisomer possessing some degree of stability (that is, one associated with an energy hollow, however shallow) as a configurational isomer, the other arrangements in space being termed conformational isomers; the term conformer (Rule E-6.1) is then superfluous. This definition, however, requires a knowledge of stability (energy relations) that is not always available.

In another view a configurational isomer is any stereoisomer that can be isolated or (for some workers) whose existence can be established (for example, by physical methods); all other arrangements then represent conformational isomers; but it is then impossible to differentiate configuration from conformation without involving experimental efficiency or conditions of observation.

Yet another definition is to regard a conformation as a precise description of a configuration in terms of bond distances, bond angles, and dihedral angles.

In none of the above views except the last is attention paid to extension or contraction of the bond to an atom that is attached to only one other atom, such as —H or =O. Yet such changes in interatomic distance due to nonbonded interactions may be important, for instance in hydrogen bonding, in differences due to crystal form, in association in solution, and in transition states. This area may repay further consideration.

Owing to the circumstances outlined above, the Rules E-1.4 and E-1.5 have been deliberately made imprecise, so as to permit some alternative interpretations, but they are not compatible with all the definitions mentioned above. The time does not seem ripe to legislate for other than the commoner usages or to choose finally between these. It is, however, encouraging that no definition in this field has (yet) involved atomic vibrations for which, in all cases, only time-average positions are considered.

Finally it should be noted that an important school of thought uses conformation with the connotation of "a particular geometry of the molecule, *i.e.*, a description of atoms in space in terms of bond distances, bond angles, and dihedral angles," a definition much wider than any discussed above.

Appendix 2. Outline of the Sequence-Rule Procedure

The sequence-rule procedure is a method of specifying the absolute molecular chirality (handedness) of a compound, that is, a method of specifying which of two enantiomeric forms each chiral element of a molecule exists. For each chiral element in the molecule it provides a symbol, usually *R* or *S*, which is independent of nomenclature and numbering. These symbols define the chirality of the specific compound considered; they may not be the same for a compound and some of its derivatives; and they are not necessarily constant for chemically similar situations within a chemical or a biogenetic class. The procedure is applied directly to a three-dimensional model of the structure, and not to any two-dimensional projection thereof.

The method has been developed to cover all compounds with ligancy up to 4 and with ligancy 6,[18] and for all configurations and conformations of such compounds. The following is an outline confined to the most common situations; it is essential to study the original papers, especially the 1966 paper,[19] before using the sequence rule for other than fairly simple cases.

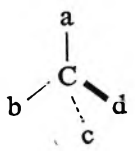
General Basis.—The sequence rule itself is a method of arranging atoms or groups (including chains and rings) in an order of precedence, often referred to as an order of preference; for discussion this order can conveniently be generalized as a > b > c > d, where > denotes "is preferred to."

The first step, however, in considering a model is to identify the nature and position of each chiral element that it contains. There are three types of chiral element, namely, the chiral center, the chiral axis, and the chiral plane. The chiral center, which is very

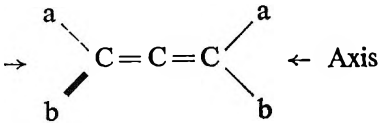
(18) Ligancy refers to the number of bonds from an atom, independently of the nature of the bonds.

(19) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966); errata, *ibid.*, **5**, 511 (1966); *Angew. Chem.*, **78**, 413 (1966). Earlier papers: R. S. Cahn and C. K. Ingold, *J. Chem. Soc.* (London), 612, (1951); R. S. Cahn, C. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956). For a partial, simplified account see R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964); *errata, ibid.*, **41**, 503 (1964).

much the most commonly met, is exemplified by an asymmetric carbon atom with the tetrahedral arrangement of ligands, as in (1). A chiral axis is present in, for instance, the chiral allenes such as (2) or the chiral

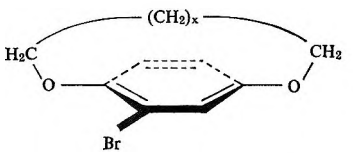


(1)

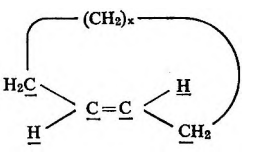


(2)

biaryl derivatives. A chiral plane is exemplified by the plane containing the benzene ring and the bromine and oxygen atoms in the chiral compound (3), or by the underlined atoms in the cycloalkene (4). Clearly,



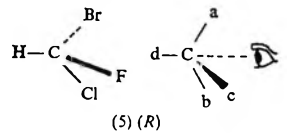
(3)



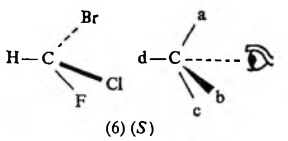
(4)

more than one type of chiral element may be present in one compound; for instance, group "a" in (2) might be a *sec*-butyl group which contains a chiral center.

The Chiral Center.—Let us consider first the simplest case, namely, a chiral center (such as carbon) with four ligands, a, b, c, d which are all different atoms, tetrahedrally arranged, as in CHFClBr. The four ligands are arranged in order of preference by means of the sequence rule; this contains five subrules, which are applied in succession so far as necessary to obtain a decision. The first subrule is all that is required in a great majority of actual cases; it states that ligands are arranged in order of decreasing atomic number, in the above case (a) Br > (b) Cl > (c) F > (d) H. There would be two (enantiomeric) forms of the compound and we can write these as (5) and (6). In the sequence-



(5) (*R*)

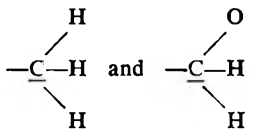


(6) (*S*)

rule procedure the model is viewed from the side remote from the least-preferred ligand (d), as illustrated. Then, tracing a path from a to b to c in (5) gives a clockwise course, which is symbolized by (*R*) (Latin *rectus*, right; for right hand); in (6) it gives an anticlockwise course, symbolized as (*S*) (Latin *sinister*, left). Thus (5) would be named (*R*)-bromochlorofluoromethane, and (6) would be named (*S*)-bromochlorofluoromethane. Here already it may be noted that converting one enantiomer into another changes each *R* to *S*, and each *S* to *R*, always. It will be seen also that the chirality prefix is the same whether the alphabetical order is used, as above, for naming the substituents or whether this is done by the order of complexity (giving fluorochlorobromomethane).

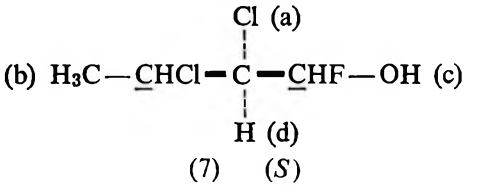
Next, suppose we have H_3C–CHClF. We deal first with the atoms directly attached to the chiral center; so the four ligands to be considered are Cl > F > C (of CH_3) > H. Here the H's of the CH_3 are not concerned, because we do not need them in order to assign our symbol.

However, atoms directly attached to a center are often identical, as, for example, the underlined C's in $H_3\underline{C}$–CHCl–$\underline{C}H_2OH$. For such a compound we at once establish a preference (a) Cl > (b, c) $\underline{C}$,$\underline{C}$ > (d) H. Then to decide between the two $\underline{C}$'s we work outward, to the atoms to which they in turn are directly attached and we then find



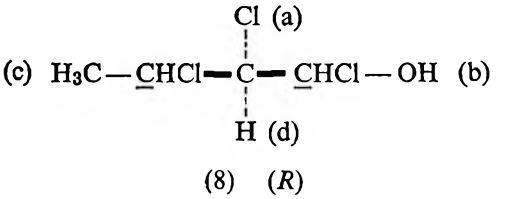
which we can conveniently write as C(H,H,H) and C(O,H,H). We have to compare H,H,H with O,H,H, and since oxygen has a higher atomic number than hydrogen we have O > H and thence the complete order Cl > C (of CH_2OH) > C (of CH_3) > H, so that the chirality symbol can then be determined from the three-dimensional model.

We must next meet the first complication. Suppose that we have a molecule (7)



(7) (*S*)

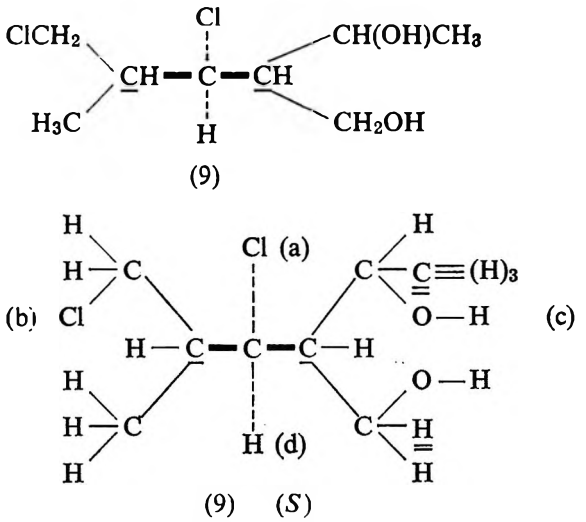
To decide between the two $\underline{C}$'s we first arrange the atoms attached to them in *their* order of preference, which gives $\underline{C}$(Cl,C,H) on the left and $\underline{C}$(F,O,H) on the right. Then we compare the preferred atom of one set (namely, Cl) with the preferred atom (F) of the other set, and as Cl > F we arrive at the preferences a > b > c > d shown in (7) and chirality (*S*). If, however, we had a compound (8)



(8) (*R*)

we should have met $\underline{C}$(Cl,C,H) and $\underline{C}$(Cl,O,H) and, since the atoms of first preference are identical (Cl), we should have had to make the comparisons with the atoms of second preference, namely, O > C, which leads to the different chirality (*R*) as shown in (8).

Branched ligands are treated similarly. Setting them out in full gives a picture that at first sight looks complex but the treatment is in fact simple. For instance, in compound (9) a first quick glance again shows (a) Cl > (b, c) $\underline{C}$, $\underline{C}$ > (d) H. When we expand the two $\underline{C}$'s we find they are both $\underline{C}$(C,C,H), so we continue exploration. Considering first the left-hand ligand we arrange the branches and their sets of atoms in order thus: C(Cl,H,H) > C(H,H,H). On the right-hand side we have C(O,$\underline{C}$,H) > C(O,$\underline{H}$,H) (because $\underline{C}$ > $\underline{H}$). We compare first the preferred of these branches from each side and we find C(Cl,H,H) > C(O,C,H) because Cl > O, and that gives the left-hand branch preference over the right-hand branch. That is all we need to do to establish chirality (*S*) for this

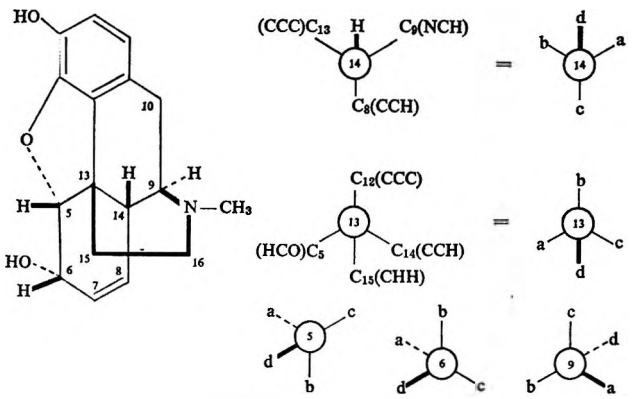


(9) (S)

highly branched compound (9). Note that it is immaterial here that, for the lower branches, the right-hand C(O,H,H) would have been preferred to the left-hand C(H,H,H); we did not need to reach that point in our comparisons and so we are not concerned with it; but we should have reached it if the two top (preferred) branches had both been the same CH_2Cl.

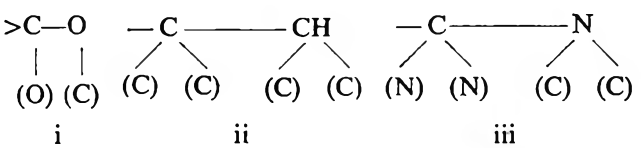
Rings, when met during outward exploration, are treated in the same way as branched chains.

With these simple procedures alone, quite complex structures can be handled; for instance, the analysis alongside formula (10) for natural morphine explains why the specification is as shown. The reason for considering C-12 as C(C,C,C) is set out in the next paragraphs.

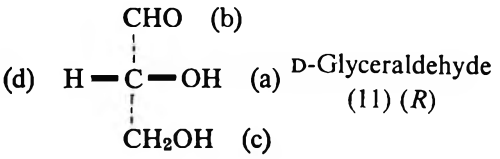


(10) (5*R*, 6*S*, 9*R*, 13*S*, 14*R*)-Morphine

Now, using the sequence rule depends on exploring along bonds. To avoid theoretical arguments about the nature of bonds, simple classical forms are used. Double and triple bonds are split into two and three bonds, respectively. A >C=O group is treated as i (below) where the (O) and the (C) are duplicate representations of the atoms at the other end of the double bond. —C≡CH is treated as ii and —C≡N is treated as iii.

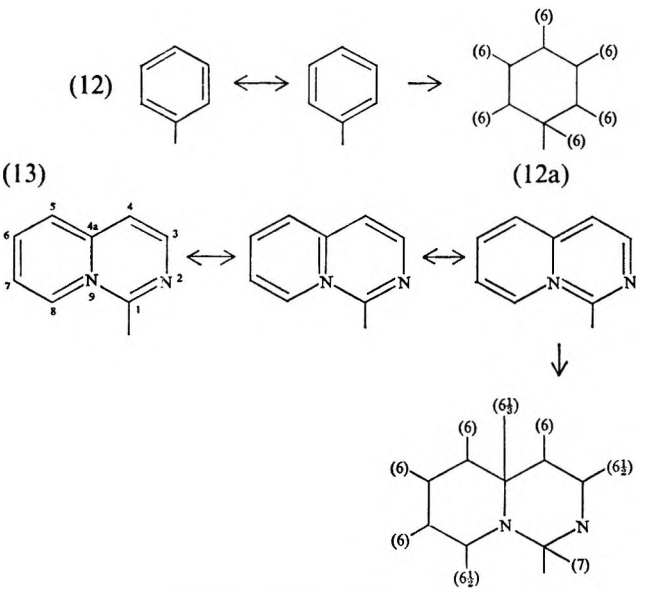


Thus in D-glyceraldehyde (11) the CHO group is treated as C(O,(O),H) and is thus preferred to the C(O,H,H) of the CH_2OH group, so that the chirality symbol is (*R*).



Only the doubly bonded atoms themselves are duplicated, and not the atoms or groups attached to them; the duplicated atoms may thus be considered as carrying three phantom atoms (see below) of atomic number zero. This may be important in deciding preferences in certain complicated cases.

Aromatic rings are treated as Kekulé structures. For aromatic hydrocarbon rings it is immaterial which Kekulé structure is used because "splitting" the double bonds gives the same result in all cases; for instance, for phenyl the result can be represented as (12a) where "(6)" denotes the atomic number of the duplicate representations of carbon.



For aromatic hetero rings, each duplicate is given an atomic number that is the mean of what it would have if the double bond were located at each of the possible positions. A complex case is illustrated in (13). Here C-1 is doubly bonded to one or other of the nitrogen atoms (atomic number 7) and never to carbon, so its added duplicate has atomic number 7; C-3 is doubly bonded either to C-4 (atomic number 6) or to N-2 (atomic number 7), so its added duplicate has atomic number $6^1/_2$; so has that of C-8; but C-4a may be doubly bonded to C-4, C-5, or N-9, so its added duplicate has atomic number 6.33.

One last point about the chiral center may be added here. Except for hydrogen, ligancy, if not already four, is made up to four by adding "phantom atoms" which have atomic number zero and are thus always last in order of preference. This has various uses but perhaps the most interesting is where nitrogen occurs in a rigid skeleton, as, for example, in α-isosparteine (14). Here the phantom atom can be placed where the nitrogen lone pair of electrons is; then N-1 appears as shown alongside the formula; and the chirality (*R*) is the

TABLE I

SOME COMMON GROUPS IN ORDER OF SEQUENCE-RULE PREFERENCE[a]

A. Alphabetical Order (Higher Number Denotes Greater Preference)

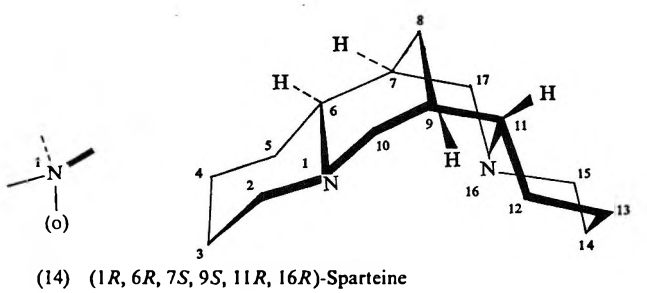
64 Acetoxy	38 Carboxyl	9 Isobutyl	55 Nitroso
36 Acetyl	74 Chloro	8 Isopentyl	6 *n*-Pentyl
48 Acetylamino	17 Cyclohexyl	20 Isopropenyl	61 Phenoxy
21 Acetylenyl	52 Diethylamino	14 Isopropyl	22 Phenyl
10 Allyl	51 Dimethylamino	69 Mercapto	47 Phenylamino
43 Amino	34 2,4-Dinitrophenyl	58 Methoxy	54 Phenylazo
44 Ammonio $^{+}H_3N-$	28 3,5-Dinitrophenyl	39 Methoxycarbonyl	18 Propenyl
37 Benzoyl	59 Ethoxy	2 Methyl	4 *n*-Propyl
49 Benzoylamino	40 Ethoxycarbonyl	45 Methylamino	29 1-Propynyl
65 Benzoyloxy	3 Ethyl	71 Methylsulfinyl	12 2-Propynyl
50 Benzyloxycarbonylamino	46 Ethylamino	66 Methylsulfinyloxy	73 Sulfo
13 Benzyl	68 Fluoro	72 Methylsulfonyl	25 *m*-Tolyl
60 Benzyloxy	35 Formyl	67 Methylsulfonyloxy	30 *o*-Tolyl
41 Benzyloxycarbonyl	63 Formyloxy	70 Methylthio	23 *p*-Tolyl
75 Bromo	62 Glycosyloxy	11 Neopentyl	53 Trimethylammonio
42 *tert*-Butoxycarbonyl	7 *n*-Hexyl	56 Nitro	32 Trityl
5 *n*-Butyl	1 Hydrogen	27 *m*-Nitrophenyl	15 Vinyl
16 *sec*-Butyl	57 Hydroxy	33 *o*-Nitrophenyl	31 2,6-Xylyl
19 *tert*-Butyl	76 Iodo	24 *p*-Nitrophenyl	26 3,5-Xylyl

B. Increasing Order of Sequence Rule Preference

1 Hydrogen	20 Isopropenyl	39 Methoxycarbonyl[b]	58 Methoxy
2 Methyl	21 Acetylenyl	40 Ethoxycarbonyl[b]	59 Ethoxy
3 Ethyl	22 Phenyl	41 Benzyloxycarbonyl[b]	60 Benzyloxy
4 *n*-Propyl	23 *p*-Tolyl	42 *tert*-Butoxycarbonyl[b]	61 Phenoxy
5 *n*-Butyl	24 *p*-Nitrophenyl	43 Amino	62 Glycosyloxy
6 *n*-Pentyl	25 *m*-Tolyl	44 Ammonio $^{+}H_3N-$	63 Formyloxy
7 *n*-Hexyl	26 3,5-Xylyl	45 Methylamino	64 Acetoxy
8 Isopentyl	27 *m*-Nitrophenyl	46 Ethylamino	65 Benzoyloxy
9 Isobutyl	28 3,5-Dinitrophenyl	47 Phenylamino	66 Methylsulfinyloxy
10 Allyl	29 1-Propynyl	48 Acetylamino	67 Methylsulfonyloxy
11 Neopentyl	30 *o*-Tolyl	49 Benzoylamino	68 Fluoro
12 2-Propynyl	31 2,6-Xylyl	50 Benzyloxycarbonylamino	69 Mercapto HS-
13 Benzyl	32 Trityl	51 Dimethylamino	70 Methylthio CH_3S-
14 Isopropyl	33 *o*-Nitrophenyl	52 Diethylamino	71 Methylsulfinyl
15 Vinyl	34 2,4-Dinitrophenyl	53 Trimethylammonio	72 Methylsulfonyl
16 *sec*-Butyl	35 Formyl	54 Phenylazo	73 Sulfo HO_3S-
17 Cyclohexyl	36 Acetyl	55 Nitroso	74 Chloro
18 1-Propenyl	37 Benzoyl	56 Nitro	75 Bromo
19 *tert*-Butyl	38 Carboxyl	57 Hydroxy	76 Iodo

[a] ANY alteration to structure, or substitution, etc., may alter the order of preference. [b] These groups are ROC(=O)-.

consequence. The same applies to N-16. Phantom atoms are similarly used when assigning chirality symbols to chiral sulfoxides (see example to Rule E-5.9).



(14) (1*R*, 6*R*, 7*S*, 9*S*, 11*R*, 16*R*)-Sparteine

Symbolism.—In names of compounds, the *R* and *S* symbols, together with their locants, are placed in parentheses, normally in front of the name, as shown for morphine (10) and sparteine (14), but this may be varied in indexes or in languages other than English. Positions within names are required, however, when more than a single series of numerals is used, as for esters and amines. When relative stereochemistry is more important than absolute stereochemistry, as for steroids or carbohydrates, a local system of stereochemical designation may be more useful and sequence-rule symbols need then be used only for any situations where the local system is insufficient.

Racemates containing a single center are labeled (*RS*). If there is more than one center the first is labeled (*RS*) and the others are (*RS*) or (*SR*) according to whether they are *R* or *S* when the first is *R*. For instance, the 2,4-pentanediols $CH_3-CH(OH)-CH_2-CH(OH)-CH_3$ are differentiated as

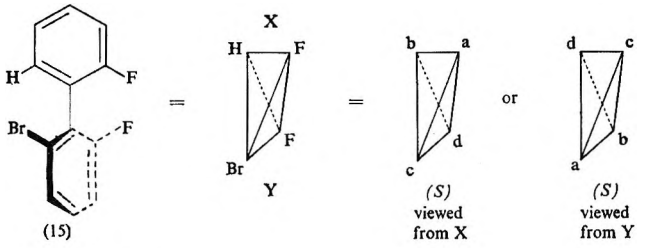
one chiral form (2*R*,4*R*)-
other chiral form (2*S*,4*S*)-
meso compound (2*R*,4*S*)-
racemic compound (2*RS*,4*RS*)-

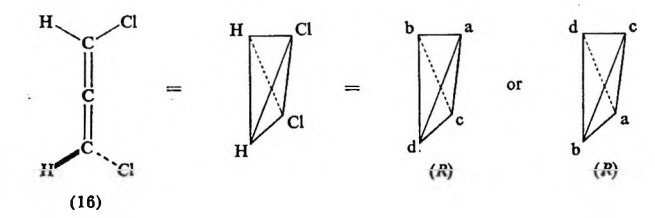
Finally the principles by which some of the least rare of

other situations are treated will be very briefly summarized.

Pseudoasymmetric Atoms.—A subrule decrees that *R* groups have preference over *S* groups and this permits pseudoasymmetric atoms, as in abC(c-*R*)(c-*S*) to be treated in the same way as chiral centers, but as such a molecule is achiral (not optically active) it is given the lower case symbol *r* or *s*.

Chiral Axis.—The structure is regarded as an elongated tetrahedron and viewed along the axis—it is immaterial from which end it is viewed; the nearer pair of ligands receives the first two positions in the order of preference, as shown in (15) and (16).

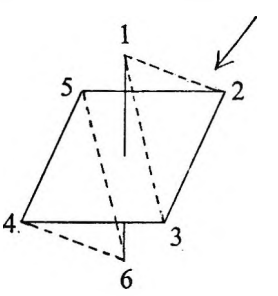




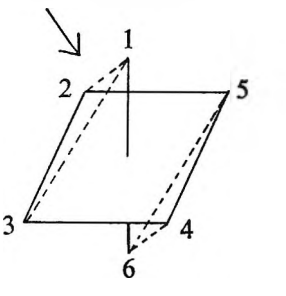
Chiral Plane.—The sequence-rule-preferred atom directly attached to the plane is chosen as "pilot atom." In compound (3) (page 2864) this is the C of the left-hand CH_2 group. Now this is attached to the left-hand oxygen atom in the plane. The sequence-rule-preferred path from this oxygen atom is then explored in the plane until a rotation is traced which is clockwise (*R*) or anticlockwise (*S*) when viewed from the pilot atom. In (3) this path is O → C → C(Br) and it is clockwise (*R*).

Other Subrules.—Other subrules cater for new chirality created by isotopic labeling (higher mass number preferred to lower) and for steric differences in the ligands. Isotopic labeling rarely changes symbols allotted to other centers.

Octahedral Structures.—Extensions of the sequence rule enable ligands arranged octahedrally to be placed in an order of preference, including polydentate ligands, so that a chiral structure can then always be represented as one of the enantiomeric forms (17) and (18). The face 1–2–3 is observed from the side remote from the



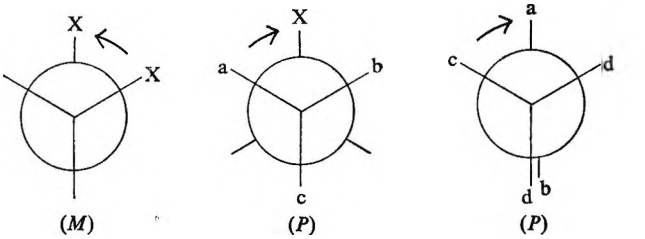
(*R*) (17)



(18) (*S*)

face 4–5–6 (as marked by arrows), and the path 1 → 2 → 3 is observed; in (17) this path is clockwise (*R*), and in (18) it is anticlockwise (*S*).

Conformations.—The torsion angle between selected bonds from two singly bonded atoms is considered. The selected bond from each of these two atoms is that to a unique ligand, or otherwise to the ligand preferred by the sequence rule. The smaller rotation needed to make the front ligand eclipsed with the rear one is noted (this is the rotatory characteristic of a helix); if this rotation is right-handed it leads to a symbol *P* (plus); if left-handed to *M* (minus). Examples are



Details and Complications.—For details and complicating factors the original papers should be consulted. They include treatment of compounds with high symmetry or containing repeating units (*e.g.*, cyclitols), also π bonding (metallocenes, etc.), mesomeric compounds and mesomeric radicals, and helical and other secondary structures.

Halo Sugar Nucleosides. II.[1] Iodination of Secondary Hydroxyl Groups of Nucleosides with Methyltriphenoxyphosphonium Iodide[2]

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The reactions of 5′-protected derivatives of thymidine with methyltriphenoxyphosphonium iodide in DMF at room temperature leads to the formation of the corresponding 3′-deoxy-3′-iodonucleosides with retention of configuration. This has been shown to occur *via* the very rapid formation of an intermediate O²,3′-cyclonucleoside which is subsequently opened by iodide ion. The reaction of **1** with the *cis*-vicinal diol grouping in 5′-protected uridine derivatives does not give iodinated products but rather a mixture of 2′(3′)-O-methylphosphonates which has also been prepared from the nucleoside and methylphosphonic acid in the presence of dicyclohexylcarbodiimide. Specific synthesis of uridine 3′-O-methylphosphonate and of the 2′- and 3′-O-methylphosphonate esters of 1-(β-D-arabinofuranosyl)uracil are also reported from methylphosphonic acid and the appropriately blocked nucleosides. The reaction of 2′,5′-di-O-trityluridine and **1** has been examined in both DMF at 25° and in hot benzene. In DMF the major product was the expected 1-(3-deoxy-3-iodo-2,5-di-O-trityl-β-D-xylofuranosyl)uracil, and there was also some selective hydrolysis of the 5′-O-trityl substituent. In benzene there was also inversion of configuration during iodination and an unexpected selective loss of the 2′-O-trityl group during work-up. Attempted reaction of 1-(2,5-di-O-trityl-β-D-xylofuranosyl)uracil with **1** in hot benzene gave a plethora of products from which only a pair of phosphorus diastereoisomers of 1-(β-D-xylofuranosyl)uracil 3′-O-(phenyl methylphosphonate) could be isolated after acidic hydrolysis. In DMF, however, slow iodination occurred giving 3′-deoxy-3′-iodo-2′,5′-di-O-trityluridine. Iodination of 3′-O-acetyluridine in DMF was not accompanied by acetyl migration and gave 3′-O-acetyl-2′,5′-dideoxy-2′,5′-diiodouridine.

In a previous paper[1] we have described the very facile iodination of the primary 5′-hydroxyl group of pyrimidine ribo- or deoxyribonucleosides through reaction with methyltriphenoxyphosphonium iodide (**1**).[3] Such reactions in dimethylformamide (DMF) are very rapid and give the corresponding 5′-deoxy-5′-iodonucleosides in high yield within a few minutes at room temperature. Attempted use of this iodination reaction with purine nucleosides, however, leads predominantly to the formation of the corresponding N³,5′-cyclonucleosides. In this paper we present the results of our studies on the reaction of **1** with secondary hydroxyl groups in various types of nucleosides.

The reaction of 5′-O-p-nitrobenzoylthymidine (**2a**)[4] with **1** in DMF required roughly 10 hr at 23° to reach completion and gave crystalline 3′-deoxy-3′-iodo-5′-O-*p*-nitrobenzoylthymidine (**5a**) in 85% yield. This product, with retention of configuration at $C_{3'}$, is perhaps unexpected since the generally accepted mechanism of the Rydon reaction[1,3] calls for inversion of configuration leading to the *threo* iodide (**6**). The *erythro* configuration was confirmed by synthesis of the same compound (**5a**) *via* *p*-nitrobenzoylation of 3′-deoxy-3′-iodothymidine (**5d**) obtained from 3′-O-mesyl-5′-O-tritylthymidine *via* the O²,3′-cyclonucleoside **4b**.[5,6] In a similar way, iodination of 5′-O-acetylthymidine (**2b**) with **1** in DMF gave 5′-O-acetyl-3′-deoxy-3′-iodothymidine (**5b**), mild alkaline hydrolysis of which gave the known **5d**. Further confirmation of the stereochemistry of the iodination reaction came from the reaction of 5′-O-tritylthymidine (**2c**) with **1** which gave a 67% yield of crystalline 3′-deoxy-3′-iodo-5′-O-tritylthymidine (**5c**) which was identical with an authentic sample *via* a different route.[5,6]

The observed retention of configuration is explained by the reaction sequence **2** → **5** involving displacement of the phenoxyphosphonium ion from **3** as diphenyl methylphosphonate and formation of the O²,3′-cyclothymidine (**4**). Subsequent opening of **4** by iodide then gives the observed *erythro* iodide (**5**). Similar interventions of O²,3′-cyclonucleosides have been invoked to explain retention of configuration during displacement of 3′-O-mesyl functions by halides,[5,6] azide,[7] carboxylate,[8] and imide[9] ions.

Direct confirmation of this idea came from examination of the reactions after short periods of time. Thus, after only 5 min of reaction between **2a** and **1**, tlc showed the complete absence of **2a** and the formation of 5′-O-*p*-nitrobenzoyl-O²,3′-cyclothymidine (the conjugate base of **4a**) which was isolated crystalline in 53% yield. The identical compound was also obtained *via* *p*-nitrobenzoylation of O²,3′-cyclothymidine (**4c**). As the reaction of **2a** and **1** was allowed to proceed the gradual disappearance of **2a** and the formation of **5a** could be readily followed by tlc. In a similar way, the reaction of 5′-O-tritylthymidine (**2c**) with **1** in either DMF or pyridine led to very rapid disappearance of the starting material and isolation of the crystalline O²,3′-cyclonucleoside (conjugate base of **4b**)[10] in 70% yield.

While iodination of 5′-O-tritylthymidine did give the 3′-iodo derivative (**5c**) in 67% yield, some loss of the trityl group occurred and led to the formation and isolation of a small amount of 3′,5′-dideoxy-3′,5′-diiodothymidine (**7a**). The same diiodothymidine (**7a**) was also obtained in 76% yield by direct iodination of thymidine with an excess of **1**, and a similar reaction with deoxyuridine gave 2′,3′,5′-trideoxy-3′,5′-diiodouridine (**7b**) in 84% yield. The configuration of the 3′-iodo function in **7a** and **7b** is based upon analogy with the above results and the nmr spectra of these compounds. Examination of the nmr spectra of many different 3′-substituted thymidine analogs has shown that, in those compounds with the *erythro* configuration, the $C_{2'}$ protons have very similar chemical shifts and

(1) For part I, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).

(2) A preliminary account of part of this work has appeared: J. P. H. Verheyden and J. G. Moffatt, *J. Amer. Chem. Soc.*, **86**, 2093 (1964).

(3) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 224 (1953).

(4) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).

(5) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

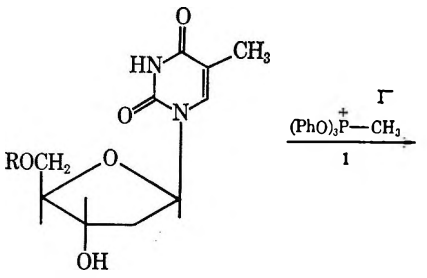
(6) K. E. Pfitzner and J. G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).

(7) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, **29**, 2076 (1964).

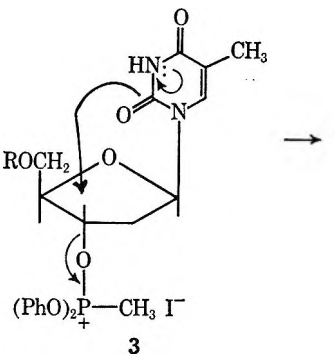
(8) J. J. Fox and N. C. Miller, *ibid.*, **28**, 936 (1963).

(9) N. C. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964).

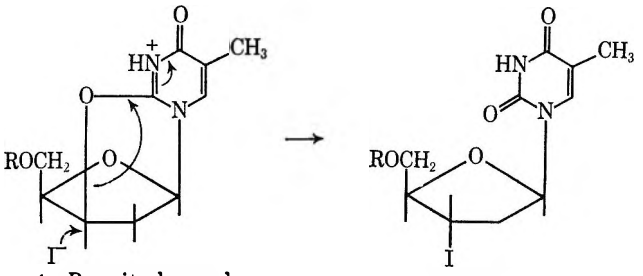
(10) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).



2a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = trityl

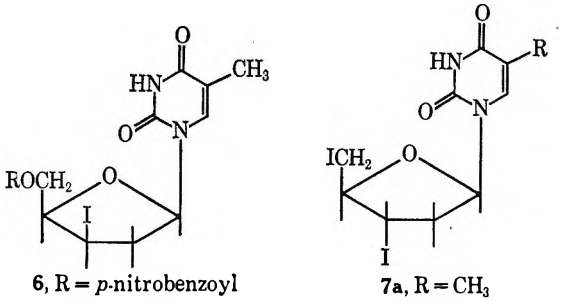


3



4a, R = nitrobenzoyl
b, R = trityl
c, R = H

5a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = trityl
d, R = H



6, R = *p*-nitrobenzoyl

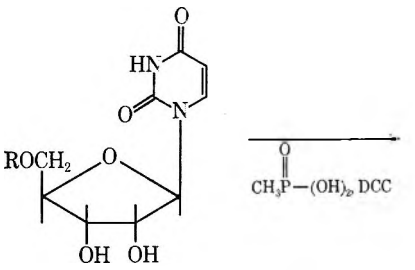
7a, R = CH_3
b, R = H

frequently occur as overlapping signals. In contrast, the $C_{2'}$ protons in compounds having the *threo* configuration have markedly different chemical shifts and are separated from each other by 0.5–1 ppm. A second differentiation can be made from the appearance of the $C_{1'}$ proton although this is likely to be less reliable than the above. In compounds with the *erythro* configuration, the coupling constants between $C_{1'}H$ and the two $C_{2'}$ protons ($J_{1',2'a}$ and $J_{1',2'b}$) are very similar and $C_{1'}H$ appears as a triplet while, in the *threo* compounds, $J_{1',2'a}$ and $J_{1',2'b}$ are different and $C_{1'}H$ appears as a quartet. A complete survey of the nmr data upon which these generalities are based will be described shortly.[11]

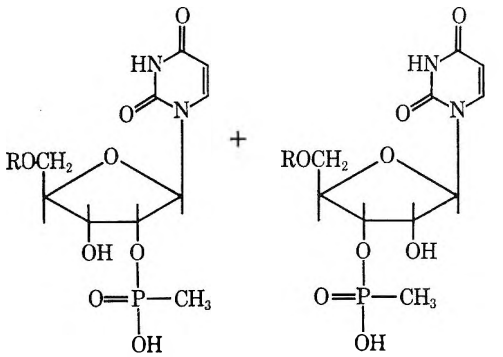
(11) J. P. H. Verheyden and J. G. Moffatt, unpublished results.

The observed partial loss of a trityl group in the reaction above is probably a consequence of the release of hydrogen iodide during formation of the cyclonucleoside (**4b**). Comparable loss of acid labile protecting groups during iodination of primary hydroxyl groups has not been noted since acidic by-products are not formed. Loss of the trityl group could be prevented by addition of 2 molar equiv of pyridine to the reaction mixture. Under these conditions, the formation of the $O^2,3'$-cyclonucleoside (**4b**) was still very rapid, but its subsequent opening by iodide ion was considerably retarded. Such an observation is entirely consistent with the known requirement for acid catalysis during opening of cyclonucleosides.[8] Acid catalysis by phenol, which is also released during reactions of **1**, does not seem to be sufficient for this purpose since prolonged treatment of **4b** with 2 equiv each of sodium iodide and phenol in DMF led to no apparent reaction. On the other hand, the reaction of free $O^2,3'$-cyclothymidine (**4c**) with **1** in DMF readily gave the crystalline diiodo compound **7a** in 58% yield. Since the latter reaction was run on a microscale it is entirely possible that the presence of traces of water led to hydrolysis of **1** with formation of the required acid. Indeed, the reaction of **4b** with pyridine hydriodide in DMF at 25° for 2 days gave **5c** in high yield.

The iodination of free *cis*-vicinal hydroxyl groups does not appear to be feasible using the reagent **1** although, as will be seen shortly,[11] some related halogenating agents may be satisfactorily employed. The reaction of 5′-O-*p*-nitrobenzoyluridine (**8a**) with **1** in anhydrous DMF gave no indication of the formation of



8a, R = *p*-nitrobenzoyl
b, R = acetyl



9a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = H

10a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = H

less polar products. In addition to unreacted **8a**, the major product was an extremely polar material that was shown to be a monoanion by paper electrophoresis at pH 3 or 7.6. Following hydrolysis of the *p*-nitrobenzoyl group from this substance a mixture of uridine

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF NUCLEOSIDE METHYLPHOSPHONATES[a]

	C_5H	C_6H	$C_{1'}H$	$C_{2'}H$, $C_{3'}H$, and $C_{4'}H$[b]	$C_{5'}H_2$	PCH_3
9c + 10c	5.98 (d, 8 Hz)	7.92 (d, 8 Hz)	5.94 (d, 5 Hz)[c]	4.1–4.6 (m)	3.88 (m)	1.28 (d, 16 Hz)
	5.91 (d, 8 Hz)	7.89 (d, 8 Hz)				1.33 (d, 16 Hz)
10c	5.90 (d, 8 Hz)	7.88 (d, 8 Hz)	5.93 (d, 5 Hz)	4.1–4.6 (m)	3.88 (m)	1.32 (d, 17 Hz)
19b	5.87 (d, 8 Hz)	7.87 (d, 8 Hz)	6.19 (d, 4 Hz)	4.1–4.6 (m)	3.91 (m)	1.34 (d, 17 Hz)
22	5.87 (d, 8 Hz)	7.81 (d, 8 Hz)	6.29 (d, 5 Hz)	4.1–4.5 (m)	3.85 (m)	1.14 (d, 17 Hz)

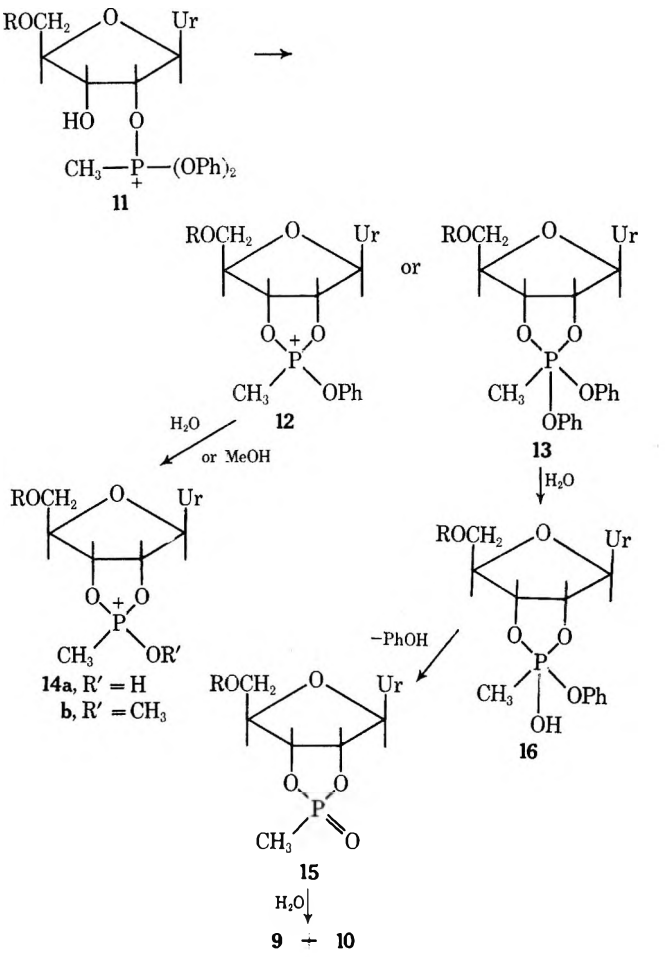
[a] Determined in D_2O at 100 MHz relative to an internal standard of 2,2-dimethyl-2-silapentane 5-sulfonate. [b] The $C_{2'}H$,$C_{3'}H$, and $C_{4'}H$ are usually superimposed upon each other and upon the HDO signal. In the case of **22** the $C_{2'}H$ signal was clearly resolved at 80° and appeared as an octet with $J_{1',2'} = 4$ Hz, $J_{2',3'} = 3$ Hz, and $J_{P,H} = 9$ Hz. [c] The second, lower intensity doublet is superimposed upon the C_5H and $C_{1'}H$ signals and cannot be precisely assigned.

2′(3′)-O-methylphosphonates (**9c**, **10c**)[12] was isolated by ion-exchange chromatography. An identical mixture was obtained by reaction of **8a** with methylphosphonic acid in the presence of dicyclohexylcarbodiimide.[13] Unexpectedly, the *p*-nitrobenzoyl group was hydrolyzed from the resulting compounds (**9a**, **10a**) during ion-exchange chromatography and a mixture of the free 2′(3′)-O-methylphosphonates (**9c**, **10c**) was once again obtained. Loss of the *p*-nitrobenzoyl group was avoided by use of preparative tlc on microcrystalline cellulose and the protected derivatives (**9a**, **10a**) were isolated and shown to be chromatographically and electrophoretically identical with the products from **8a** and **1** prior to hydrolysis.

The two isomers **9c** and **10c** could not be separated by paper or ion-exchange chromatography but could be distinguished by nmr spectroscopy since the C_5H, C_6H, and PCH_3 resonances appeared as pairs of doublets in a ratio of roughly 2:1 (see Table I). Definitive assignments of the observed resonances to each isomer could be made following a specific synthesis of the 3′-O-methylphosphonate ester (**10c**) from 2′,5′-di-O-(4-methoxytetrahydropyran-4-yl)uridine[14] and methylphosphonic acid in the presence of DCC and showed the 3′ ester to be the major isomer. Since the signal due to $C_{1'}H$ of the minor isomer could not be readily assigned, it was impossible to further confirm this conclusion using the empirical rules of Fromageot, *et al.*[15]

Very similar results were obtained from the reaction of 5′-O-acetyluridine (**8b**) with **1** which gave a mixture of 5′-O-acetyluridine 2′(3′)-O-methylphosphonates (**9b**, **10b**) and the corresponding deacetylated products (**9c**, **10c**) that were indistinguishable from the products from the carbodiimide condensation of **8b** and methylphosphonic acid.

The formation of **9c** and **10c** can be explained *via* attack of the *cis*-vicinal hydroxyl on the initial adduct (**11** or its 3′ isomer) giving **12** or **13**. Hydrolysis of **12** or **13** can then give the cyclic phosphonate **15** *via* either **14a** or **16**, and further rapid hydrolysis would then lead to the observed 2′(3′)-O-methylphosphonates. Alternatively, the accumulated **12** could react with methanol during work-up of the reaction giving a methoxyphosphonium compound (**14b**) which could undergo rapid dealkylation by iodide ion once again forming **15**.



The above mechanism appears to require the accumulation of a cyclic intermediate (**12** or **13**) which undergoes decomposition only during work-up of the reaction. Since acylic oxyphosphonium salts such as **3** are known to undergo intramolecular displacement with formation of O²,3′-cyclothymidine derivatives, it would appear likely that **12** could also undergo attack at $C_{2'}$ by the 2-carbonyl group of the uracil ring with formation of the O²,2′-cyclouridine 3′-O-(phenyl methylphosphonate) (**18b**).[16] There were, however, no observable neutral products of this sort formed during reaction of

(12) It has previously been noted that the reaction of vicinal diols with **1** leads to acidic products that were assumed to be phosphites [J. B. Lee and M. M. El Sawi, *Chem. Ind. (London)*, 839 (1960)] but were later referred to as phosphonates [J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966)].

(13) A similar preparation of 6-azauridine 2′(3′)-O-methylphosphonate has been described by A. Holy, *Collect. Czech. Chem. Commun*, **32**, 3713 (1967).

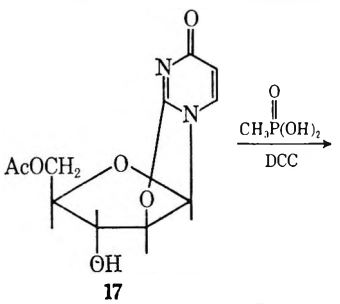
(14) C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Amer. Chem. Soc.*, **89**, 3366 (1967). We are very grateful to Dr. N. P. Damodaran of this laboratory for a sample of this compound.

(15) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, J. E. Sulston, and D. R. Trentham, *Tetrahedron*, **22**, 705 (1966).

(16) Other work from this laboratory has shown that the related 2′,3′-acetoxonium ion of uridine undergoes specific attack at $C_{2'}$ by the 2-keto group giving 3′-O-acetyl-O²,2′-cyclouridine; see S. Greenberg and J. G. Moffatt, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, Abstract C54.

8a with **1**, and the absence of the hydrolysis product 1-(β-D-arabinofuranosyl)uracil 3′-O-methylphosphonate (**19b**) in the isolated products (**9c**, **10c**) was confirmed by nmr spectroscopy. The apparent lack of attack by the uracil ring in **12** is perhaps due to a decreased electrophilicity of the alkoxy groups ($C_{2'}$ or $C_{3'}$) relative to those in alkoxydiphenoxyphosphonium species such as **3**. Even less electrophilic character is shown by trialkoxyphosphonium salts as indicated by the high temperatures required for the Arbusov reaction which involves dealkylation by iodide ion.[17]

A synthesis of the authentic arabinoside **19b** was achieved through the condensation of 5′-O-acetyl-O²,2′-cyclouridine (**17**)[18] with methylphosphonic acid using DCC and gave the 3′-O-methylphosphonate (**18a**) which was hydrolyzed with acid and then with ammonium hydroxide giving **19b** in an overall yield of 97% from **17**. The preparation of **17** was conveniently achieved in 89% yield through reaction of 5′-O-acetyl-2′-O-tosyluridine[19] with triethylamine in pyridine under reflux for 2 hr. Under these conditions there was no loss of the acetyl group and no formation of the isocytosine derivatives which accompany the use of methanolic ammonia.[20] Selective hydrolysis of the acetyl group from **17** can be accomplished by treatment with methanolic triethylamine at 37° which leads to direct crystallization of O²,2′-cyclouridine in 90% yield.



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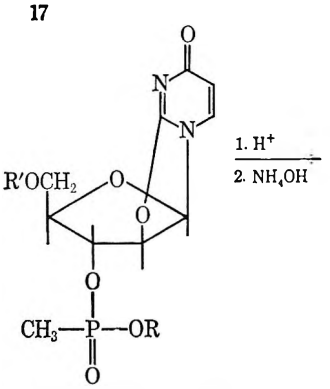
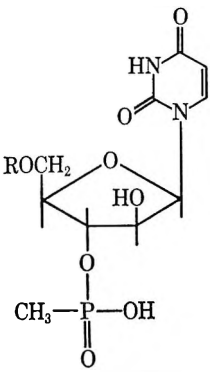
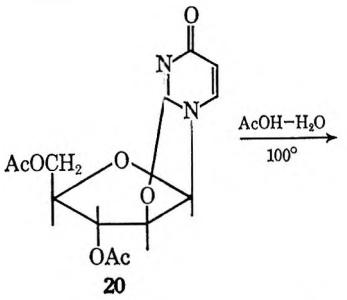


18a, R = H; R′ = acetyl
b, R = C_6H_5; R′ = *p*-nitrobenzoyl



19a, R = acetyl
b, R = H

The synthesis of 1-(β-D-arabinofuranosyl)uracil 2′-O-methylphosphonate (**22**) was also accomplished *via* treatment of 3′-5′-di-O-acetyl-O²,2′-cyclouridine (**20**)[18] with 50% acetic acid giving crystalline 1-(3,5-di-O-acetyl-β-D-arabinofuranosyl)uracil (**21**). Under these conditions there was relatively little solvolysis of the cyclonucleoside leading to compounds with the *ribo* configuration as shown by borate electrophoresis following hydrolysis of the acetyl groups from the crude reaction mixture. Subsequent condensation of **21** with methylphosphonic acid in the presence of DCC followed by hydrolysis of the acetyl groups gave **22** in 87% yield.



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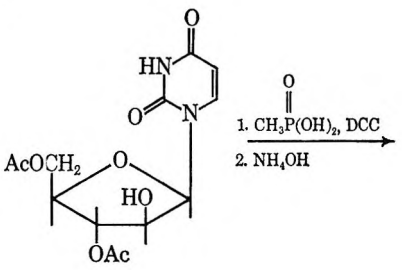

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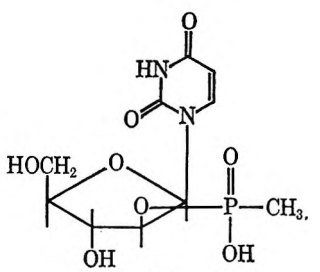
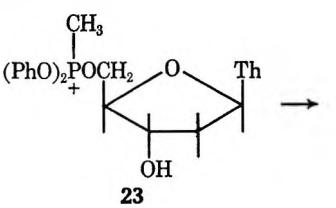


22

Another somewhat related case of intramolecular participation by a free hydroxyl group was observed during selective iodination of the 5′-hydroxyl group of thymidine with **1**.[1] During this reaction a compound which we have characterized by nmr and mass spectrometry as thymidine 3′,5′-cyclic methylphosphonate (**25**) was isolated in 3% yield. This suggests attack by the 3′-hydroxyl group upon the phosphorus atom of the initial 5′-alkoxyphosphonium intermediate (**23**) with formation of the cyclic phosphonium salt (**24**) or the related phosphorane (*cf.* **12** or **13**) which decomposes during work-up giving **25**. Being a six-membered cyclic phosphonate, **25** does not undergo further hydrolysis to acidic products as did the five-membered analog **15**.



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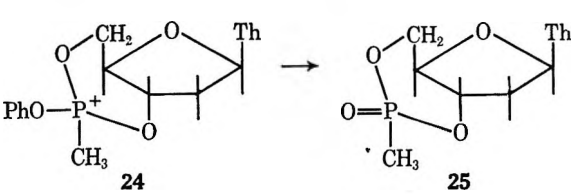
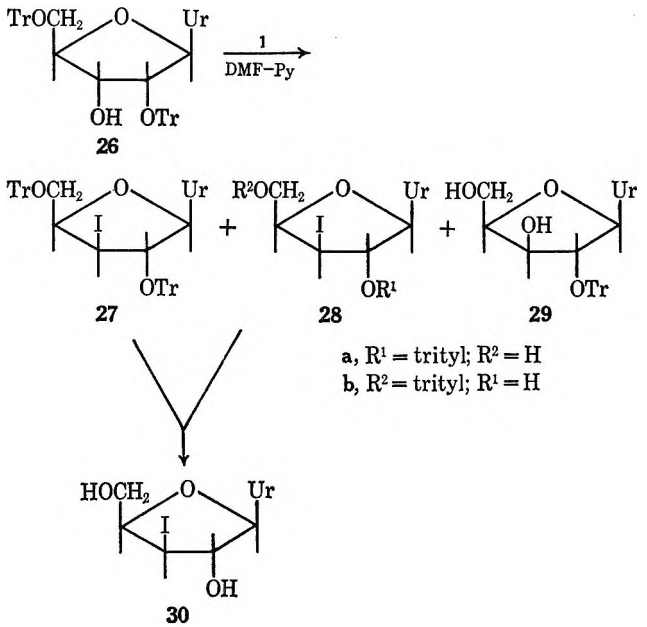


24 **25**

(17) G. M. Kosolapoff, *Org. React.*, **6**, 273 (1951).
(18) D. M. Brown, D. B. Parihar and A. R. Todd, *J. Chem. Soc.*, 4242 (1958).
(19) D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).
(20) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *ibid.*, 3028 (1958).

Recently, Johnston[21] reported that the reactions of both 2′,5′-di-O-trityluridine (**26**) and 1-(2,5-di-O-trityl-β-D-xylofuranosyl)uracil (**31**) with **1** in benzene at 50° for 18 hr give the 3′-deoxy-3′-iodo derivative (**27**) with the *xylo* configuration. Neither **27** nor its detritylated derivative (**30**) was obtained in pure form and the structures were deduced by hydrogenolysis of **30** to give 3′-deoxyuridine and by its conversion into O²,2′-cyclouridine upon treatment with base. While the known reluctance of uridine derivatives to form O²,3′-cyclo derivatives.[22,23] offers a tentative explanation for the observed inversion of configuration during conversion of **26** to **27**, the reason for the reported retention of configuration during the reaction with **31** remains obscure.

In our hands the reaction of **26** with **1** was carried out both in benzene at 50° according to Jonhston and in DMF at room temperature in the presence of a little pyridine to minimize the hydrolysis of trityl groups. The reaction in DMF for 24 hr contained three major tritylated uridine derivatives which were isolated by preparative tlc giving crystalline 1-(3-deoxy-3-iodo-2,5-di-O-trityl-β-D-xylofuranosyl)uracil (**27**, 32%), 1-(3-deoxy-3-iodo-2-O-trityl-β-D-xylofuranosyl)uracil (**28a**, 12%), and 1-(2-O-trityl-β-D-xylofuranosyl)uracil (**29**, 15%). The isolation of these compounds required quite extensive chromatography and hence the yields, which are of analytically pure material, are probably not optimal. Hydrolysis of either **27** or **28** with acetic acid gave the same noncrystalline 3′-deoxy-3′-iodonucleoside (**30**) which gave O²,2′-cyclouridine almost



quantitatively upon reaction with 0.05 *N* ethanolic potassium hydroxide presumably *via* the 2′,3′-*ribo*-epoxide. These results appear to confirm the overall inversion of configuration reported by Johnston during iodination of **26** in hot benzene. The selective loss of the 5′-O-trityl group during formation of **28a** and **29** is of some interest and was confirmed by nmr spectroscopy in DMSO-d_6 which showed the free hydroxyl group of **28a** as a triplet at 4.94 ppm clearly demonstrating it to be primary in nature. In a similar way, the 3′ and 5′ hydroxyls of **29** appear as an exchangeable doublet and triplet at 5.08 and 4.65 ppm, respectively. The inversion of configuration of the hydroxyl group during formation of **29** strongly suggests that at least some O²,3′-cyclonucleoside was formed during this reaction and subsequently underwent hydrolysis during work-up. In the presence of pyridine it is probably not surprising that this hindered cyclonucleoside did not undergo detectable opening by iodide ion.

A comparable reaction between **26** and **1** in benzene at 50° as described by Johnston[21] appeared to give the same ditrityl iodo compound (**27**) when an aliquot of the crude reaction mixture was examined by tlc. When the reaction was worked up, however, there was selective loss of the 2′-O-trityl group and syrupy 1-(3-deoxy-3-iodo-5-O-trityl-β-D-xylofuranosyl)uracil (**28b**) was isolated in 41% yield together with only 7% **27**. The aqueous phase during work-up of the reaction was only slightly acidic (pH 3–4) and the reason for the consistent and specific loss of the 2′-O-trityl group remains obscure. The isomeric monotrityl derivatives **28a** and **28b** were clearly resolved from each other by tlc and once again the presence of only a free 2′-hydroxyl group in **28b** was confirmed by its nmr spectrum in DMSO. The nmr spectrum of **28b** in $CDCl_3$ was remarkably different and indicated extensive conformational changes (see Experimental Section). Since pure **1** has only poor solubility in benzene, the reaction mixture was never homogeneous even when using twice the amount of solvent specified by Johnston.[21] A comparable reaction in refluxing benzene for 17 hr gave similar results with isolation of 52% **28b** and only a trace of **27**. Acidic hydrolysis of either **27** or **28b** gave **30** which was chromatographically identical with that from the reaction in DMF and subsequent alkaline treatment once again gave O²,2′-cyclouridine.

No reason is apparent for the selective loss of the 5′-O-trityl group during the reaction in DMF and of the 2′-O-trityl group in the benzene reaction. Model experiments on the reaction of **26** with about 1 molar equiv of trifluoroacetic acid in benzene and in DMF clearly showed that hydrolysis to a mixture of uridine and monotrityl uridine rapidly occurred in benzene but not in DMF. No clear-cut preference for removal of a specific trityl group could be discerned.

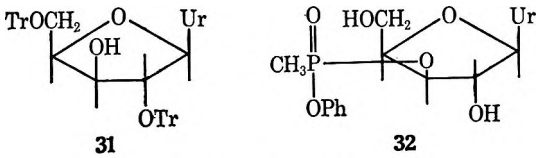
Recent work by Kitugawa, *et al.*,[24] has shown that, while 2′,5′-di-O-trityl-O²,3′-cyclouridine does not react with sodium iodide and benzoic acid, more acidic conditions leading to loss of trityl groups result in the formation of 1-(5-deoxy-5-iodo-β-D-xylofuranosyl)uracil *via* an interesting series of rearrangements. The iodination reactions reported above give products with the 3′-deoxy-3′-iodo *xylo* configuration and thus do not involve the intermediacy of O²,3′-cyclonucleosides. In the case of the 5′-hydroxy-3′-iodo compound **28a** there is no question from the nmr spectrum that the 5′-hydroxyl group is free, and hence unexpected rearrangements such as observed by Kitugawa, *et al.*,[24] did not occur.

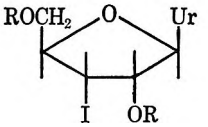
The reaction of 1-(2,5-di-O-trityl-β-D-xylofuranosyl)-uracil (**31**)[22] with **1** was also examined in both benzene

(21) G. A. R. Johnston, *Aust. J. Chem.*, **21**, 513 (1968).
(22) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961).
(23) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961).
(24) (a) K. Kitugawa and T. Ukita, *Chem. Pharm. Bull.*, **17**, 775 (1969); (b) K. Kitugawa, M. Schino, and T. Ukita, *ibid.*, **17**, 785 (1969).

and DMF. In benzene under the conditions described by Johnston[21] at least ten significant ultraviolet absorbing products, many of which contained trityl groups, were present and no effort was made to separate and characterize them. Following acidic hydrolysis of the crude mixture, the number of resolved spots was considerably reduced but only a very faint spot had the same mobility as **30**. Two compounds were isolated, albeit in quite low yield, by preparative tlc and both of these were shown to contain phosphorus. While neither was analytically pure, they could be tentatively identified by nmr spectroscopy as the phosphorus diastereoisomers of 1-(β-D-xylofuranosyl)uracil 3′-O-(phenyl methylphosphonate) (**32**). The *xylo* configuration for compounds **32** is based primarily upon the mechanism that we have proposed for the formation of phenyl methylphosphonate esters from hindered alcohols and **1**.[1] It is difficult to conceive of a mechanism involving inversion of configuration during phosphonate formation, and the small amount of **32** available has prevented any serious effort at providing a chemical confirmation of the proposed structure.

The reaction of **31** with **1** in DMF behaved in quite a different fashion. The reaction appeared to be very slow and even after 7 days at 37° unreacted **31** was the predominant product. The reagent **1** was, however, still present and rapidly iodinated a sample of 2′,3′-O-isopropylideneuridine added to a small aliquot. After 8 days, even after further addition of **1**, unreacted **31** was still the major component and the mixture was worked up. Once again there was extensive loss of a trityl group during the work-up since very little unreacted **31** was then present and the major product isolated by preparative tlc was 1-(2-O-trityl-β-D-xylofuranosyl)uracil (**29**) which was obtained in 47% yield. A ditrityl iodonucleoside was also obtained in 15% yield and found to have a melting point vastly different from that of *xylo* compound **27**. The two compounds were clearly distinguishable by tlc and by their nmr spectra and the product from the DMF reaction is considered to be 3′-deoxy-3′-iodo-2′,5′-di-O-trityluridine (**33a**). Thus, in this case, where the intermediacy of cyclonucleosides was not possible, iodination did take place with inversion of configuration. Hydrolysis of the trityl groups from **33a** led to quite unexpected complications. Under the same conditions used without difficulty for **27** or **28** pure **33a** gave 3′-deoxy-3′-iodouridine (**33b**), uracil, a monotrityl-3′-deoxy-3′-iodo-



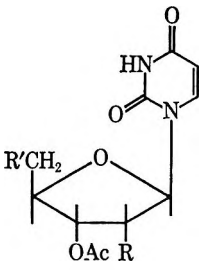


33a, R = trityl
b, R = H

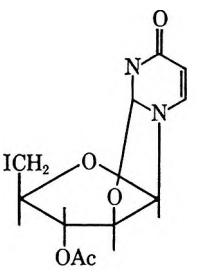
uridine, and uridine in a molar ratio of 6:3:1:1. The free uridine definitely had the *ribo* configuration as shown by borate electrophoresis and the reason for the formation of this compound and of uracil remains unknown. Treatment of **33b** with ethanolic potassium hydroxide under the same conditions used to convert **30** into O²,2′-cyclouridine gave only unreacted **33b** and a trace of uracil. This is consistent with the known difficulty in preparing O²,3′-cyclouridine derivatives[22,23] and further supports the *ribo* configuration for **33**.

Thus, while the reaction of **31** in benzene is so complex that we cannot exclude the formation of 3′-deoxy-3′-iodo *xylo* compounds, we have no evidence for iodinated products with other than the expected *ribo* configuration in DMF.

Johnston has also reported that iodination of 3′,5′-di-O-acetyluridine with **1** in benzene at 50° is accompanied by acetyl migration and leads to a mixture of 2′-deoxy-2′-iodo and 3′-deoxy-3′-iodo derivatives. We have, however, successfully iodinated 3′-O-acetyluridine (**34a**)[25] with **1** in DMF without detectable acetyl migration. Prior to this experiment we showed by nmr spectroscopy that **34a** undergoes no detectable acetyl migration during storage in DMF for 24 hr. The reaction of **34a** with **1** in DMF was followed by tlc which showed that after 15 min the nucleoside had completely disappeared, being converted into a less polar material with a uridine spectrum (presumably **34b**) and a more polar product with a typical O²,2′-cyclouridine spectrum (**35**). During the next few



34a, R; R′ = OH
b, R = OH; R′ = I
c, R; R′ = I
d, R; R′ = H



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hours the former disappeared and was sequentially replaced by **35** and the final product, 3′-O-acetyl-2′,5′-dideoxy-2′,5′-diiodouridine (**34c**), which was ultimately isolated as a homogeneous syrup in 46% yield. In order to prove convincingly that acetyl migration had not occurred, this material was hydrogenolyzed and the nmr spectrum of the resulting product was taken without any purification. The resulting spectrum was clearly that of pure 3′-O-acetyl-2′,5′-dideoxyuridine (**34d**) without the presence of any detectable isomers. The nmr spectrum of analytically pure **34d** was identical with that of the crude hydrogenolysis product prior to any work-up. This experiment convincingly shows that iodination in DMF can be achieved without complications due to acyl migration.

The results reported in this and the previous paper[1] clearly point out the versatility of **1** as a reagent for use in nucleoside chemistry and we will shortly report on a variety of reactions involving the iodonucleosides prepared in the present work.

(25) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).

Experimental Section

General methods are described in the previous paper.[1]

3′-Deoxy-3′-iodo-5′-O-*p*-nitrobenzoylthymidine (5a).—A solution of 5′-O-*p*-nitrobenzoylthymidine (391 mg, 1 mmol)[4] and **1** (1 g, 2 mmol) in anhydrous DMF (10 ml) was stored at 25° for 24 hr. Methanol (2 ml) was added and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate, extracted with aqueous sodium thiosulfate and water, dried (Na_2SO_4), and evaporated *in vacuo* giving a syrup that was chromatographed on two preparative tlc plates using chloroform–ethyl acetate (3:2). The major ultraviolet-absorbing band was eluted with acetone giving 514 mg of a homogeneous syrup that was crystallized from chloroform–hexane giving 425 mg (85%) of **5a** with mp 154–155°: λ_{max}^{MeOH} 261 mμ (ε 21,700); nmr ($CDCl_3$) 1.81 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.86 (q, 2, $J_{1',2'}$ = 5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 4.5–5.6 (m, 4, $C_{3'}H$, $C_{4'}H$, $C_{5'}H_2$), 5.97 (t, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.13 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H), 8.27 (s, 4, Ar), 9.32 (br s, 1, NH).

Anal. Calcd for $C_{17}H_{16}N_3O_7I$: C, 40.73; H, 3.22; N, 8.38. Found: C, 40.88; H, 3.14; N, 8.21.

The identical compound was obtained from 3′-deoxy-3′-iodothymidine (86 mg, 0.25 mmol)[5,6] and *p*-nitrobenzoyl chloride (51 mg, 0.27 mmol) in pyridine.

5′-O-*p*-Nitrobenzoyl-O²,3′-cyclothymidine (4a).—5′-O-*p*-Nitrobenzoylthymidine (391 mg, 1 mmol) and **1** (1 g, 2 mmol) were allowed to react in DMF (1.5 ml) at 25° for 15 min. Addition of ethanol and cooling to −15° gave 130 mg of **4a** as very pale yellow needles. The evaporated mother liquors were partitioned between water and ethyl acetate and further amounts of **4a** were separated from both phases (total yield 197 mg, 53%). This compound is extremely insoluble and could only be recrystallized from hot DMSO–ethanol giving 170 mg of white needles of mp 252–254°: λ_{max}^{MeOH} 254 mμ (ε 19,900); mass spectrum (70 eV) *m/e* 373 (M^+), 247 (M − thymine), 206 (M − *p*-$NO_2C_6H_4COOH$), 167 (*p*-$NO_2C_6H_4COOH$), 126 (thymine).

Anal. Calcd for $C_{17}H_{15}N_3O_7$: C, 54.69; H, 4.05; N, 11.26. Found: C, 54.63; H, 4.09; N, 11.21.

The identical compound was also obtained by reaction of O²,3′-cyclothymidine (10 mg) with *p*-nitrobenzoyl chloride (18 mg) in a mixture of DMF (0.5 ml) and pyridine (0.01 ml). Pure **4a** (8 mg, 47%) crystallized directly from the reaction medium with mp 252–254°.

The ethyl acetate phase from the above reaction (0.93 g) was purified by preparative tlc using two developments with chloroform–ethyl acetate (3:2) giving 160 mg (32%) of **5a** with mp 154–155°.

5′-O-Acetyl-3′-deoxy-3′-iodothymidine (5b).—5′-O-Acetylthymidine (171 mg, 0.6 mmol) and **1** (271 mg, 0.6 mmol) were allowed to react as above in DMF (5 ml). Chromatography on a column of neutral alumina using methylene chloride–methanol (19:1) followed by crystallization from methylene chloride–ether–hexane gave 120 mg (50%) of **5b** with mp 134–135°: λ_{max}^{MeOH} 266 mμ (ε 10,600); nmr ($CDCl_3$) 1.94 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.15 (s, 3, OAc), 2.7–2.9 (m, 2, $C_{2'}H_2$), 4.15 (m, 1, $C_{3'}H$), 4.40 (m, 1, $C_{4'}H$), 4.47 (d, 2, $J_{4',5'}$ = 2 Hz, $C_{5'}H_2$), 6.11 (q, 1, $J_{1',2'a}$ = 4 Hz, $J_{1',2'b}$ = 6 Hz, $C_{1'}H$), 7.34 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Anal. Calcd for $C_{12}H_{15}N_2O_5I$: C, 36.56; H, 3.84; N, 7.12. Found: C, 36.81; H, 4.06; N, 7.13.

Treatment of **5b** (60 mg) with 0.2 *N* sodium hydroxide in 80% methanol for 30 min followed by neutralization with Dowex 50 (H^+) resin and crystallization from water gave 38 mg (72%) of **5d** with mp 165.5–166° (lit.[6] mp 166°): nmr (pyridine-d_5) 1.87 ppm (d, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.65 (q, 2, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.71 (m, 2, $C_{5'}H_2$), 4.1–4.5 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.23 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 6.14 (t, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.76 (q, $J_{allylic}$ = 1.5 Hz, C_6H); mass spectrum (70 eV) *m/e* 352 (M^+), 334 (M − H_2O), 227 (M − thymine), 226 (thymine).

5′-O-Trityl-O²,3′-cyclothymidine (4b).—5′-O-Tritylthymidine (970 mg, 2 mmol) and **1** (1.0 g, 2 mmol) were reacted with anhydrous pyridine for 1 hr. After addition of methanol (1 ml) the solvent was evaporated *in vacuo* and ethyl acetate was added giving a yellow precipitate that was shown to be a mixture of N-methylpyridinium iodide and pyridine hydriodide. The filtrate was washed with dilute sodium thiosulfate and water, dried, and evaporated. Addition of ether gave 655 mg (70%) of pure **4b** which was recrystallized from methanol and melted at 148–153°, resolidified at 200°, and remelted at 225–227° much as described by Horwitz, *et al.*:[10] λ_{max}^{MeOH} 250 (sh, ε 8600) 227 mμ (sh, ε 15,000); ORD (MeOH) positive Cotton effect with a peak at 276 mμ (Φ +9900°), crossover at 264 mμ and a trough at 245 mμ (Φ −23,800°); nmr ($CDCl_3$) 1.88 ppm (d, 3, C_5Me), 2.32 (hex, 1, J_{gem} = 13 Hz, $J_{1',2'a}$ = 3.5 Hz, $J_{2'a,3'}$ = 3.5 Hz, $C_{2'a}H$), 2.68 (q, 1, J_{gem} = 13 Hz, $J_{2'b,3'}$ = 0.5 Hz, $J_{1',2'b}$ = 0 Hz, $C_{2'b}H$), 3.35 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.26 (hex, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 7 Hz, $C_{4'}H$), 5.09 (br s, 1, $C_{3'}H$), 5.49 (d, 1, $J_{1',2'a}$ = 3.5 Hz, $C_{1'}H$), 6.95 (q, $J_{allylic}$ = 1.5 Hz, C_6H), 7.2–7.5 (m, 15, Ar).

3′-Deoxy-3′-iodo-5′-O-tritylthymidine (5c).—5′-O-Tritylthymidine (1.21 g, 2.5 mmol) and **1** (2.4 g, 5 mmol) were dissolved in DMF (20 ml). After 15 min tlc (chloroform–ethyl acetate, 65:35) showed almost complete conversion to **4b** which was then slowly converted to **5c**. After 24 hr methanol (5 ml) was added and the reaction was worked up as usual. The chloroform soluble material was dissolved in methanol (5 ml) from which 994 mg (67%) of **5c** crystallized with mp 158–159° (lit.[5,6] mp 147–148°, but samples of material with both melting points had identical infrared, nmr, and ultraviolet spectra): λ_{max}^{MeOH} 267 mμ (ε 10,200); nmr ($CDCl_3$) 1.50 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.77 ppm (q, 2, $J_{1',2'}$ = 5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.51 (m, 2, $C_{5'}H_2$), 4.25 (m, 1, $C_{4'}H$), 4.46 (q, 1, $J_{2',3'}$ = 8 Hz, $J_{3',4'}$ = 8 Hz, $C_{3'}H$), 6.12 (t, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.62 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Anal. Calcd for $C_{25}H_{27}N_2O_5I$: C, 58.60; H, 4.68; N, 4.71; I, 21.35. Found: C, 58.56; H, 4.86; N, 4.64; I, 21.14.

Hydrolysis of **5c** with 80% acetic acid at 100° for 15 min gave 3′-deoxy-3′-iodothymidine of mp 166–166.5° (lit.[5,6] 166–167°): nmr (DMSO-d_6) 1.78 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.65 (q, 2, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.71 (m, 2, $C_{5'}H_2$), 4.1–4.5 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.23 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 6.14 (t, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.77 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Preparative tlc (carbon tetrachloride–acetone, 2:1) of the mother liquors from crystallization of **5c** gave 70 mg of the crystalline diiodo compound **7a** (see below).

3′,5′-Dideoxy-3′,5′-diiodothymidine (7a). **A.**—Thymidine (2.42 g, 10 mmol) and **1** (12 g, 26 mmol) were allowed to react overnight in DMF (100 ml). The usual work-up followed by direct crystallization from chloroform–hexane gave 3.51 g (76%) of **7a** which melted at 74–77°, resolidified as needles, and melted at 121–123°: λ_{max}^{MeOH} 265 mμ (ε 9000); nmr ($CDCl_3$) 1.95 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.65–2.90 (m, 2, $C_{2'}H_2$), 3.58 (d, 2, $J_{4',5'}$ = 3 Hz, $C_{5'}H_2$), 4.08 (q, 1, $J_{2',3'}$ = $J_{3',4'}$ = 8 Hz, $C_{3'}H$), 3.92 (hex, 1, $J_{3',4'}$ = 8 Hz, $J_{4',5'}$ = 3 Hz, $C_{4'}H$), 6.18 (q, 1, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 7 Hz, $C_{1'}H$), 7.48 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H), 9.20 (br s, 1, NH); mass spectrum (15 eV) *m/e* 462 (M^+), 335 (M − I), 337 (M − thymine), 206 (M − 2HI), 126 (thymine), and 81 (M − thymine − 2HI).

Anal. Calcd for $C_{10}H_{12}N_2O_5I$: C, 25.99; H, 2.62; N, 6.06; I, 54.93. Found: C, 25.88; H, 2.55; N, 5.96; I, 54.75.

B.—O²,3′-cyclothymidine (6.7 mg, 30 μmol) and **1** (40 mg, 93 μmol) were allowed to react overnight in DMF (0.5 ml) and after addition of methanol the mixture was evaporated to dryness. Preparative tlc using chloroform–acetone (9:1) gave a major band which was eluted and crystallized from chloroform–hexane giving 8 mg (58%) of **7a** identical with that above.

2′,3′,5′-Trideoxy-3′,5′-diiodouridine (7b).—2′-Deoxyuridine (228 mg, 1 mmol) and **1** (1 g, 2 mmol) were allowed to react overnight in DMF (5 ml). After the usual work-up the chloroform-soluble material was chromatographed on a column of silicic acid using a gradient (0–30%) of acetone in chloroform. Crystallization of the major peak from chloroform–hexane gave 375 mg (84%) of **7b** which sintered at 77–80° and melted at 136–139°: λ_{max}^{MeOH} 260 mμ (ε 11,200); nmr ($CDCl_3$) 2.65–2.95 ppm (m, 2, $C_{2'}H_2$), 3.59 (br d, 2, $J_{4',5'}$ = 2.5 Hz, $C_{5'}H_2$), 3.85–4.2 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.80 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.19 (q, $J_{1',2'a}$ = 7 Hz, $J_{1',2'b}$ = 5 Hz, $C_{1'}H$), 7.67 (d, $J_{5,6}$ = 8 Hz, C_6H), 9.55 (br s, 1, NH); mass spectrum (70 eV) *m/e* 337 (M − uracil), 321 (M − I), 210 (M − uracil − I), 112 (uracil), 81 (M − uracil − 2HI).

Anal. Calcd for $C_9H_{10}N_2O_3I_2$: C, 24.13; H, 2.25; N, 6.25. Found: C, 24.37; H, 2.43; N, 6.17.

Uridine 2′(3′)-O-Methylphosphonate (9c, 10c). **A.**—5′-O-Nitrobenzoyluridine (196 mg, 0.5 mmol)[16] and **1** (0.5 g, 1 mmol) were allowed to react overnight in DMF (2 ml) and after addition of methanol (1 ml), the mixture was evaporated to dryness. The residue was partitioned between water and ether, the aqueous phase (7800 OD units at 260 mμ) being a roughly equal mixture

of unreacted **8a** and a monoanion by paper electrophoresis at pH 7.6. Concentrated ammonium hydroxide (2.5 ml) was added and, after 30 min at 25°, paper electrophoresis showed hydrolysis of the *p*-nitrobenzoyl group to be complete. After partial evaporation of the solvent the solution was applied to a 3 × 30 cm column of DEAE Sephadex (HCO_3^-), washed with water, and eluted with a linear gradient of triethylammonium bicarbonate (4 l., 0.005–0.2 *M*) giving two ultraviolet-absorbing peaks. The second of these, (2140 OD units at 273 mμ, 0.21 mmol), was shown to be *p*-nitrobenzoic acid, while the first (1740 OD units at 260 mμ, 35%) was a chromatographically homogeneous mixture of **9c** and **10c**. The first peak was evaporated to dryness and residual bicarbonate was carefully removed by repeated evaporation with methanol. An aqueous solution of the final residue was passed through a 1 × 10 cm column of Dowex 50 (H^+) resin and the acidic effluent was partially evaporated *in vacuo* prior to neutralization to pH 6 with sodium hydroxide. After evaporation to dryness, the residue was dissolved in methanol (1 ml) and precipitated by addition of acetone (12 ml) giving the sodium salts of **9c** and **10c** (65 mg, 33%) as the trihydrate. After drying *in vacuo* at 60°, the hygroscopic monohydrate was obtained with λ_{max}^{MeOH} 260 mμ (ε 9950); see Table I for nmr.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot H_2O$: C, 33.15; H, 4.45; N, 7.74. Found: C, 33.40; H, 4.50; N, 7.20.

B.—5′-O-*p*-Nitrobenzoyluridine (98 mg, 0.25 mmol), methylphosphonic acid (60 mg, 0.5 mmol),[26] and dicyclohexylcarbodiimide (206 mg, 1 mmol) were dissolved in anhydrous pyridine (4 ml). After 2 hr water (0.5 ml) was added and after a further 30 min the mixture was diluted with water, filtered, evaporated to dryness, and partitioned between water and ether. The aqueous phase was adjusted to pH 8.5 and chromatographed on a 2 × 34 cm column of DEAE Sephadex as above. Two peaks were obtained, the second (2270 OD units at 270 mμ, 91%) being *p*-nitrobenzoic acid[27] and the first (2235 OD units at 260 mμ, 89.5%) being a chromatographically homogeneous mixture of **9c** and **10c**. The latter material was isolated as above giving 80 mg of the sodium salt with identical nmr ultraviolet and chromatographic behavior with that from the material from method A.

5′-O-*p*-Nitrobenzoyluridine 2′(3′)-O-Methylphosphonate (9a, 10a).—A reaction was carried out exactly as above in B except that purification was effected by preparative tlc on microcrystalline cellulose (Avicel) using 1-butanol–acetic acid–water (5:2:3) rather than by ion-exchange chromatography. Elution of the single intense uv-absorbing band with methanol followed by isolation as the sodium salt as above gave 108 mg of the sodium salts of **9a** and **10a** as an off-white solid that was chromatographically homogeneous and identical with the initial product in A or B above: $\lambda_{max}^{H_2O}$ 261 mμ. The elemental analysis indicated the presence of some nonnitrogenous contaminants presumably originating from the cellulose plates.

Uridine 3′-O-Methylphosphonate (10c).—A solution of DCC (300 mg, 1.6 mmol), 2′,5′-di-O-(4-methoxytetrahydropyran-4-yl)uridine (0.37 mmol),[14] and methylphosphonic acid (0.8 mmol) in anhydrous pyridine (5 ml) was kept for 4 hr, and water (2 ml) was then added. The mixture was evaporated to dryness, partitioned between water and ether, and filtered, and the aqueous phase was evaporated to dryness. The residue was treated with 80% acetic acid for 2 hr 25°, evaporated to dryness, adjusted to pH 8, and chromatographed as before on a 2 × 30 cm column of DEAE Sephadex. A single ultraviolet-absorbing peak (3620 OD units at 260 mμ, 97%) was obtained, and **10c** was isolated as above as its sodium salt (125 mg): $\lambda_{max}^{H_2O}$ 260 mμ (ε 10,100); ORD (H_2O) positive Cotton effect with a peak at 282 mμ (Φ +1000°), crossover at 270 mμ and a trough at 251 mμ (Φ −2500°); the nmr spectrum (see Table I) indicated the presence of less than 5% 2′ isomer.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot 2H_2O$: C, 31.59; H, 4.77; N, 7.37. Found: C, 31.19; H, 4.97; N, 6.66.

5′-O-Acetyl-O²,2′-cyclouridine (17).—A solution of 5′-O-acetyl-2′-O-tosyluridine (664 mg, 2.5 mmol)[19] in pyridine (30 ml) and triethylamine (30 ml) was heated under reflux for 2 hr under nitrogen. After evaporation of the solvent, the residue was dissolved in methylene chloride (10 ml) from which 295 mg of pure **17** with mp 166–167° (lit.[18] mp 168–169°) rapidly crystallized. The mother liquors were passed through a 1 × 15 cm column of Dowex-1 (acetate) resin and the effluent was evaporated and crystallized from methanol–ethyl acetate giving a further 65 mg (total yield 89%) of pure **17**. An analytical sample had mp 169–170°: λ_{max}^{MeOH} 225 (ε 8400) and 249 mμ (7700); nmr (DMSO-d_6) 1.92 ppm (s, 3, OAc), 3.97 (d, 2, $J_{4',5'}$ = 5.5 Hz, $C_{5'}H_2$), 4.28 (q, 1, $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 5 Hz, $C_{4'}H$), 4.40 (m, 1, $C_{3'}H$), 5.24 (d, 2, $J_{1',2'}$ = 5.5 Hz, $C_{2'}H_2$), 5.85 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.05 (br s, 1, $C_{3'}OH$), 6.34 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.88 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H).

O²,2′-Cyclouridine.—A solution of **17** (1.08 g) in methanol (40 ml) and distilled triethylamine (40 ml) was stored at 25° for 4 days during which time O²,2′-cyclouridine (825 mg, 90%) separated as white crystals with mp 235–237° (lit.[20] mp 234–236°) and was identical with an authentic sample.

1-(β-D-Arabinofuranosyl)uracil 3′-O-Methylphosphonate (19b).—A solution of DCC (82 mg, 0.4 mmol), methylphosphonic acid (20 mg, 0.2 mmol), and **17** (26 mg, 0.1 mmol) in anhydrous pyridine (2 ml) was kept for 3 hr at 23°. Water (0.5 ml) was added; the mixture was diluted with water, filtered, evaporated to dryness, and partitioned between water and ether. Upon electrophoresis at pH 7.6, the aqueous phase contained a single ultraviolet-absorbing product with the ultraviolet spectrum of **17**.

This solution was passed through a 1 × 10 cm column of Dowex 50 (H^+) resin and the acidic effluent was concentrated *in vacuo* to roughly 10 ml and heated at 100° for 15 min. At this time, the solution had λ_{max} 262 mμ and concentrated ammonium hydroxide (2 ml) was added. After 1 hr at 25° the solution was evaporated and chromatographed on a 2 × 30 cm column of DEAE Sephadex (HCO_3^-) as before.[28] The single ultraviolet-absorbing peak (972 OD units at 262 mμ, 97% overall from **17**) was isolated as above giving 34 mg of the sodium salt of **19b** as the dihydrate: $\lambda_{max}^{H_2O}$ 262 mμ (ε 10,000); nmr in Table I.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot 2H_2O$: C, 31.59; 4.76; N, 7.37. Found: C, 31.1; H, 4.5; N, 6.6.

1-(3,5-Di-O-acetyl-β-D-arabinofuranosyl)uracil (21).—3′,5′-Di-O-acetyl-O²,2′-cyclouridine (150 mg)[18] was heated at 100° for 1 hr in 50% acetic acid (2 ml) and then evaporated to dryness leaving a froth that was separated by preparative tlc using chloroform–methanol (9:1) into four bands. The fastest band[29] contained 96 mg of a chromatographically pure syrup that was crystallized from benzene–hexane giving 84 mg (53%) of **21** with mp 78–79°: λ_{max}^{MeOH} 258 mμ (ε 10,000); ORD positive Cotton effect with a peak at 278 mμ (Φ +15,700°), crossover at 266 mμ and a trough at 250 mμ (Φ −23,300°); nmr ($CDCl_3$) 2.12 (s, 6, OAc), 4.1–4.3 (m, 1, C_4H), 4.32 (q, 1, J_{gem} = 9 Hz, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 4.51 (q, 1, J_{gem} = 9 Hz, $J_{4',5'b}$ = 4 Hz, $C_{5'b}H$), 4.66 (q, 1, $J_{1',2'}$ = 3 Hz, $J_{2',3'}$ = 1 Hz, $C_{2'}H$), 5.08 (br s, 1, $C_{3'}H$), 5.55 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.13 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 7.71 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{16}N_2O_8$: C, 47.55; H, 4.91; N, 8.54. Found: C, 47.28; H, 5.19; N, 8.36.

1-(β-D-Arabinofuranosyl)uracil 2′-O-Methylphosphonate (22).—Dicyclohexylcarbodiimide (83 mg, 0.4 mmol) was added to an anhydrous pyridine solution **21** (33 mg, 0.1 mmol) and methylphosphonic acid (20 mg, 0.2 mmol). After 24 hr the mixture was worked up in the usual way and then treated for 1 hr with dilute ammonium hydroxide prior to chromatography on a column of DEAE Sephadex (HCO_3^-) as above. The single ultraviolet-absorbing peak (870 OD units at 262 mμ, 87%) was isolated as before giving 37 mg of the somewhat hygroscopic sodium salt of **22** which appeared to contain 1 mol equiv of sodium bicarbonate: $\lambda_{max}^{H_2O}$ 262 mμ (ε 9900); ORD positive Cotton effect with a peak at 277 mμ (Φ +18,500), crossover at 261 mμ and a trough at 244 mμ (Φ −19,900); see Table I for nmr data.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot NaHCO_3$: C, 28.07; H, 3.53; N, 6.54. Found: C, 27.41; H, 3.32; N, 6.57.

Reaction of 2′,5′-Di-O-trityluridine (26) with 1. A. In DMF.—A solution of **26** (728 mg, 1 mmol) and **1** (678 mg, 1.5 mmol) in DMF (15 ml) containing pyridine (0.4 ml) was kept at 25° for 24 hr. Methanol (2 ml) was added and after 30 min the solvent was evaporated to dryness and the residue was separated by preparative tlc on two plates using two developments with carbon tetrachloride–ethyl acetate (9:1) giving a strong ultra-

(26) A generous gift from the Hooker Chemical Co.

(27) A sample immediately prior to ion-exchange chromatography still maintained its 5′-O-nitrobenzoyl group.

(28) Paper chromatography using 1-butanol–acetic acid–water (5:2:3) showed that roughly half of the acetyl group was lost during acidic hydrolysis of **18a**. R_f values were 0.47 (**17**), 0.09 (**18a**), 0.18 (**19a**), and 0.08 (**19b**).

(29) By hydrolysis with ammonium hydroxide followed by borate electrophoresis[30] the other bands were tentatively identified as a diacetyluridine (26 mg), a monoacetylarabinosyluracil (14 mg), and unchanged **20** (9 mg).

(30) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960).

violet-absorbing band on the origin and a second major band which was partially contaminated with diphenyl methylphosphonate. Rechromatography of the latter band using carbon tetrachloride–ethyl acetate (3:1) gave 310 mg of a homogeneous solid that was crystallized from methanol giving 256 mg (32%) of **27** with mp 146.5–147.5°: λ_{max}^{MeOH} 260 mμ (ε 11,000); nmr ($CDCl_3$) 2.93 ppm (q, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.26 (d, 1, $J_{2',3'}$ = 0 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 3.48 (m, 1, $C_{4'}H$), 3.49 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 6 Hz, $C_{5'b}H$), 4.55 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 5.66 (q, 1, $J_{5,6}$ = 8 Hz, J_{5,N_3H} = 1.5 Hz, C_5H), 6.41 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 7.1–7.6 (m, 30, Ar), 7.65 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 8.98 (br s, 1, N_3H).

Anal. Calcd for $C_{47}H_{39}N_2O_5I$: C, 67.31; H, 4.68; N, 3.34. Found: C, 67.27; H, 4.62; N, 3.16.

Rechromatography of the band on the origin of the original plates using two developments with chloroform–methanol (93:7) gave two major products. The faster of these was eluted giving 70 mg (12%) of **28a** as a homogeneous syrup with λ_{max}^{MeOH} 260 mμ (ε 9600); nmr ($CDCl_3$) 3.46 (br s, 1, $C_{3'}H$), 3.5–3.85 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.51 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{2'}H$), 5.69 (d, 1, $J_{5,6}$ = 8.5 Hz, C_5H), 6.43 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.68 (d, 1, $J_{5,6}$ = 8.5 Hz, C_6H), 8.80 (br s, 1, NH); nmr (DMSO-d_6) shows in addition 4.94 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$).

Anal. Calcd for $C_{28}H_{25}N_2O_5I$: C, 56.38; H, 4.23; N, 4.70. Found: C, 55.68; H, 4.23; N, 4.37.

The slower band (75 mg, 15%) was crystallized from methanol giving 50 mg of **29** with mp 147–149°: λ_{max}^{MeOH} 260 mμ (ε 9900); nmr ($CDCl_3$) 3.66 (br s, 1, $C_{4'}H$), 3.9–4.15 (m, 3, $C_{3'}H$ and $C_{5'}H_2$), 4.25 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 5.50 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.97 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.47 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); nmr (DMSO-d_6) shows in addition 4.65 (t, 1, $J_{H,OH}$ = 6 Hz, $C_{5'}OH$), 5.08 (d, 1, $J_{H,OH}$ = 4 Hz, $C_{2'}OH$). Hydrolysis with 80% acetic acid at 100° for 1 hr gave only 1-β-D-xylofuranosyluracil as judged by borate electrophoresis[30] and tlc using ethyl acetate–methanol (9:2).

Anal. Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.38; N, 5.76. Found: C, 68.91; H, 5.44; N, 5.63.

B. In Benzene.[21]—**1** (1.36 g, 3 mmol) was added to a solution of **26** (728 mg, 1 mmol) in anhydrous benzene (75 ml) giving a suspension that was stirred and heated at 50° for 18 hr. Tlc using carbon tetrachloride–ethyl acetate (85:15) showed the absence of **26** and **28a** and a heavy spot of **27**. After addition of methanol (2 ml) the mixture was evaporated, dissolved in ethyl acetate, extracted with thiosulfate and then water, dried ($MgSO_4$), and evaporated leaving 1.6 g of a syrup that now contained very little **27**, the major product moving near **28a**. Preparative tlc using carbon tetrachloride–ethyl acetate (7:3) gave a major band containing 240 mg (41%) of **28b** as a syrup that resisted crystallization: λ_{max}^{MeOH} 261 mμ (ε 9800); nmr ($CDCl_3$), 3.26 ppm (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 3.58 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 5 Hz, $C_{5'b}H$), 4.2 (m, 1, $C_{4'}H$), 4.29 (br s, 1, $C_{3'}H$), 4.83 (s, 1, $C_{2'}H$), 5.68 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.70 (s, 1, $C_{1'}H$), 7.2–7.6 (m, 15, Ar), 7.66 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); nmr (DMSO-d_6) 3.1–3.5 (m, 2, $C_{5'}H_2$ superimposed upon DMSO), 4.10 (m, 1, $C_{4'}H$), 4.36 (q, 1, $J_{2',3'}$ = 3 Hz, $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.52 (quint, 1, $J_{1',2'}$ = $J_{2',3'}$ = 3 Hz, $J_{H,OH}$ = 6 Hz becoming t, $J_{1',2'}$ = $J_{2',3'}$ = 3 Hz with D_2O, $C_{2'}H$), 5.48 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.62 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 6.34 (d, 1, $J_{H,OH}$ = 6 Hz, $C_{2'}OH$).

Anal. Calcd for $C_{28}H_{25}N_2O_5I$: C, 56.38; H, 4.23; N, 4.70. Found: C, 55.73; H, 4.39; N, 4.26.

A faster moving band contained 60 mg (7%) of **27** identical with that above. A comparable reaction in refluxing benzene for 17 hr raised the yield of **28b** to 52%.

1-(3-Deoxy-3-iodo-β-D-xylofuranosyl)uracil (30).—A solution of **28b** (90 mg) in 80% acetic acid was heated at 100° for 1 hr, evaporated to dryness, and freed from tritanol by preparative tlc using chloroform–methanol (9:1). The single nucleoside band was eluted giving a yellow syrup that was treated with charcoal giving 38 mg (72%) of **30** as a foam: λ_{max}^{MeOH} 261 mμ (ε 9900); ORD (MeOH) positive Cotton effect with a peak at 282 mμ (Φ +14,200°), crossover at 261 mμ and a broad trough at 245 mμ (Φ −13,700°); nmr (pyridine-d_5) 4.0–4.5 ppm (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.86 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 5–5.5 Hz, $C_{3'}H$), 5.29 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ 5 Hz, $C_{2'}H$), 5.81 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 6.48 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 8.36 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_9H_{11}N_2O_5I$: C, 30.52; H, 3.13; N, 7.91. Found: C, 30.81; H, 3.11; N, 7.91.

Acid and Alkali Treatment of 27, 28a, and 28b.[21]—Solutions of **27**, **28a**, and **28b** (4 mg) in 80% acetic acid were separately treated at 60° for 1 hr, and the resulting 3′-iodonucleosides were isolated by tlc using chloroform–methanol (9:1). The eluted materials were dissolved in 0.05 *N* ethanolic potassium hydroxide (0.05 ml), heated in sealed capillaries at 80° for 30 min, and then purified by tlc using acetone–methanol (3:1). In each case, there was almost complete conversion to $O^2,2'$-cyclouridine (λ_{max} 225 and 250 mμ) which was eluted and crystallized from methanol with mp 235–237°.

Reaction of 1-(2,5-Di-O-trityl-β-D-xylofuranosyl)uracil (31) with 1. A. In DMF.—A solution of **31** (450 mg, 0.62 mmol)[22] and **1** (420 mg, 0.9 mmol) in DMF (10 ml) containing pyridine (0.3 ml) was kept at 37° for 7 days at which point unreacted **31** was by far the major product. A further 420 mg of **1** was added, and, after 24 hr at 37°, the mixture was worked up in the usual way, tlc now showing almost complete loss of one trityl group. Preparative tlc using two developments with carbon tetrachloride–ethyl acetate (87:13) gave a sharp band just ahead of diphenyl methylphosphonate and an intense band on the origin. The homogeneous fast band (76 mg, 15%) was crystallized from methanol giving 57 mg of **33a** with mp 254–256°: λ_{max}^{MeOH} 261 mμ (ε 9400); nmr ($CDCl_3$) 3.12 ppm (m, 2, $C_{5'}H_2$), 3.45 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 1.5 Hz, $C_{3'}H$), 3.88 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.68 (br s, 1, $C_{4'}H$), 5.07 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.54 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.0–7.6 (m, 30, Ar), 7.64 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 8.84 (br s, 1, NH).

Anal. Calcd for $C_{47}H_{39}N_2O_5I$: C, 67.31; H, 4.69; N, 3.34. Found: C, 67.39; H, 5.07; N, 3.32.

Preparative tlc of the band on the origin using chloroform–acetone (7:3) gave 140 mg (47%) of **29** which was crystallized from methanol with 147.5–149.5° and found to be identical with the sample obtained earlier.

B. In Benzene.—A mixture of **31** (450 mg, 0.62 mmol) and **1** (920 mg, 2 mmol) in anhydrous benzene (4 ml) was stirred at 50° for 18 hr as described by Johnston.[21] After the usual work-up, the ethyl acetate phase was shown by tlc to contain at least ten ultraviolet-absorbing products among which **33a**, **28**, and unreacted **31** could not be detected. Rather than attempt isolation of individual components the entire mixture was treated with 80% acetic acid at 100° for 1 hr, evaporated to dryness, and purified by preparative tlc using methylene chloride–ethanol (19:1). Two bands located in the region of a monoiodo nucleoside (**30**) were eluted and rechromatographed giving the phosphorus diastereoisomers of **32** which did not give acceptable analyses. The faster isomer (38 mg, 15%) was a syrup with λ_{max}^{MeOH} 262 mμ; nmr (acetone-d_6) 1.78 (d, 3, $J_{P,CH}$ = 17 Hz, PCH_3), 3.59 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.22 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{2'}H$), 4.65 (m, 1, $C_{4'}H$), 4.97 (oct, 1, $J_{H,P}$ = 9 Hz, $J_{2',4'}$ = 3 Hz, $J_{2',2'}$ = 0.5 Hz, $C_{3'}H$), 5.57 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.79 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{1'}H$), 7.1–7.4 (m, 5, Ar), 7.60 (d, 1, $J_{5,6}$ = 8 Hz, C_6H). The slower isomer (16 mg, 6%) had λ_{max}^{MeOH} 262 mμ; nmr (acetone-d_6) 1.70 (d, 3, $J_{P,CH}$ = 18 Hz, PCH_3), 3.42 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.63 (d, 1, $J_{1',2'}$ = 1 Hz, $C_{2'}H$), 4.92 (oct, $J_{P,H}$ = 9 Hz, $J_{2',2'}$ = 1 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 5.65 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.85 (d, 1, $J_{1',2'}$ = 1 Hz, $C_{1'}H$), 7.1–7.5 (m, 5, Ar), 7.68 (s, 1, $J_{5,6}$ = 8 Hz, C_6H).

Attempted hydrolysis of the phenyl methylphosphonate moiety from **32** by treatment with 1 *N* sodium hydroxide at 120° failed, uracil being the only neutral product formed.

Acidic and Alkaline Treatment of 33.—A solution of **33** (4 mg) in 80% acetic acid was heated at 100° for 15 min, evaporated to dryness, and separated by tlc using methylene chloride–methanol (9:1) giving four ultraviolet-absorbing bands in addition to tritanol. These were eluted and identified spectrally and chromatographically as uridine, uracil, 3′-deoxy-3′-iodouridine, and a monotrityl-3′-deoxy-3′-iodouridine (increasing mobilities) in molar ratios of 1:3:6:1. Alkaline treatment of the 3′-deoxy-3′-iodouridine fraction under the same conditions used for **30** gave only unreacted **30** and a trace of uracil with no formation of $O^2,2'$-cyclouridine.

3′-O-Acetyl-2′,5′-dideoxy-2′,5′-diiodouridine (34c).—3′-O-Acetyluridine (286 mg, 1 mmol)[25] and **1** (1.8 g, 4 mmol) were allowed to react at 25° in DMF (20 ml) for 20 hr; the reaction was followed by tlc using chloroform–methanol (9:1) (see text). After addition of methanol the mixture was worked up as usual and the ethyl acetate phase purified by preparative tlc using chloroform–acetone (9:1). Elution of the major band gave 230 mg (46%) of **34c** as a clear syrup: λ_{max}^{MeOH} 256 mμ (ε 10,500); ORD (MeOH) positive Cotton effect with a peak at 275 mμ (Φ +4700°), crossover at 267 mμ and a trough at 250 mμ (Φ −9200°); nmr ($CDCl_3$) 2.20 ppm (s, 3, OAc), 3.56 (d, 2,

$J_{4',5'}$ = 4 Hz, $C_{5'}H_2$), 4.05 (hex, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 4 Hz, $C_{4'}H$), 4.54 (q, 1, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.96 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 2.5 Hz, $C_{3'}H$), 5.88 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.37 (d, 1, $J_{1',2'}$ = 8.5 Hz, $C_{1'}H$), 7.61 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 9.81 (br s, 1, NH); mass spectrum (70 eV) *m/e* 506 (M^+), 379 (M − I), 319 (M − I − AcOH), 192 (M − I_2 − AcOH).

Anal. Calcd for $C_{11}H_{12}N_2O_5I_2$: C, 26.11; H, 2.39; N, 5.54. Found: C, 26.04; H, 2.43; N, 5.08.

3'-O-Acetyl-2',5'-dideoxyuridine (34d).—A solution of **34c** (85 mg) in 85% methanol (8 ml) containing sodium acetate (84 mg) was hydrogenated for 2 hr at 25° in the presence of 10% palladium on charcoal (32 mg). The mixture was then filtered through Celite, evaporated, and partitioned between ethyl acetate and very dilute aqueous sodium thiosulfate. Evaporation of the organic phase left 21 mg (50%) of **34d** as crystals, mp 182–183°. An analytical sample from chloroform–hexane had mp 185.5–186°: λ_{max}^{MeOH} 260 mμ (ε 10,200); ORD (MeOH) positive Cotton effect with a peak at 283 mμ (Φ +4400°), crossover at 273 mμ and a trough at 254 mμ (Φ −10,000°); nmr of the crude or recrystallized sample ($CDCl_3$) was very sharp with 1.42 ppm (d, 3, $J_{4',5'}$ = 6.5 Hz, $C_{5'}H_3$), 2.12 (s, 3, OAc), 2.16 (oct, 1, J_{gem} = 15 Hz, $J_{1',2'a}$ = 8 Hz, $J_{2'a,3'}$ = 6.5 Hz, $C_{2'a}H$), 2.54 (oct, 1, J_{gem} = 15 Hz, $J_{1',2'b}$ = 6 Hz, $J_{2'b,3'}$ = 3 Hz, $C_{2'b}H$), 4.23 (oct, 1, $J_{4',5'}$ = 6.5 Hz, $J_{3',4'}$ = 3 Hz, $C_{4'}H$), 4.88 (quint, 1, $J_{2'b,3'}$ = $J_{3',4}$ = 3 Hz, $J_{2'a,3'}$ = 6.5 Hz, $C_{3'}H$), 5.81 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.21 (q, 1, $J_{1',2'a}$ = 8 Hz, $J_{1',2'b}$ = 6 Hz, $C_{1'}H$), 7.46 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.14; H, 5.96; N, 10.76.

Registry No.—**4a,** 25442-40-4; **4b,** 25442-42-6; **5a,** 14260-81-2; **5b,** 14259-59-7; **5c,** 25442-44-8; **7a,** 14260-87-8; **7b,** 14260-83-4; **9c,** 25383-77-1; **10c,** 25442-45-7; **17,** 25383-78-2; **19b,** 25442-46-0; **21,** 25383-79-3; **22,** 25383-80-6; **27,** 25383-81-7; **28a,** 25442-47-1; **28b,** 25383-82-8; **29,** 25442-48-2; **30,** 24514-27-0; **32,** 25442-49-3; **33a,** 25383-84-0; **34c,** 25383-85-1; **34d,** 25442-50-6; 3'-deoxy-3'-iodothymidine, 14260-82-3; methyltriphenoxyphosphonium iodide, 17579-99-6.

Synthesis of *p*-Aminobenzoyl Peptides[1a,b]

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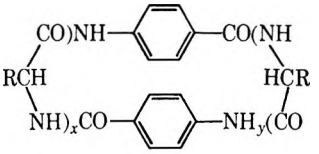
Cyclic peptides incorporating *p*-aminobenzoic acid are proposed as enzyme models. The *p*-aminobenzoyl residues may provide a relatively apolar cavity and substrate binding site, and the peptide bridges joining the *p*-aminobenzoyl residues allow the placement of functional side chains which can serve as a catalytic site. The synthesis of glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproic acid dihydrobromide (**4**) was carried out using the solid-phase method of peptide synthesis. Peptide **4** was cyclized using excess N,N'-dicyclohexylcarbodiimide in aqueous methanol to give *cyclo*-(glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (**3**). Peptide **3** was hydrogenated to give *cyclo*-(glycyl-*p*-aminobenzoylglycyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (**2**), a simple example of the proposed class of peptides. The peptide was not sufficiently soluble in water to test its validity as an enzyme model. The saponification of *p*-aminobenzoyl peptide esters proceeds without major side reactions, contrary to reports in the literature. *p*-Aminobenzoyl peptides are cleaved by sodium in liquid ammonia.

The use of cyclic molecules as enzyme models has been explored in recent years. Synthetic cyclic peptides[2–5] and cycloamyloses[6–9] have been investigated. We propose molecules of the type **1** as enzyme models. The incorporation of *p*-aminobenzoyl residues into a cyclic peptide provides a relatively apolar cavity that, in aqueous solution, might act as a substrate binding site. The peptide bridges between the *p*-aminobenzoyl residues allow the placement of functional side chains which can serve as a catalytic site. The preparation of *p*-aminobenzoyl peptides using conventional methods of peptide synthesis has received limited attention,[10–13] and the solid-phase method has not been used at all. In this communication we report the synthesis of the cyclic heptapeptide **2**, and also our investigation of two side reactions accompanying the synthesis of *p*-aminobenzoyl peptides.



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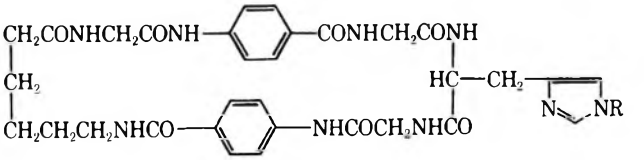

2, R = H
3, R = $C_6H_5CH_2$–

The synthesis of **2** is outlined in Figure 1. The linear heptapeptide **4** was prepared by the solid-phase method of Merrifield,[14] starting with N-*t*-butyloxy-

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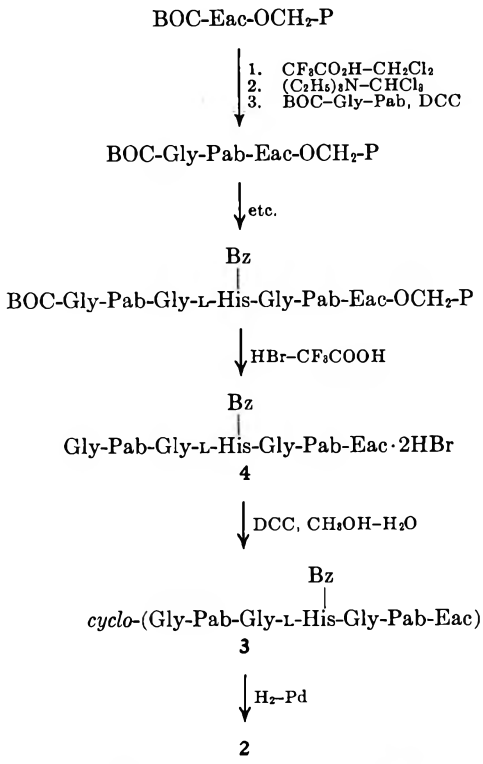


Figure 1.—Outline of synthesis of *cyclo*-(glycyl-*p*-aminobenzoylglycyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (**2**); Eac, ε-aminocaproyl; Pab, *p*-aminobenzoyl; BOC–, *t*-butyloxycarbonyl–; Bz, benzyl; DCC, N,N′-dicyclohexylcarbodiimide; P, polystyrene–2% divinyl benzene copolymer.

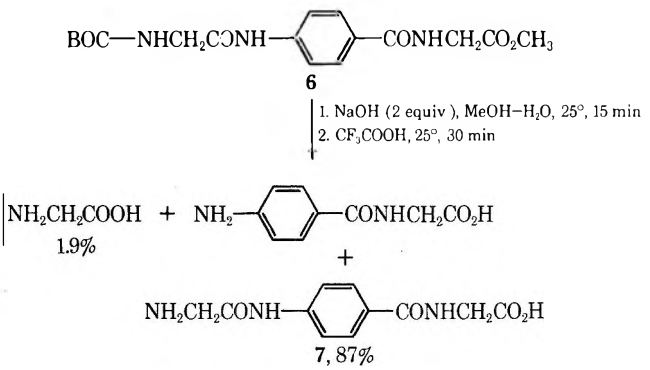
carbonyl-ε-aminocaproyl resin.[15] The peptide chain was lengthened using 4 equiv of the *t*-butyloxycarbonyl derivatives of glycyl-*p*-aminobenzoic acid, *im*-benzyl-L-histidine, glycine, and glycyl-*p*-aminobenzoic acid, in that order. The dipeptide, *t*-butyloxycarbonylglycyl-*p*-aminobenzoic acid (**5**), was added as a unit because we were unable to prepare *t*-butyloxycarbonyl-*p*-aminobenzoic acid conveniently. Addition of the dipeptide as a unit also enabled us to monitor the coupling at this step with the amino acid analyzer, which we could not have done otherwise, since *p*-aminobenzoic acid does not give a positive ninhydrin test. Compound **5** was prepared from *t*-butyloxycarbonylglycine and *p*-aminobenzoic acid by the mixed anhydride procedure. All coupling reactions were carried out using N,N′-dicyclohexylcarbodiimide and were allowed to proceed for at least 15 hr. The linear heptapeptide was cleaved from the resin with hydrogen bromide in trifluoroacetic acid and purified by chromatography on Sephadex LH-20. The yield of purified **4** was 33%, based on ε-aminocaproyl resin. Peptide **4** was cyclized using a tenfold excess of N,N′-dicyclohexylcarbodiimide in aqueous methanol[16] to yield protected cyclic peptide **3** in 25% yield. Debenzylation of **3** by catalytic hydrogenolysis was monitored by thin layer chromatography. The slow disappearance of **3** and the appearance of a single ninhydrin-negative and Pauly-positive spot is evidence for the monomeric structure of **3** and **2**. Had **3** been a dimer containing two histidine residues, we should have observed during the hydrogenolysis an additional spot due to a monobenzyl derivative.

Determination of the molecular weight of **2** by X-ray diffraction also indicated a monomer, although the imperfect form of the crystals did not allow an accurate measurement (see Experimental Section). When peptide **4** was cyclized and hydrogenated without isolation of **3**, peptide **2** was obtained in 23% yield after chromatography. Titration of **2** in dimethyl sulfoxide–water (2:1) indicated a pK' of 5.8, compared with a value of 6.4 for imidazole in the same solvent.

The cyclic peptide **2** has a very low solubility (2×10^{-6} M) in neutral and basic aqueous solutions, which precludes a detailed study of its interaction with substrates. However, we were able to measure its activity in catalyzing the hydrolysis of an easily hydrolyzed substrate, 2,4-dinitrophenyl acetate. Table I summarizes the kinetic results. Peptide **2** is less active than unsubstituted imidazole in the catalysis of hydrolysis of 2,4-dinitrophenyl acetate, which is not surprising since molecular models indicate that the imidazole side chain of the peptide cannot interact easily with the substrate's carbonyl group when the substrate is in the cavity of the peptide ring. We are currently working on the synthesis of cyclic *o*-, *m*-, and *p*-aminobenzoyl peptides that are designed to be more water soluble than **2** and to have cooperatively interacting functional groups.

It has been claimed[12] that extensive peptide bond scission occurs during the basic hydrolysis of methyl, ethyl, and *p*-nitrophenyl esters of *p*-aminobenzoyl peptides. In order to evaluate this quantitatively, we synthesized N-*t*-butyloxycarbonylglycyl-*p*-aminobenzoylglycine methyl ester (**6**) and, after treating it with sodium hydroxide and removing the BOC group with trifluoroacetic acid, analyzed the products with an amino acid analyzer. The results are shown in Scheme I. Since no glycyl-*p*-aminobenzoic acid could be

SCHEME I



detected in the products, we assume that all the glycine arose from hydrolysis of the peptide bond preceding the *p*-aminobenzoic residue. When the saponification was allowed to run for 29 hr, glycine was formed in 8.4% yield and **7** in 92% yield. In a control experiment in which **6** was treated directly with trifluoroacetic acid at 25° for 30 min, no glycine was formed.

Subsequently, numerous hydrolytic reactions have been carried out on esters of other peptides containing *p*-aminobenzoyl residues, and good yields of the intact

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TABLE I

HYDROLYSIS OF 2,4-DINITROPHENYL ACETATE (6×10^{-6} *M*) IN 0.01 *M* PHOSPHATE BUFFER (pH 7.19) AT 26°[a]

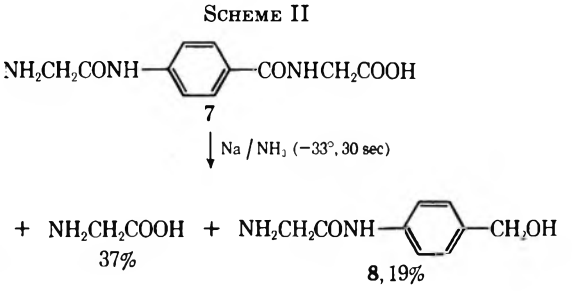
Catalyst	Molarity	$10^3 k_{obsd}$, min^{-1} (%)	Determinations	k_2, l./mol/min[b]
Buffer		3.58 ± 0.12 (3.4)	6	
2	1.0×10^{-6}	3.75 ± 0.02 (0.5)	3	170
2	2.0×10^{-6}	3.89 ± 0.02 (0.5)	3	155
Imidazole	1.0×10^{-6}	3.90 ± 0.05 (1.3)	3	320
Imidazole	2.0×10^{-6}	4.15 ± 0.12 (2.9)	3	300

[a] The solutions were 0.2% in acetonitrile and 0–0.15% in dimethylformamide. [b] $k_2 = (k_{obsd} - k_{solv})/c$ where k_{obsd} is the observed first-order rate constant measured in the presence of catalyst, k_{solv} is the constant in the absence of peptide or imidazole catalysts, and c is the molar concentration of catalyst.

peptide carboxylic acid have been obtained.[17] Compound **6** was prepared by coupling *t*-butyloxycarbonylglycine and *p*-aminobenzoylglycine methyl ester[18] using 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride.[19]

The treatment of *p*-aminobenzoyl peptides with sodium in liquid ammonia, *e.g.*, to remove the iminobenzyl protecting group of histidine, results in extensive fragmentation of the peptide chain. Peptide **7** was almost completely destroyed under these conditions, and some of the products of the reaction were identified (Scheme II). Reductive cleavage of the *p*-aminobenzoyl

SCHEME II



residue was suggested by analogy to the cleavage of benzoyl amino acids by tetramethylammonium, generated at a mercury electrode,[20] but only partially accounts for the degradation of **7** by sodium in liquid ammonia. The product **8** was synthesized by coupling N-carbobenzyloxyglycine with *p*-aminobenzyl alcohol[21] using DCC, followed by catalytic hydrogenolysis of the carbobenzyloxy group.

The partial destruction of an N-*p*-aminobenzoyl derivative of lysine vasopressin by sodium in liquid ammonia was recently reported,[13] and the reductive cleavage of acylproline bonds by the same reagent has been observed.[22–24]

Experimental Section[25]

N-*t*-Butyloxycarbonylglycyl-*p*-aminobenzoic Acid (5).—A solution of N-*t*-butyloxycarbonylglycine[26] (14.0 g, 0.080 mol) and triethylamine (11.2 ml, 0.081 mol) in 200 ml of tetrahydrofuran was cooled to −15° in an ice–salt bath. Isobutyl chloroformate (10.2 ml, 0.078 mol) was added over a 10-min period. *p*-Aminobenzoic acid (11.0 g, 0.080 mol) in 50 ml of tetrahydrofuran was added. The reaction mixture was stirred in the ice bath for 1 hr, followed by stirring at room temperature for 10 hr. The mixture was evaporated *in vacuo* to a moist residue which was dissolved in 100 ml of 50% aqueous acetic acid. The solution was chilled and 600 ml of water was added with vigorous stirring. An off-white material (18.1 g) precipitated, mp 153–157°. The crude product was crystallized from tetrahydrofuran–petroleum ether (bp 30–60), yielding 10.4 g (44%) of a white powder, mp 167–169°, R_f (TCW) 0.50. Recrystallization from acetone gave an analytical sample, mp 170–172°.

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.35; H, 6.44; N, 9.57.

N-*t*-Butyloxycarbonylglycyl-*p*-aminobenzoylglycine Methyl Ester (6).—A solution of N-*t*-butyloxycarbonylglycine (14.7 g, 0.084 mol) and *p*-aminobenzoylglycine methyl ester[18] (15.6 g 0.075 mol) in dichloromethane was cooled in an ice bath and 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride[19] (15.0 g, 0.074 mol) was added. This was stirred at ice-bath temperature for 1 hr and overnight at room temperature. The resulting solution was washed with water, 1% sodium bicarbonate, 1% citric acid, and water. After the solution was dried over magnesium sulfate, the methylene chloride was removed *in vacuo* to give a white material which was crystallized from methanol–water (1:1) to give 24.0 g (87%) of white plates, 173–174°, R_f (CMA) 0.56. An analytical sample was recrystallized from ethyl acetate, mp 167.5–168°.

Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.90; H, 6.31; N, 11.50. Found: C, 56.29; H, 6.57; N, 11.40.

N-*t*-Butyloxycarbonylglycyl-*p*-aminobenzoylglycine.—Compound **6** (1.30 g, 0.0037 mol) was saponified for 30 min in a solution containing 5 ml of 1.5 *N* sodium hydroxide and 15 ml of methanol. The light yellow solution obtained was diluted with water (50 ml) and extracted with ethyl acetate. The ethyl acetate extract was discarded and the aqueous phase was acidified to pH 3.0 with citric acid, saturated with sodium chloride, and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to give 1.00 g (96.1%) of a white crystalline compound: decomposing over 320°; R_f (BAWP) 0.59, R_f (PW) 0.56. The analytical sample was obtained through recrystallization from methanol–ethyl acetate–ether.

Anal. Calcd for $C_{16}H_{21}N_3O_6$: C, 54.69; H, 6.02; N, 12.01. Found: C, 54.73; H, 6.20; N, 12.18.

Glycyl-*p*-aminobenzoylglycine (7).—The above compound (0.20 g, 0.57 mmol) was treated with trifluoroacetic acid (2 ml) for 1 hr at 25°. The excess solvent was removed *in vacuo* and the resulting residue was triturated with ethyl acetate to give 200 mg of a white solid, melting and decomposing over 215°. The compound was crystallized from methanol–water–ethyl acetate (5:1:10) to yield the free tripeptide, melting with decomposition slowly over 215°, R_f (BAWP) 0.28.

(17) Experiments by Dr. Anand S. Dutta in this laboratory.

(18) K. Miyatake and S. Kaga, Japan Patent 6468 (1951); *Chem. Abstr.*, **47**, 11251a (1953).

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(20) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 3462 (1965).

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(22) W. F. Benisek and R. D. Cole, *Biochem. Biophys. Res. Comm.*, **20**, 655 (1965).

(23) W. F. Benisek, M. A. Raftery, and R. D. Cole, *Biochemistry*, **6**, 3780 (1967).

(24) M. Wilchek, S. Sarid, and A. Patchornik, *Biochim. Biophys. Acta*, **104**, 616 (1965).

(25) Melting points were taken in capillary tubes and are corrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind. The solvents used for thin layer chromatography on silica gel G were *n*-butyl alcohol–acetic acid–water (BAW) in a ratio of 4:1:1, *n*-butyl alcohol–acetic acid–water–pyridine (BAWP) in a ratio of 30:6:24:20, chloroform–methanol–acetic acid (CMA) in a ratio of 85:10:5, propanol–water (PW) in a ratio of 70:30, and tetrahydrofuran–cyclohexane–water (TCW) in a ratio of 93:7:5. A Technicon amino acid autoanalyzer was used for amino acid and peptide determinations. Amino acid hydrolyses were carried out in 6 *N* HCl in sealed evacuated tubes for 20 hr at 110° unless otherwise specified.

(26) E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).

Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.21; N, 16.72. Found: C, 52.35; H, 5.36; N, 16.46.

N-Carbobenzoxyglycyl-*p*-aminobenzyl Alcohol.—N-Carbobenzoxyglycine (2.09 g, 0.010 mol) and *p*-aminobenzyl alcohol[21] (1.23 g, 0.010 mol) were dissolved in 20 ml of tetrahydrofuran and cooled in an ice bath. N,N′-Dicyclohexylcarbodiimide (2.27 g, 0.011 mol) was added in 5 ml of tetrahydrofuran. The solution was stirred in the ice bath for 45 min and at room temperature overnight. The resulting suspension was filtered and the residue was washed well with tetrahydrofuran. The filtrate was evaporated *in vacuo* to yield a residue which was dissolved in 50 ml of hot methanol. Upon cooling 1.00 g (32%) of white crystals separated out of the solution: mp 160–162°; R_f (PW) 0.75, R_f (BAWP) 0.75. Recrystallization from ethyl acetate did not raise the melting point.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.80; H, 5.92; N, 8.69.

Glycyl-*p*-aminobenzyl Alcohol Hydrochloride (8).—The above compound (0.385 g, 0.001 mol) was dissolved in 150 ml of 95% ethanol containing 1 ml of 1 *N* HCl. Palladium (5%) on charcoal (0.100 g) was added and the suspension was hydrogenated at 46 psi for 1.5 hr. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The resulting residue was dissolved in hot methanol and ether was added until the solution became faintly turbid. White needles separated from the solution upon cooling. The material slowly decomposes above 280°: R_f (PW) 0.27, R_f (BAWP) 0.57.

Anal. Calcd for $C_9H_{13}N_2O_2Cl$: C, 49.89; H, 6.05; N, 12.93; Cl, 16.36. Found: C, 49.79; H, 6.35; N, 12.87; Cl, 16.49.

Reaction of 6 with Sodium Hydroxide.—A solution of 6 (0.130 g, 0.372 mmol) in 1.50 ml of methanol was treated with 0.50 ml of 1.50 *N* sodium hydroxide solution and the resulting solution was stirred at room temperature for 29 hr. At 0.25 hr and 29 hr, 0.050-ml aliquots were removed and treated with trifluoroacetic acid (10 ml) for 0.50 hr. The solutions were evaporated *in vacuo*. The resulting materials were dissolved in 1% HCl and applied to an amino acid analyzer previously calibrated with glycine, glycyl-*p*-aminobenzoic acid,[11] and compound **7**. The presence of 0.008 mmol of glycine (1.9%) and 0.322 mmol of **7** (87%) was shown for the 0.25-hr sample. In the 29-hr sample, the release of 0.031 mmol of glycine (8.4%) and 0.340 mmol of **7** (92%) was indicated. No glycyl-*p*-aminobenzoic acid could be detected in either sample.

Reaction of 7 with Sodium in Liquid Ammonia.—A solution of **7** (0.106 g, 0.422 mmol) in approximately 20 ml of liquid ammonia (freshly distilled from sodium) was treated with freshly cut pieces of sodium until a blue color persisted for 30 sec. The color was discharged with ammonium bromide and the ammonia was allowed to evaporate at atmospheric pressure and then under reduced pressure. The resulting residue was dissolved in 58 ml of 50% aqueous acetic acid. An aliquot of this solution was placed on an amino acid analyzer previously calibrated with glycine, compound **7**, and compound **8**. The chromatogram indicated the release of 0.313 mmol of glycine (38% based on 0.844 mmol of glycine in 0.422 mmol of **7**), 0.082 mmol of **8** (19%), and 0.004 mmol of **7** (0.9%).

N-*t*-Butyloxycarbonyl-ε-aminocaproyl Resin.—A solution of N-*t*-butyloxycarbonyl-ε-aminocaproic acid[15] (5.39 g, 23.3 mmol) and triethylamine (3.24 ml, 23.3 mmol) in 40 ml of ethanol was added to 10.00 g of chloromethylated polystyrene–2% divinyl benzene copolymer, 200–400 mesh (2.33 mmol of Cl/g). The mixture was stirred under reflux for 46 hr and filtered. The resin was washed thoroughly with ethanol and methanol. A sample of the dried resin was hydrolyzed in 1:1 dioxane–12 *N* HCl for 24 hr at 110°. Amino acid analysis showed the ε-aminocaproic acid content to be 0.620 mmol/g.

N-*t*-Butyloxycarbonylglycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl Resin.—A portion of N-*t*-butyloxycarbonyl-ε-aminocaproyl resin (3.20 g, 2.20 mmol) was treated in the following manner for the incorporation of each residue: (1) washed (three 50-ml portions) with methylene chloride, (2) mixed with trifluoroacetic acid–methylene chloride (2:3) (50 ml) for 15 min, (3) washed (three 50-ml portions) with methylene chloride, (4) washed (three 50-ml portions) with ethanol, (5) washed (three 50-ml portions) with chloroform, (6) mixed with 40 ml of 10% triethylamine in chloroform for 10 min, (7) washed (three 50-ml portions) with chloroform, (8) washed (three 50-ml portions) with coupling solvent, (9) introduced 8.80 mmol of appropriate N-*t*-butyloxycarbonyl amino acid or peptide in 30–40 ml of coupling solvent and mixed for 10 min, (10) introduced 9.24 mmol of N,N′-dicyclohexylcarbodiimide in 10 ml of coupling solvent and let reaction proceed for 15 hr, (11) washed (three 50-ml portions) with coupling solvent, and (12) washed (three 50-ml portions) with ethanol.

The coupling solvents for the incorporation of N-*t*-butyloxycarbonylglycyl-*p*-aminobenzoic acid (**5**), N-*t*-butyloxycarbonyl-*im*-benzyl-L-histidine, and N-*t*-butyloxycarbonylglycine were tetrahydrofuran, dimethylformamide, and methylene chloride, respectively. After the first reaction cycle, the unreacted ε-aminocaproyl resin was acetylated with acetic anhydride (3 ml) and triethylamine (1 ml) in 20 ml of dimethylformamide. Three syntheses of protected heptapeptide resin were carried out, all starting with N-*t*-butyloxycarbonyl-ε-aminocaproyl resin (3.20 g, 2.20 mmol). Amino acid analyses were performed after each coupling step during the first synthesis of protected heptapeptide resin. The results are given in Table II.

TABLE II

Cooling step	Gly	Bz^{im}-His	Eac
1	0.80		1.0
2	0.72	0.80	1.0
3	1.62	0.78	1.0
4	2.05	0.76	1.0

Glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidyl-glycyl-*p*-aminobenzoyl-ε-aminocaproic Acid Dihydrobromide (4).—The above protected heptapeptide resin was suspended in 40 ml of trifluoroacetic acid and a stream of hydrogen bromide (pretreated with 10% resorcinol in acetic acid) was passed through the suspension for 30 min with occasional shaking. The mixture was filtered and the resin was washed with trifluoroacetic acid (two 20-ml portions), trifluoroacetic acid–methylene chloride (1:1) (20 ml), and methylene chloride (two 25-ml portions). The pooled filtrates were evaporated *in vacuo* to yield a brown oil. The oil was taken up in methylene chloride which was removed *in vacuo*. The process was repeated and the resulting oil was triturated with ether to give a cream-colored powder. The material was washed well with ether and dried *in vacuo* to give 1.24 g of crude material displaying one major component and several minor components in BAW, PW, and BAWP. Amino acid analysis gave Gly:Bz^{im}-His:Eac (3.18:1.00:1.37). The other syntheses yielded 1.10 g (first synthesis) and 1.40 g (second synthesis) of crude heptapeptide dihydrobromide **4**.

The crude material (1.16 g) was purified on a column (4.2 × 53 cm) of Sephadex LH-20 washed with methanol. Purified heptapeptide dihydrobromide (**4**) (0.566 g) was obtained in 33% yield (based on N-*t*-butyloxycarbonyl-ε-aminocaproyl resin): mp 162–164°; $[\alpha]^{26}D$ −7.50° (*c* 1, methanol); R_f (BAW) 0.09, R_f (PW) 0.31.

Anal. Calcd for $C_{39}H_{47}N_9O_8Br_2$: N, 13.56. Found: N, 13.68.

Amino acid analysis gave Gly:Bz^{im}-His:Eac (3.04:1.00:1.10).

***cyclo*-(Glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (3).**—Heptapeptide dihydrobromide **4** (0.156 g, 0.168 mmol) was dissolved in 80% aqueous methanol (168 ml). The solution was cooled to 0° and N,N′-dicyclohexylcarbodiimide (0.346 g, 1.68 mmol) was added in methanol (4 ml). The solution was stored at 5° for 2 days and at room temperature for 13 days. Acetic acid (2 ml) was added to destroy unreacted N,N′-dicyclohexylcarbodiimide and the solution was evaporated *in vacuo*. The resulting mixture was resolved on a column of Sephadex LH-20 (washed with methanol) to yield 0.031 g (25%) of a white material which began to brown at 245° and charred at 280–290°. Thin layer chromatograms of the material gave single components that were ninhydrin and Pauly negative and chlorine positive: R_f (BAW) 0.19, R_f (PW) 0.54, R_f (BAWP) 0.60.

Anal. Calcd for $C_{39}H_{43}N_9O_7 \cdot CH_3OH$: C, 61.44; H, 6.06; N, 16.12. Found: C, 61.66; H, 5.87; N, 16.36.

Amino acid analysis gave Gly:Bz^{im}-His:Eac (2.88:1.00:0.94).

***cyclo*-(Glycyl-*p*-aminobenzoylglycyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (2) (Directly from 4).**—A solution of **4** (0.465 g, 0.500 mmol) in 80% aqueous methanol was cooled to 0° and N,N′-dicyclohexylcarbodiimide (1.03 g, 5.00 mmol) in methanol (20 ml) was added. The solution was stored at 5° for 3 days and at room temperature for 3 days. Acetic acid (6 ml) was added and the solution was evaporated to near dryness *in vacuo*. The wet residue was suspended in 50% aqueous acetic acid (50

ml) and shaken well. The suspension was filtered and the residue was washed with additional aqueous acetic acid (50 ml) and filtered. Palladium (5%) on charcoal (0.500 g) was added to the combined filtrates. The suspension was hydrogenated (40 psi) at room temperature for 66 hr. An aliquot taken at 66 hr gave a single Pauly-positive spot (R_f 0.41) on a thin layer plate developed with PW. The suspension was filtered and the filtrate was evaporated *in vacuo* to give 0.858 g of a foamy residue. A portion (0.644 g) of the residue was dissolved in 6 ml of butanol–water (6:1) and applied to a column (2.3 × 74 cm) of cellulose powder that had been washed with the same solvent mixture. Cyclic heptapeptide **2** was obtained as 0.057 g (23%) of a fine white material which charred at 279–282°. Thin layer chromatograms gave single components that were Pauly and chlorine positive and ninhydrin negative: R_f (BAW) 0.09, R_f (PW) 0.39, R_f (BAWP) 0.47.

Anal. Calcd for $C_{32}H_{37}N_9O_7 \cdot H_2O$: C, 56.71; H, 5.79; N, 18.60. Found: C, 56.42; H, 5.51; N, 18.51.

Amino acid analysis gave Gly:His:Eac (2.84:1.00:1.00).

Compound **2** has very limited solubility in water and is sparingly soluble in most organic solvents (methanol, pyridine, dimethyl sulfoxide, dimethylformamide) which precluded a molecular weight determination *via* osmometry. Compound **2** is soluble in acidic solvents (trifluoroacetic acid, formic acid, and 50% aqueous acetic acid.)

Compounds **2** and **3** were submitted for mass spectrometry. The samples were introduced using a direct probe. High-inlet temperatures (>290°) were required to volatilize the materials. No parent peaks were observed as the peptides decomposed under these conditions. The largest observable fragments were approximately 500 mass units.[27]

X-Ray Determinations of 2.[28]—Compound **2** (2.2 mg) was dissolved in 50% acetic acid (0.22 ml) and added to a flask containing approximately 30 ml of 0.01 *M* phosphate buffer (pH 7.19). The flask was sealed and upon several weeks' standing small clusters of very fine needles (barely visible without magnification) appeared. X-ray diffraction patterns were obtained with difficulty and the cell dimensions which were obtained from rotation and Weissenberg photographs are as follows: a = 9.32 ± 0.03 Å; b = 9.95 ± 0.03 Å; c = 36.57 ± 0.02 Å. The crystal system is orthorhombic, but the space group was not determined owing to difficulties in obtaining good films. As the crystals were small and badly formed, it was impossible to measure the density with any reasonable accuracy. Assuming four molecules per unit cell and a minimum density of 1.30 g/cc, the molecular weight would be 665 (theory 678). The crystals exhibited no obvious effects of drying out, so it is unlikely that they contain much solvent.

Kinetic Measurements.—The kinetic runs were performed with a Cary 14 recording spectrophotometer using a 10-cm silica cuvette. The reactions were carried out in 0.01 *M* phosphate buffer (pH 7.19) containing less than 0.4% organic solvents. Recrystallized imidazole was used for comparison with compound **2**. The cuvette was filled with 50 ml of buffer, with or without catalyst, and placed in a 26 ± 0.1° circulating bath for at least 15 min. The cuvette was placed in the cell compartment (thermostated at 26°) and balanced against air. The substrate, 2,4-dinitrophenyl acetate, was added in acetonitrile and the cuvette was gently agitated and returned to the cell compartment. The recording of a run began 60 sec after the addition of substrate. The appearance of 2,4-dinitrophenylate anion was measured at 360 mμ. All reactions were followed to greater than 90% completion. At the end of each run the pH was 7.19 ± .02. Infinity absorbances were taken at greater than ten half-lives. First-order rate plots were obtained for all reactions. The first-order rate constants were obtained by the method of Guggenheim.[29] The kinetic results are summarized in Table I.

Registry No.—**2**, 25383-41-9; **3**, 25533-69-1; **4**, 25442-38-0; **5**, 25442-39-1; **6**, 25383-67-9; **7**, 25383-68-0; **8**, 25383-69-1; N-*t*-butyloxycarbonylglycyl-*p*-aminobenzoylglycine, 25383-70-4; N-carbobenzoxyglycyl-*p*-aminobenzyl alcohol, 25383-71-5.

(27) The authors are indebted to Mr. Karl Kohler (Department of Chemistry, Indiana University, Bloomington, Ind.) and to Dr. William Hargrove (Eli Lilly and Co., Indianapolis, Ind.) for several attempts to obtain the molecular weights of compounds **2** and **3** by mass spectrometry.

(28) This work was performed by Dr. Jean Hamilton of this department.

(29) "Kinetics and Mechanism," 2nd ed, Frost and Pearson, Ed., Wiley, New York, N. Y., p 49, 1961.

Selective Phosphorylation of the *cis*-2′,3′-Diol of Unprotected Ribonucleosides with Trimetaphosphate in Aqueous Solution

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Unprotected ribonucleosides are selectively phosphorylated at the *cis*-2′,3′-diol in high yield by trimetaphosphate at high pH. The reaction is used to prepare several ribonucleoside 2′(3′)-phosphates including α-cytidine 2′(3′)-phosphate.

Most methods of phosphorylating unprotected ribonucleosides with activated phosphates or with orthophosphate and a condensing agent yield mixtures of 2′-, 3′-, and 5′-monophosphates as well as di- and triphosphates.[1-4] The 5′-phosphate is usually the major monophosphate formed, atlhough the ratio of the products does depend on the nature of the reactants and solvent.[4] Holý and Smrt[5] have reported the synthesis of ribonucleoside 2′(3′)-phosphites from the unprotected ribonucleoside and triethyl phosphite and their oxidative cyclization to 2′,3′-cyclic phosphates, but there is no convenient method of directly phosphorylating the *cis*-2′,3′-diol of an unprotected ribonucleoside in good yield.

Feldman[6] has reported that sodium trimetaphosphate reacts with ethylene glycol at high pH to give β-hydroxyethyl phosphate. Sucrose yields sucrose phosphate under similar conditions, although the position of phosphorylation was not determined. Here we wish to report the synthesis of ribonucleoside and ribonucleotide 2′(3′)-phosphates by a modification of this reaction.

In a preliminary experiment adenosine (Ia) was treated with 10 mol equiv of sodium trimetaphosphate and 10 mol equiv of 1 *N* aqueous sodium hydroxide; there was a 63% conversion to adenosine 2′(3′)-phosphate (IIa) on standing overnight at room temperature. There was no further reaction after an additional day. When tri(tetramethylammonium) trimetaphosphate

(1) G. R. Barker and J. M. Gulland, *J. Chem. Soc.*, 231 (1942).

(2) J. Baddily, J. G. Buchanan, and R. Letters, *ibid.*, 1000 (1958).

(3) A. Beck, R. Lohrmann, and L. E. Orgel, *Science*, **157**, 952 (1967).

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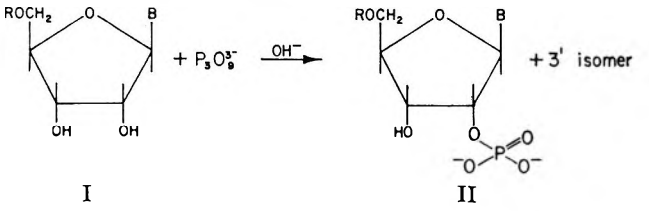
(5) (a) A. Holý and J. Smrt, *Collect. Czech. Chem. Commun.*, **31**, 1528 (1966); (b) A. Holý and J. Smrt, *ibid.*, **31**, 1562 (1967).

(6) W. Feldman, *Chem. Ber.*, **100**, 3850 (1967).

was used in place of the sodium salt, there was a similar overnight conversion, but the reaction proceeded further. After 4 days, the conversion to the 2′(3′)-phosphate was 90%. In all subsequent work the tri(tetramethylammonium) salt was used.

Removal of inorganic phosphates could be accomplished by absorbing the material on activated charcoal,[7] washing away the inorganic salts with water, and eluting the nucleosidic and nucleotidic material with 50% aqueous pyridine. The material was further purified on a column of Dowex-1 anion-exchange resin, formate form, eluting the product with aqueous formic acid. The product was precipitated as its lithium salt in 79% yield and was identified as adenosine 2′(3′)-phosphate by chromatography and electrophoresis in several systems. Nmr spectroscopy[8] showed the material to be a mixture of 2′- and 3′-phosphates.

Similar reactions were carried out with uridine (Ib), cytidine (Ic), guanosine (Id), and the disodium salt of adenosine 5′-phosphate (Ie). After 4 days at room



I II

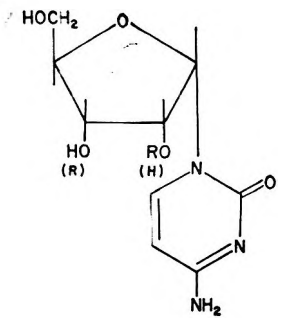
a, R = H; B = A
b, R = H; B = U
c, R = H; B = C
d, R = H; B = G
e, R = PO_3^{2-}; B = A

temperature, the conversions to the 2′(3′)-phosphates were 78, 82, 79, and 71% respectively. After removal of inorganic phosphates, the mixtures were examined by chromatography and electrophoresis. In each case the only product corresponded to an authentic sample of the corresponding 2′(3′)-phosphate (II). No 5′-phosphate (or diphosphate or triphosphate)[9] could be detected.

The reaction product from adenosine 5′-phosphate was further purified on a column of Dowex-1, chloride form, eluting with a lithium chloride gradient in dilute hydrochloric acid. The adenosine 2′(3′),5′-diphosphate (IIe) was precipitated as its lithium salt in 64% yield.

α-Cytidine 2′(3′)phosphate (IIIb) has been isolated by Gassen and Witzel[10] from yeast RNA. α-cytidine (IIIa), prepared by the method of Sanchez and Orgel,[11] was phosphorylated by the above procedure (63% conversion) and worked up in the same way as the reaction with adenosine. The yield of α-cytidine 2′(3′)-phosphate (IIIb) as its lithium salt was 53%, and 29% of the original α-cytidine was recovered.

This method should be useful for the preparation of ribonucleoside 2′(3′)-phosphates that cannot be readily



IIIa, R = H
b, R = PO_3^{2-}

obtained from natural sources, *e.g.*, ribonucleotides containing unnatural or minor bases, particularly as the unreacted ribonucleoside may be recovered. The nucleoside, however, must be stable at high pH. The procedure should also be applicable to many bifunctional compounds possessing suitably oriented hydroxyl or amino groups,[12] etc.

The possible significance of trimetaphosphate in prebiotic chemistry has been pointed out by Rabinowitz.[13] Preliminary results of our further experiments at lower pH's suggest that the phosphorylation of ribonucleosides with trimetaphosphate could have proceeded at a reasonable rate under presumed prebiotic conditions. Some 2′,3′-cyclic phosphate is found in the reaction mixture at lower pH's. While the amounts of 2′(3′)-phosphate increases with time, the amount of cyclic phosphate remains constant after its initial buildup. The reaction probably proceeds *via* the 2′,3′-cyclic phosphate which hydrolyzes too rapidly at higher pH's to accumulate to detectable levels in the reaction mixture.

Since this work was completed, Schwartz[14] has reported the selective phosphorylation of the *cis*-2′,3′-diol of ribonucleosides using sodium trimetaphosphate.[15]

Experimental Section

Chromatography was carried out by the descending technique on Whatman number 1 paper in the following systems: system A, isopropyl alcohol, concentrated ammonia, 0.1 *M* boric acid (7:1:2); system B, isopropyl alcohol, concentrated ammonia, water (7:1:2); system C, *n*-propyl alcohol, concentrated ammonia, water (7:1:2); system D, 95% ethanol, 1 *M* ammonium acetate pH 7.5 (7:3). Electrophoresis was carried out on Whatman no. 4 paper at 80 V./cm in system E [0.03 *M* potassium phosphate (pH 7.1)] and system F [0.05 *M* borate (pH 8.5)]. Optical densities were measured in 1-cm cells with a Zeiss PMQ II spectrophotometer. The charcoal used for absorbing nucleosides and nucleotides was 20–40 mesh activated charcoal supplied by Matheson Coleman and Bell.

Tri(tetramethylammonium) Trimetaphosphate.—A solution of sodium trimetaphosphate (2 l. of 0.1 *M*) was passed through a bed of Dowex-50 cation-exchange resin, tetramethylammonium form (7 cm × 150 cm^2), and the resin was washed with water (1 l.). The combined filtrate and washings were evaporated to small volume under reduced pressure and an equal volume of dioxane was added. The solution was lyophilized and the white

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(9) Feldman[8] reports that methanol reacts with trimetaphosphate under these conditions to give methyl triphosphate. As the number of carbon atoms in the primary alcohol increases, the amount of triphosphate formed decreases. *n*-Propyl alcohol gives a negligible amount of triphosphate. One would, therefore, expect a negligible amount of phosphorylation at the 5′-hydroxyl group of a nucleoside.

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(15) NOTE ADDED IN PROOF.—Further work in this laboratory investigating the reaction between trimetaphosphate and amino acids indicates that there may be a sodium ion catalyzed hydrolysis of trimetaphosphate. This may explain the higher yield obtained with the tri(tetramethylammonium) salt. The amount of trimetaphosphate used in these phosphorylation reactions may possibly be lowered if the sodium hydroxide is replaced by tetramethylammonium hydroxide.

solid was broken up and placed *in vacuo* over phosphorus pentoxide; yield 89 g (97%).

Reaction between Trimetaphosphate and Nucleosides and 5′-Nucleotides.—The nucleoside or disodium salt of the 5′-nucleotide (0.1 mmol) and tri(tetramethylammonium) trimetaphosphate (0.459 g, 1 mmol) were dissolved in 1 *N* sodium hydroxide (1 ml, 1 mmol) and kept at room temperature. At intervals the reaction mixture (5 μl) was examined by electrophoresis in system E. The phosphorylated and unreacted materials were eluted from the paper with water, the solutions made up to 5 ml, and their optical densities measured. The percentage conversions were 90% for adenosine, 78% for uridine, 82% for cytidine, 79% for guanosine, and 71% for adenosine 5′-phosphate after 4 days.

After 4 days the reaction mixture was stirred with activated charcoal (250 mg) and centrifuged. The charcoal was washed with water (five 0.5-ml portions) and the nucleosidic and nucleotidic material was eluted with 50% aqueous pyridine (five 1 ml portions). The pyridine washings were combined and evaporated down. The residue was examined by chromatography and electrophoresis in systems A, B, C, D, E, and F. In each case (starting with adenosine, uridine, cytidine, guanosine, or adenosine 5′-phosphate), the product corresponded to an authentic sample of the corresponding 2′(3′)-phosphate, and the only other uv-absorbing material present was the starting compound.

General Procedure for the Preparation of a Nucleoside or Nucleotide 2′(3′)-Phosphate.—The nucleoside or disodium salt of the nucleotide (1 mmol) and tri(tetramethylammonium) trimetaphosphate (4.59 g, 10 mmol) were dissolved in 1 *N* sodium hydroxide (10 ml, 10 mmol), and the solution was kept at room temperature for 4 days. The solution was slowly passed through a column of activated charcoal (18 cm × 3 cm² of 20–40 mesh) and the column was washed with water (150 ml). The nucleosidic and nucleotidic material was eluted with 50% aqueous pyridine (500 ml) and the solvents were removed under reduced pressure (bath temperature <40°). The residue was evaporated with water (50 ml) and then purified further according to the procedures below for individual compounds.

Adenosine 2′(3′)-Phosphate.—After desalting, the residue contained 14,100 OD^{259} units (92% of original material recovered). The residue was dissolved in water (3 ml) and applied to a column of Dowex-1 anion-exchange resin, formate form (15 cm × 1.5 cm²). The column was washed with water (500 ml) which removed unconverted adenosine (1350 OD^{259} units). Elution with 0.5 *M* formic acid (500 ml) removed the adenosine 2′(3′)-phosphate. The solvents were removed under reduced pressure and the residue was evaporated several times with water and kept *in vacuo* over potassium hydroxide pellets overnight. The residue was then dissolved in water (2 ml) and adjusted to pH 7 with lithium hydroxide solution. The product was precipitated by the addition of acetone. The precipitate was centrifuged down, washed with acetone and then with ether, and dried *in vacuo* over phosphorus pentoxide, yield 293 mg (12,300 OD^{259} units) (79%). The product corresponded to an authentic sample of adenosine 2′(3′)phosphate on chromatography and electrophoresis in systems A, B, C, D, E, and F.

Adenosine 2′(3′),5′-Diphosphate.—The material, after desalting, was dissolved in water (2 ml) and applied to a column of Dowex-1 anion-exchange resin, chloride form (22 cm × 16 cm²). The column was washed with water (500 ml) and eluted with a linear gradient of lithium chloride in 0.01 *N* hydrochloric acid (0.0 to 0.2 *M*). The first material to come off was unconverted adenosine 5′-phosphate. This was followed by the diphosphate. The fractions containing the diphosphate were combined and neutralized with lithium hydroxide and then concentrated under reduced pressure to small volume. Addition of a 1:1 mixture of ethanol and acetone (250 ml) precipitated the product which was centrifuged down, washed with ethanol–acetone, acetone, and ether, and dried *in vacuo* over phosphorus pentoxide, yield 299 mg (9870 OD^{259} units) (64%). The product corresponded to an authentic sample of adenosine 2′(3′),5′-diphosphate on chromatography and electrophoresis in systems A, B, C, D, E, and F.

α-Cytidine 2′(3′)-Phosphate.—There was a 65% conversion to α-cytidine 2′(3′)phosphate after 4 days at room temperature. The material was worked up in the same way as adenosine 2′(3′)-phosphate, yield 169 mg (4820 OD^{271} units) (52%). The product had the same chromatographic properties in system B as reported by Gassen and Witzel.[10] In systems A, C, D, E, and F, the product did not separate from a sample of the β isomer. Analysis on material precipitated three times with ethanol–acetone (1:1) and dried over phosphorus pentoxide gave the following results.

Anal. Calcd C, 32.3; H, 3.6; N, 12.6; P, 9.3. Found: C, 32.8; H, 3.3; N, 12.2; P, 8.9.

The aqueous washings from the column were evaporated and the residue was evaporated several times with ethanol. The crystalline solid was collected. This was unconverted α-cytidine, recovery 71 mg (2690 OD^{271} units) (29%).

Registry No.—Tri(tetramethylammonium) trimetaphosphate, 25383-76-0; IIa 2′ isomer, 130-49-4; IIa 3′ isomer, 84-21-9; IIc 2′ isomer, 85-94-9; IIc 3′ isomer, 84-52-6; IIe 2′ isomer, 3805-37-6; IIe 3′ isomer, 1053-73-2.

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Synthesis of Isoquinoline Alkaloids. IV. Steric Effects in the Electrolytic and Catalytic Oxidative Coupling of Phenolic Tetrahydroisoquinolines[1]

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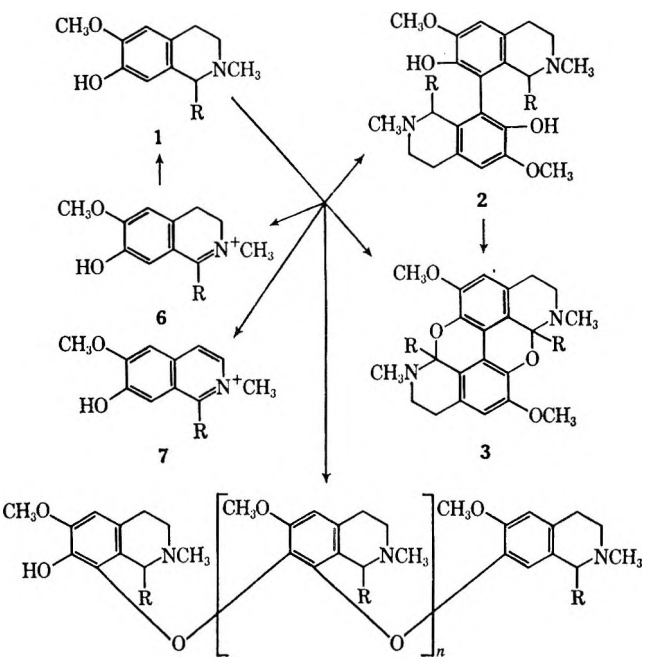
A series of 7-hydroxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolines with various substituents at the 1 position has been oxidized electrolytically on a platinum anode and catalytically with oxygen over platinum. In both methods, the increased size of the 1 substituent causes an increase in the proportion of carbon–oxygen dimers over the carbon–carbon dimers. Electrolytic oxidation appeared to be more sensitive to steric factors and to produce less oxidation in the nitrogen ring.

The oxidative coupling of phenols is one of the more important reactions used in nature for the elaboration of complex substances from simple precursors[3] and is especially important in the production of isoquinoline alkaloids.[4] These reactions may be intramolecular or intermolecular and generally lead, at least as a first step, to C–C linkages (such as in **2**) or C–O–C linkages (such as in **4**; the formation of both **2** and **4** being intermolecular). Many oxidizing systems have been explored over the last 50 years for carrying out these reactions in the laboratory.[5] The trimeric cactus alkaloid, pilocereine (**5d**), and its dimeric analog, **4d**, have been prepared by the $FeCl_3$ and $K_3Fe(CN)_6$ oxidation of the monomeric alkaloid lophocerine (**1d**).[1,6]

Of the various oxidation methods, two have been relatively unexplored. These are electrolytic oxidation, which has lain essentially dormant since the pioneering work of Fichter and his group prior to 1925,[3,7] and catalytic oxygenation over a platinum catalyst.[8] Of these two methods, electrolytic oxidation offers the greater promise as far as specificity and control are concerned.[3b] In recent years, the electrochemical reaction has been studied mechanistically[9] and preparatively (for nonalkaloidal materials).[10] We have published two brief communications on the preparative oxidation of the alkaloid corypalline (**1a**).[11] In this paper, we would like to describe the details of the corypalline work and to present a study of the oxidation of the series, **1a–c**, by catalytic and electrolytic oxidation. During the course of this work, papers have appeared on the $K_3Fe(CN)_6$ oxidation of **1a** and its metho salt,[12] on the $K_3Fe(CN)_6$ oxidation of **1b**,[13] and on the enzymatic oxidation of **1b** and **1d**.[14]

Oxidation of **1** can lead to two general types of products: compounds arising from oxidative coupling reactions, such as **2**, **4**, and **5**, and compounds arising from oxidation within the nitrogen ring, such as **3**, **6**, and **7** (Scheme I). **3** falls in both classes. The coupled products fall in two general groups, the C–C products, such as **2**, and the C–O–C products, such as **4** and **5**. One of the basic goals of this work was to show, within an homologous series, that the amount of C–O–C prod-

SCHEME I



4, $n=0$
5, $n=1$

a, series, R = H
b, series, R = CH_3
c, series, R = CH_2CH_3
d, series, R = $CH_2CH(CH_3)_2$

(1) Paper III: J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Lett.*, 575 (1963). This work was sponsored, in part, by Training Grant GM-1139 from the National Institutes of Health, U. S. Public Health Service and Research Grant GP-7601 from the National Science Foundation. It was described partially at the IUPAC Congress on Natural Product Chemistry in London, 1968.

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TABLE I

OXIDATION OF 1-SUBSTITUTED N-METHYL-7-HYDROXY-6-METHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES

Method	Yield of products, %[a]					
	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
			1a			
Electrolytic	34 (31)		3 (2.7)			
Catalytic	51	2	2		2	4
Chemical	28[b]					
	55 (40)[c]					
			1b			
Electrolytic	0.7 (0.6)		22 (20.4)	5 (4.4)		
Catalytic	25.5 (23.7)		18.2 (17)	0.8 (0.74)	3.1 (2.9)	3.4 (3.2)
Chemical[d]	(*ca.* 6)		(*Ca.* 1.2)			
Enzymatic[e]	(5.5)		(8)			
			1c			
Electrolytic[f]			30.5 (29.4)			
Catalytic			24.8 (14.9)		6.8 (4.1)	7.8 (4.5)
			1d			
Chemical[g]			32	3		
Enzymatic[e]			3			

[a] The yields are actually conversions since they have been corrected for recovered starting materials. True yields are given in parentheses. In the case of the catalytic oxygenation of 1a and electrolytic oxidation of 1a, greater than 96% of the starting material was consumed. [b] See ref 12a. [c] See ref 12b. [d] See ref 13. [e] See ref 14. [f] This oxidation was carried out in a H_2O–CH_3CN system. [g] See ref 1.

ucts formed is a function of the steric hindrance around the incipient diphenyl ether. This has been postulated,[5,6c,12] but only fragmentary evidence has been presented to support the hypothesis. Nitrogen ring oxidation is undesirable for our general purpose of preparing coupled products. Since the material balance was not complete in any of the experiments, other types of oxidation or decomposition leading to polymeric products[15] seem to have taken place.

The three compounds, **1a–c**, were prepared as previously described[16,17] and oxidized as described in the Experimental Section. The crude reaction mixtures were examined by tlc, and all of the major components were isolated using chromatography (column and preparative tlc). The products were identified as described below, and the results are shown in Table I along with the results of chemical oxidations. The data for **1d** is taken from our previous work[1] and the enzymatic work mentioned previously.[14]

Two structures corresponding to type **2** were obtained, **2a** and **2b**. The nmr spectrum of **2a** corresponded exactly to the one reported by Tomita, Fujitani, Masaki, and Lee,[12a] although the melting point did not agree. However, the compound was identical with an authentic sample.[12b,25] Structure **2b** is much more complex since an asymmetric center at C-1 of each isoquinoline has been introduced. Furthermore, the strong probability of restricted rotation at the diphenyl linkage and the creation of atropisomers must be considered. A study of molecular models suggests that three pairs of enantiomers will be formed from the coupling of racemic **1b** to yield **2b**. The compounds which are *RS* and *SR* with respect to C-1 stereochemistry and which would normally produce a *meso* situation give rise instead to two rotamers, which are enantiomers. In the case of the *RR* and *SS* dimers which would normally constitute an enantiomeric pair, four rotamers can exist. However, the rotamers of one form (the *RR*), although diastereomers of one another, are *also enantiomers of the rotamers* of the other form (the *SS*). In summary, one would expect the formation of three separable enantiomeric pairs: *RS* rotamer A and *RS* rotamer B, *RR* rotamer A and *SS* rotamer A, and *RR* rotamer B and *SS* rotamer B. All three pairs were isolated. Two were crystalline and one was a glass. The nmr spectra of the three isomers were almost identical and essentially identical with the spectrum of **2b** as published by Tomita, Masaki, and Fujitani.[13,18] We were not able to establish, with certainty, the exact structures of the isomers.

One substance corresponding to type **3** was obtained, **3a**. The compound appears to have been formed by an intermolecular coupling, followed by oxidation within the nitrogen rings and ring closure. Compound **3a** is identical, by melting point and spectra, with a substance of the same structure isolated by Kametani and Yagi[19] from a coupling reaction of N-methylcoclaurine. Compound **3a** could also be formed in 71% yield from **2a** by allowing it to stand in chloroform under an inert atmosphere. The reaction occurred only in chlorinated solvents and may be traceable to the charge-transfer complex formation between amines and halomethanes. This complex formation leads to decomposition of the amines.[20] One structure of this type, **3b**, was observed[13] in the chemical oxidation of **1b**.

Three substances corresponding to type **4** were obtained, **4a**, **4b**, and **4c**. Of these, only **4b** is known.[13,14]

(15) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966), and papers cited therein.

(16) J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *ibid.*, **32**, 2225 (1967).

(17) J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgraber, and S. Dutta, *ibid.*, **34**, 2478 (1969).

(18) The nmr spectrum reported[13] was said to be quite dependent upon the mode of isolation of the material. The presence of two isomers was suggested, but the mixture was not resolved.

(19) T. Kametani and H. Yagi, *J. Chem. Soc. C*, 2182 (1967).

(20) W. J. Lautenberger, E. N. Jones and J. G. Miller, *J. Amer. Chem. Soc.*, **90**, 1110 (1968).

The nmr spectrum of our **4b** corresponded exactly to the one published,[13] although both are almost surely mixtures of stereoisomers. We could not resolve the mixture nor could the other group. The mass spectra of compounds **4a**, **4b**, and **4c** showed each to be a dimer. The nmr spectrum in the region of δ 6–7 of **4b** is quite characteristic of this type of dimer, since is shows three sharp singlets attributable to the three aromatic protons. Compound **4a** has no stereochemical complications and was obtained as a noncrystalline material. It had an nmr spectrum identical with that of **4b**[13] except for the regions involved with the C–CH_3 groups of **4b**. Structure **4c** should consist of a mixture of two pairs of enantiomers. This was resolved, and both pairs were isolated as glasses. Each isomeric pair had an nmr spectrum identical with the published spectrum of **4b** except for the regions involved with the ethyl groups.

Only one substance corresponding to the trimeric type **5** was obtained, **5b**. The mass spectrum showed its trimeric nature. The nmr spectrum contained four aromatic singlets. Furthermore, the mass spectrum splitting pattern corresponded closely with that reported by Franck[6] for pilocereine, (**5d**). The substance is a glass and almost surely consists of a mixture of stereoisomers.

The dimers and the trimer are not very stable materials. Some are sensitive to heat and gave poor microanalysis owing to the difficulty involved in removing the last traces of solvent, mainly methanol. However, each was homogeneous in tlc and, except as noted for mixtures of isomers, each gave a clean nmr spectrum which could be completely interpreted. Precision mass spectra were measured for the molecular ions of several of the compounds and showed excellent agreement with the calculated values.

Three substances corresponding to type **6** were obtained, **6a**, **6b**, and **6c**. All were rather unstable glasses which showed, in their nmr and ir spectra, typical patterns for the grouping $C{=}N^+{-}CH_3$. Furthermore, the nmr spectrum of **6a** contained a singlet at δ 8.5 corresponding to the C-1 proton. If compounds **6** had had an alternate structure such as the 1,2-dihydroisoquinoline, such would not have been the case. Compounds **6a**, **6b**, and **6c** were reduced back to the known compounds **1a**, **1b**, and **1c** as further proof of structure.

Three substances corresponding to type **7** were obtained, **7a**, **7b**, and **7c**. After correction for the anion present, all were shown to be identical with crystalline compounds formed by known methods.

It is difficult to draw any conclusions from the comparison of our work with the chemical oxidations reported in Table I. As far as the relative amounts of C–C and C–O–C dimers formed, we are in essential agreement, but our yields are generally higher. One does not know whether such compounds, as types **6** and **7**, were looked for in the chemical oxidations. In our work they were definitely shown to be absent in the electrolytic oxidations. It should be noted also that the metho salts of **1a** and **1b** were oxidized chemically[12] and that the metho salts of dimers of type **2** were obtained from **1a** in yields of 33[12a] and 10%.[12b]

A few conclusions can be drawn from our work, subject, of course, to the lack of a complete materials balance. First, C–O–C dimers can be formed by both electrolytic oxidation (agreeing with the older literature[7]) and catalytic oxygenation. These methods now become attractive for the synthesis of complex natural products. Second, electrolytic oxidation leads to less oxidation of the nitrogen ring system (no **6** or **7** formed) than many of the better known phenol coupling reagents. Third, the proportion of C–O–C dimer formed, in the isoquinoline series at least, is definitely a matter of steric hindrance since the amount of C–O–C dimer increases markedly (3 to 22 to 30.5% by electrolysis and 2 to 18 to 24% by oxygenation), and the amount of C–C dimer decreases markedly (34 to 0.7 to 0% by electrolysis and 51 to 25.5 to 0% by oxygenation) as a substituent is built up on the 1 position. Finally, electrolytic oxidation seems to be somewhat more sensitive to steric effects, since the transition from C–C to C–O–C dimers is much sharper than that seen in catalytic oxygenation. We are presently applying electrolytic oxidation to a number of precursors of natural products.

Experimental Section[21]

Isoquinoline Methiodides (**7**).—6-Methoxy-7-hydroxyisoquinoline[22] (0.2 g) was warmed with 2 ml of CH_3I in 15 ml of benzene for 1 hr. The quaternary salt, **7a** (0.28 g, 78%), precipitated from the cooled solution. The analytical sample, mp 217–218°, was crystallized from ethanol.

Anal. Calcd for $C_{11}H_{12}NO_2I$: C, 41.68; H, 3.79; N, 4.42. Found: C, 41.62; H, 3.83; N, 4.41.

6-Methoxy-7-hydroxy-1-methylisoquinoline[23] was prepared from its 1,2,3,4-tetrahydro derivative[17] by dehydrogenation over Pd on carbon[22] and was converted to **7b** as described above. The yield of **7b** for the quaternization step was 80%. The analytical sample, mp 224–227°, was crystallized from ethanol.

Anal. Calcd for $C_{12}H_{14}NO_2I$: C, 43.54; H, 4.23; N, 4.23; I, 38.34. Found: C, 43.02; H, 4.27; N, 4.18; I, 38.66.

1-Ethyl-7-hydroxy-6-methoxyisoquinoline was prepared by dehydrogenation[22] of its 1,2,3,4-tetrahydro derivative.[17] It was obtained in 59% yield and melted at 166–170°.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.77; H, 6.47; H, 6.95.

N-Methyl-1-ethyl-7-hydroxy-6-methoxyisoquinolinium iodide, **7c**, was prepared from the isoquinoline by quaternization (83% yield) as described above. The analytical sample, mp 197.5–199°, was crystallized from ethanol.

Anal. Calcd for $C_{13}H_{16}NO_2I$: C, 45.26; H, 4.64; N, 4.09. Found: C, 44.80; H, 4.53; N, 4.05.

Catalytic Oxygenation of Corypalline (1a).—Platinum oxide (1.7 g) was catalytically hydrogenated at room temperature in ethanol. The platinum black, so obtained, was separated from the ethanol by decantation, washed with water, and added to 750 ml of 0.3 *M* aqueous $NaHCO_3$. The solution was stirred and oxygen was passed into it through a sintered-glass disk for 15 min. Corypalline hydrochloride (11 g) was dissolved in water and added to the solution. The reaction was monitored by tlc (5% NH_4OH in methanol) and was stopped when the starting material was essentially gone. The catalyst was removed by filtration and the solution was basified (NH_4OH) and extracted several times with $CHCl_3$.

The aqueous phase was evaporated under vacuum. As the volume was reduced, inorganic salts precipitated and were

(21) The melting points were taken on a Kofler hot-stage apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument, mass spectra were measured on an AEI MS-12 instrument and on a Hitachi Perkin-Elmer RMU-7 instrument, and the microanalyses were carried out by Baron Consulting Co., Orange, Conn. The tlc was carried out on silica gel GF layers and the column chromatography was carried out on silica gel M, obtained from Hermann Brothers in Cologne, Germany. The analytical samples of the noncrystalline dimers and the trimer were prepared by dissolving them in methanol, passing the solution over a short column of silica gel, evaporating to dryness, and drying under vacuum at room temperature. Nmr spectra of the analytical samples showed the presence of methanol.

(22) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(23) H. Brüderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).

removed by filtration and discarded. The residue was taken up in methanol, filtered, and chromatographed over 100 g of silica gel using CH_3OH–NH_4OH (50:1) as developer. Two compounds were obtained and were converted to chlorides with HCl gas. The first compound, **7a** (0.2 g), was identical with the synthetic sample of **7a** by tlc comparison and ir spectra.[24] The second compound, **6a** (0.4 g), could not be crystallized or purified to any extent. When evaporated to a glass, it showed the following properties: nmr (D_2O) δ 8.50 (s, 1, $ArCH{=}N^+$), 6.89 (s, 1, aromatic), 6.74 (s, 1, aromatic), 3.78 (s, 3, $ArOCH_3$), 3.50 (s, 3, N^+CH_3); ir 1655 cm^{-1} ($ArC{=}N^+$). Catalytic hydrogenation of **6a** over platinum gave a 53% yield of starting material, **1a**.

The chloroform phase from the extraction was dried (Na_2SO_4), evaporated to dryness, dissolved in a few milliliters of ethanol and cooled. The C–C dimer, **2a**, precipitated, giving 3.5 g of product, mp 235–237° (lit.[12] 247–249°[25] and 229°). The spectral properties agree completely with the literature.[12]

The mother liquor from the crystallization of **2a** was chromatographed over 100 g of silica gel using benzene–methanol (3:1) as a developer. Three major fractions were obtained. The first contained 0.3 g of starting material, **1a**. The third fraction contained an additional 1.1 g of C–C dimer, **2a**. The second fraction, a mixture of two components by tlc, was rechromatographed on silica gel using the same developer. The first fraction eluted contained 0.2 g of the C–O–C dimer, **4a**, which was obtained as a glass: nmr ($CDCl_3$) δ 6.59 (s, 1, aromatic), 6.40 (s, 1, aromatic), 6.10 (s, 1, aromatic), 5.30 (s, 1, ArOH), 3.82 (s, 3, $ArOCH_3$), 3.71 (s, 3, $ArOCH_3$), 2.32 (s, 6, NCH_3); mass spectrum M^+ 384.2049 (calcd 384.2049).

Ancl. Calcd for $C_{22}H_{28}N_2O_4 \cdot CH_3OH$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.71; H, 7.16; N, 6.81.

The second fraction contained 0.1 g of **3a**, mp 218–220° (lit.[17] 219–220°).

Catalytic Oxygenation of 1b.—Compound **1b** (6.0 g) was oxygenated as described above over the platinum from 0.9 g of PtO_2. The reaction mixture was separated in the same manner to yield residues from the $CHCl_3$ and the aqueous phases. The residue from the aqueous phase was chromatographed over 200 g of neutral alumina (Woelm) using $CHCl_3$–CH_3OH–NH_4OH (300:50:1) as the developer. Two compounds were obtained. Both were quaternary and were converted to the chlorides with HCl gas. The first fraction contained 0.19 g of **7b** chloride, mp 258° dec, which was identical with a synthetic sample.[22] The second compound, **6b** chloride (0.19 g), was obtained as an unstable glass: nmr (D_2O) δ 6.66 (s, 1, aromatic), 6.40 (s, 1, aromatic), 3.46 (s, 3, $ArOCH_3$), 3.30 (s, 3, NCH_3), 2.26 (s, 3, $N^+{=}CCH_3$); ir 1650 cm^{-1} ($ArC{=}N^+$). Compound **6b** was reduced to starting material, **1b**, in 43% yield.

The dried residue from the $CHCl_3$ phase was chromatographed over 275 g of silica gel using 0.3% NH_4OH in CH_3OH as developer. The first fraction contained 0.55 g of starting material, **1b**. The second fraction contained 0.83 g (18.5%) of the C–O–C dimer, **4b**, a noncrystalline glass: nmr ($CDCl_3$) δ 6.72 (s, 1, aromatic), 6.58 (s, 1, aromatic), 6.38 (s, 1, aromatic), 6.29 (s, 1, ArOH), 3.90 (s, 3, $ArOCH_3$), 3.88 (s, 3, $ArOCH_3$), 2.48 (s, 1, NCH_3), 1.37 (m, 6, C–CH_3); uv max (95% EtOH) 285 mμ (ϵ 5410), shifted to 292 mμ in base; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4 \cdot CH_3OH$: C, 67.54; H, 8.16; N, 6.30. Found: C, 67.86; H, 7.74; N, 6.69.

The third fraction contained 0.4 g of one of the crystalline isomers of **2b**: mp 222–224°; nmr ($CDCl_3$) δ 6.69 (s, 2, aromatic), 5.35 (s–broad, 2, ArOH), 3.89 (s, 6, $ArOCH_3$), 2.42 (2, 6, NCH_3), 0.95 (d, J = 7.5 cps, 6, $CHCH_3$); uv max (absolute EtOH) 290 mμ (ϵ 7190) shifted to 306 mμ in base; mass spectrum M^+ 412.2361 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.50; H, 7.98; N, 7.16.

The fourth fraction contained a mixture of the crystalline isomer of **2b**, mp 222–224°, and the noncrystalline isomer of **2b**. The crystalline isomer was removed by crystallization from acetone. The mother liquor appeared to contain only the noncrystalline isomer (tlc), a glass (0.34 g): nmr ($CDCl_3$) δ 6.63 (s, 2, aromatic), 4.94 (s, 2, ArOH), 3.83 (s, 6, $ArOCH_3$), 2.31 (s, 6, NCH_3), 1.08 (d, J = 7.5 cps, 6, $CHCH_3$); uv max (absolute EtOH) 289 mμ (ϵ 6320) shifted to 303 mμ in base; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 62.77; H, 6.97; N, 5.89.[26]

The fifth fraction was a mixture of the second crystalline isomer of **2b** and the C–O–C trimer, **5b**. The fraction was evaporated to dryness and taken up in acetone. The isomer of **2b**, mp 132–134° (0.16 g), precipitated: uv max (absolute EtOH) 292.5 mμ (ϵ 6590) shifted in base to 310 mμ; mass spectrum M^+ 412.2365 (calcd 412.2361).

Anal. Calcd for $C_{24}H_{32}N_2O_4 \cdot CH_3OH$: C, 67.54; H, 8.16; N, 6.30. Found: C, 66.76; H, 8.09; N, 6.56.

The mother liquor was separated by preparative tlc on silica gel using 5% NH_4OH in CH_3OH as a developer to yield an additional 0.05 g of the crystalline isomer of **2b**, mp 132–134°, and 0.04 g of the trimer, **5b**. Compound **5b** was a glass: nmr ($CDCl_3$) δ 6.48 (s, 1, aromatic), 6.46 (s, 1, aromatic), 6.37 (s–broad, 1, aromatic), 6.20 (s, 1, aromatic), 3.70 (s, 3, $ArOCH_3$), 3.68 (s, 3, $ArOCH_3$), 3.59 (s, 3, $ArOCH_3$), 2.37 (s, 9, NCH_3), 1.19 (m, 9, $CHCH_3$); uv max (95% EtOH) 285 mμ (ϵ 5555) shifted in base to 287 mμ; mass spectrum M^+ 617.3464 (calcd 617.3463).

Anal. Calcd for $C_{36}H_{47}N_3O_6 \cdot CH_3OH$: C, 68.39; H, 7.91; N, 6.47. Found: C, 68.75; H, 7.65; N, 6.84.

Catalytic Oxygenation of 1c.—The oxygenation of **1c** was carried out as described above except that small amounts of methanol were added to prevent foaming. The mixture was treated as described to yield an aqueous phase and a $CHCl_3$ phase.

The aqueous phase was treated as described for **1b** and chromatographed over 100 g of neutral alumina using $CHCl_3$–MeOH–NH_4OH (300:25:1) as developer, resulting in the isolation of 0.113 g of **7c** and 0.132 g of **6c**, which were converted to their chloride salts as described before. Compound **7c** was identical with the synthetic sample after its conversion to a chloride.[22] Compound **6c** chloride existed as a glass: nmr (D_2O) δ 6.88 (s, 1, aromatic), 6.71 (s, 1, aromatic), 3.76 (s, 3, $ArOCH_3$), 3.68 (s, 3, NCH_3), 1.20 (t, J = 7.5 cps, 3, CH_2CH_3); ir 1642 cm^{-1} ($ArC{=}N^+{-}$). It was reduced over a platinum catalyst to yield starting material in 59% yield.

The dried $CHCl_3$ residue was chromatographed over 150 g of silica gel as described above. The first fraction contained starting material which was isolated as its hydrochloride (1.175 g).[12] The second fraction contained one isomer of **4c** (0.137 g) and the third fraction contained the second isomer (0.250 g). Both were noncrystalline, and they had virtually identical spectra. They had different R_f values on tlc, however. The spectral properties were nmr ($CDCl_3$) δ 6.56 (s, 1, aromatic), 6.42 (s, 1, aromatic), 6.17 (s, 1, aromatic), 5.09 (s, broad, 1, ArOH), 3.83 (s, 3, $ArOCH_3$), 3.79 (s, 3, $ArOCH_3$), 2.31 (s, 3, N–CH_3), 2.29 (s, 3, NCH_3); uv max (absolute EtOH) 286 mμ (ϵ 6240) shifted in base to 294 mμ; mass spectrum M^+ 440 (calcd 440).

Anal. Calcd for $C_{26}H_{36}N_2O_4 \cdot CH_3OH$: C, 68.62; H, 8.53; N, 5.93. Found for first isomer: C, 68.72; H, 8.24; N, 5.73. Found for second isomer: C, 69.83; H, 7.98; N, 6.11.

Anodic Oxidation of 1a.—Sodium bicarbonate solution (140 ml of 0.1 M) was placed in an electrolytic cell[11b] containing a platinum gauze anode (5 × 7.5 cm). The cathode was separated by a porous disk and was also platinum. The cell was connected to a saturated calomel electrode through a salt bridge. The anode potential was controlled at +0.3 V[27] (Wenking potentiostat, Model 61TR).[28] The circuit was opened and compound **1a** (0.6 g) dissolved in 50 ml of ethanol was added in 1-ml portions fast enough to maintain a current of 50 mA. After 15 min, the current fell below 40 mA and did not respond to additional **1a**. The remainder of **1a** was added over 10 min. The reaction was monitored by tlc (CH_3OH–NH_4OH 97:3). After 5 hr, the current was down to about 3 mA and little starting material was detectable (although present). The reaction mixture was removed from the cell, basified with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extracts were concentrated almost to dryness and cooled. Starting material (0.057 g) crystallized. The mother liquor was evaporated to dryness and taken up in ethanol whereupon the C–C dimer, **2a**, crystallized (0.18 g). The mother

(24) The synthetic methiodides were passed over a short column of silica gel (CH_3OH–NH_4OH, 10:1) and converted to chlorides with HCl gas.

(25) Through the courtesy of Dr. O. Hoshino of the Science University of Tokyo, we have obtained an authentic sample of **2a**. He now believes the melting point to be the same as ours, 235–237°. The compounds were identical in all respects.

(26) This analysis did not check and could not be repeated for lack of material. However, the structure is almost surely correct on spectral grounds.

(27) The voltage for the reaction was chosen after a valtammetric study.

(28) U. S. Distributor, Brinkmann Instruments, Inc., Westbury, N. Y.

liquor was evaporated to dryness and chromatographed by preparative tlc (CH_3OH–NH_4OH 97:3) to yield 0.016 g of **4a**. Compounds **1a**, **2a**, and **4a** were all identical with the compounds described above.

Examination of the aqueous phase by tlc showed the absence of any of the monomeric compounds, **6a** or **7a**. No other compounds could be isolated from this fraction.

Anodic Oxidation of 1b.—Compound **1b** was oxidized in the same manner as described above. After 12 hr, the reaction mixture was processed to yield a $CHCl_3$ extract.[29] The extract derived from the oxidation of 2.4 g of **1b** (four runs) was chromatographed over 200 g of silica gel using methanol–NH_4OH (99.75:0.25) as developer. Three fractions were obtained. The first fraction contained 0.23 g of starting material, **1b**. The second fraction contained 0.47 g of **4b**. The third fraction consisted of two compounds and was rechromatographed over neutral alumina using benzene–methanol (99:1) as a developer. The first fraction contained 0.104 g of the C-O-C trimer, **5b**. The developer was changed to benzene–methanol (49:1) and **2b** came off contaminated with **5b**. Preparative tlc yielded 0.016 g of the C-C dimer, **2b**. Compounds **1b**, **2b**, **4b**, and **5b** were identical with the compounds described above. No products could be isolated from the aqueous phase.

Anodic Oxidation of 1c.—Compound **1c** was oxidized as described above except that the medium consisted of 0.1 *M* $Na_2B_4O_7$–CH_3CN (7:3) rather than aqueous bicarbonate. The oxidation was carried out at +0.4 V. Periodically, the anode was removed and washed with acetone to remove the product coating it. After 24 hr, the reaction was stopped and the buffer mixture was extracted with $CHCl_3$. The $CHCl_3$ extract and the acetone washings from the electrode were combined and the solvent was evaporated. The residue was chromatographed over 150 g of silica gel using CH_3OH–NH_4OH (99.9:0.1) as developer. The first fraction contained 0.023 g of starting material, **1c**. The second fraction contained a mixture of the isomers of **4c** as described previously (0.176 g). The mixture was not separated. Compounds **1c** and **4c** were identical with the compounds described above.

(29) It was necessary to clean the electrode in HNO_3 frequently to keep the current at a reasonable level (30–40 mA).

Registry No.—**2b**, 25383-49-7; **4a**, 25383-50-0; **4b**, 19626-08-5; **4c**, 25383-52-2; **5b**, 25383-53-3; **7a**, 25383-54-4; **7b**, 25442-32-4; **7c**, 25383-55-5; 1-ethyl-7-hydroxy-6-methoxyisoquinoline, 25383-56-6.

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Tetraneurin-E and -F. New C-15 Oxygenated Pseudoguaianolides from *Parthenium* (*Compositae*)

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Three sesquiterpene lactones were isolated from *Parthenium confertum* var. *lyratum* (Gray) Rollins collected in Nuevo Laredo, Mexico. Two of the compounds, tetraneurin-E (**1**) and -F (**2**), are new C-15 oxygenated pseudoguaianolides, and their structure determinations are reported here; the third compound, tetraneurin-A, was previously isolated from *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins. *Parthenium integrifolium* L. yielded tetraneurin-E and tetraneurin-C (**3**), a compound previously isolated from a number of *Parthenium* species.

In a continuation of our chemosystematic investigation[1-3] of the genus *Parthenium*, a May 1969 collection of *Parthenium confertum* var. *lyratum* from Nuevo Laredo, Mexico, yielded two new sesquiterpene lactones, tetraneurin-E (**1**), $C_{17}H_{24}O_6$, mp 200–201°, $[\alpha]^{25}D$ −70.3°, and tetraneurin-F (**2**), $C_{19}H_{26}O_7$, mp 135–136°, $[\alpha]^{25}D$ −47.4°, and tetraneurin-A (**4**),[1] which was previously isolated from *Parthenium alpinum* var. *tetraneuris*. A 1969 collection of *Parthenium integrifolium* from near Cisco, Ill., also yielded tetraneurin-E (**1**) and the previously described tetraneurin-C (**3**).[2]

Tetraneurin-E (1) and -F (2).—The uv, ir, and nmr data for tetraneurin-E (**1**) and -F (**2**) indicated that both were pseudoguaianolides with structural features similar to the C-15 oxygenated compounds which had been previously isolated from other *Parthenium* species [hysterin (**5**)[4] tetraneurin-A (**4**)[1] and conchosin-A and -B[3]]. The presence of an α,β'-unsaturated γ-lactone ring, an acetate function, and a tertiary hydroxyl group in tetraneurin-E (**1**) was evident from the following data: λ_{max} 212 nm (ϵ 10,000); ir bands at 1730, 1750, and 3500 cm^{-1} (the latter was still observed after acetylation); the nmr spectrum in deuterated acetone exhibited signals typical for protons associated with a lactone function (see Table I). Although the nmr spectrum of tetraneurin-E displayed a three-proton singlet at 0.83,[5] typical for a C-5 tertiary methyl group, a doublet for a C-10 secondary methyl group was missing. Instead the spectrum displayed a two-proton multiplet at 3.75, which could be attributed to the presence of a C-10 CH_2OH group. An acetate three-proton singlet occurred at 1.99.

Treatment of the monoacetate tetraneurin-E (**1**) with acetic anhydride and pyridine yielded a diacetate which was identical in all respects with tetraneurin-F (**2**) and thus established that tetraneurin-E is the deacetyl analog of tetraneurin-F.

Treatment of tetraneurin-E with *p*-toluenesulfonyl chloride afforded a monotosylate, $C_{24}H_{30}O_8S$, mp 170–171°, whose structure appeared from nmr data to correspond to **6**. When compound **6** was refluxed with 2,6-lutidine it was converted into $\Delta^{10(15)}$-anhydrotetraneurin-E (**7**), $C_{17}H_{22}O_5$, mp 177–179°, whose 10,15-exocyclic double bond was evidenced on nmr by two

(1) H. Rüesch and T. J. Mabry, *Tetrahedron*, **25**, 805 (1969).

(2) H. Yoshioka, H. Rüesch, E. Rodriguez, A. Higo, J. A. Mears, T. J. Mabry, J. G. Calzada Alan, and X. A. Dominguez, *ibid.*, in press.

(3) A. Romo de Vivar, H. Aguilar, H. Yoshioka, A. Higo, E. Rodriguez, J. Mears, and T. J. Marbry, *ibid.*, in press.

(4) A. Romo de Vivar, E. A. Bratoeff, and T. Rios, *J. Org. Chem.*, **31**, 673 (1966).

(5) All chemical shift values are reported in parts per million, δ scale.

TABLE I

NMR DATA FOR TETRANEURIN-E AND -F AND DERIVATIVES[a]

Compd	H-2	H-4	H-6	H-7	H-9	C-5 Me	C-10 CH_2O or C-10 $=CH_2$	C-11 $=CH_2$	Acetyl Me	Other
1[b]		5.73 brd tr (J = 8)	5.17 d (J = 9)			0.83	3.75 m	5.55 d (J = 3.0) 6.05 d (J = 3.5)	1.99	
2		5.74 brd tr (J = 7)	5.18 d (J = 9)	3.38 m		0.87	4.30	5.50 d (J = 3.0) 6.20 d (J = 3.5)	2.06 2.09	
6		5.68 brd tr (J = 7)	5.13 d (J = 9)	3.33 m		0.72	4.22 m	5.42 d (J = 3.0) 6.16 d (J = 3.4)	2.07	2.47 (tosyl Me) 7.42 and 7.85 d (J = 8.5 each) (aromatic)
7		5.74 dd (J = 9 and 6)	5.24 d (J = 9.0)	3.42 m		0.78	5.00 m	5.47 d (J = 3.0) 6.17 d (J = 3.5)	2.07	
8		4.75 m	5.46 d (J = 9.5)	3.45 m		0.71	5.00 m	5.53 d (J = 3.0) 6.24 d (J = 3.5)		
9			4.75 d (J = 7.5)	3.50 m		0.94	5.03 and 5.12 brd each	5.63 d (J = 1.8) 6.23 d (J = 2.3)		
10	5.73 brd tr (J = 2)	5.31 dd (J = 6 and 2.5)	4.32 d (J = 8.5)	3.40 m		1.08	4.14 brd d (J = 8)	5.54 d (J = 3.0) 6.25 d (J = 3.4)	2.06 2.03	
11		5.7 brd tr (J = 7)	5.20 d (J = 9.5)	3.45 m		0.85	4.45 m	5.56 d (J = 3.0) 6.21 d (J = 3.2)	2.10	3.08 (mesyl Me)
13		5.40 dd (J = 7 and 6)	4.48 d (J = 8.5)	3.30 m	5.81 tr (J = 3)	1.17		5.57 d (J = 2.2) 6.27 d (J = 2.8)	2.10	1.91 c (C10 Me)

[a] Spectra were recorded in $CDCl_3$ on a Varian A-60 spectrometer unless otherwise stated. Values are given in parts per million (δ scale) relative to TMS as an internal standard. Numbers in parentheses denote coupling constants in cycles per second. Signals are singlets unless otherwise noted: d (doublet), dd (double doublet), tr (triplet), m (multiplet), c (complex), and brd (broad). [b] Recorded in acetone-d_6.

overlapped singlets at 5.00. Alkaline hydrolysis of compound **7** with aqueous K_2CO_3, gave the crystalline diol **8**, $C_{15}H_{20}O_4$, mp 145–147°. Oxidation of **8** with CrO_3–H_2SO_4 afforded a product, $C_{15}H_{18}O_4$, mp 204–205°, identical by melting point, ir, and nmr with dehydrocoronopilin **9**, previously prepared from tetraneurin-A (**4**)[1]. The correlation of tetraneurin-E with **9** established structure **1** for tetraneurin-E with the exception of the stereochemistry at C-10 and C-4.

The absolute configuration at C-4 in **8** (and thus in tetraneurin-E) was determined by the Horeau method.[6] After asymmetric esterification[7] of **8** with excess racemic α-phenylbutyric acid anhydride, (−)-α-phenylbutyric acid was recovered in an optical yield of 69%; this result indicated a β orientation for the C-4 oxygen function. The assigned stereochemistry at C-4 in tetraneurin-E (**1**) and -F (**2**) accorded with the observation that no increase in the intensity of the H_4 proton signal was observed upon NOE irradiation (Varian HA-100 spectrometer) at the nmr frequency of the C-5 methyl group of tetraneurin-F.

The stereochemistry at C-10[8] for both tetraneurin-E and -F was assigned as β since dehydration of tetraneurin-F with thionyl chloride gave as the major product compound **10** which contains a double bond between C-1 and C-2 (C-2 vinyl proton signal at 5.73 and a complex signal at 4.14 for the CH_2OAc function). This

(6) A. Horeau, *Tetrahedron Lett.*, 506 (1961).

(7) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

(8) In connection with this aspect of the investigation an attempt was made to prepare a C_{15}-deoxy derivative of tetraneurin-E without altering the original C-10 stereochemistry. Tetraneurin-E was converted with methanesulfonyl chloride and pyridine to the mesylate (**11**). However, all attempts to transform **11** into the corresponding iodide (**12**) by treatment with sodium iodide in different polar solvents were unsuccessful. For example, the treatment of **11** with sodium iodide in acetonitrile yielded a compound whose spectral properties were compatible with formula **13** (see Table I).

result indicated[1,9] a *trans* relationship for the C-1 hydroxyl group and the C-10 CH_2OAc function; since the former is known to be α, the latter must be β. The evidence described above establishes that tetraneurin-E and -F correspond to structures 1 and 2, respectively.

Experimental Section[10]

Isolation of Tetraneurin-A (4), -E (1), and -F (2) from *Parthenium confertum* var. *lyratum* (Gray) Rollins.—Air-dried and ground material (346 g) of *Parthenium confertum* var. *lyratum* (Gray) Rollins (voucher no. 277591)[11] collected in the summer of 1969 near Nuevo Laredo, Tamaulipas, Mexico, was extracted with $CHCl_3$ and worked up in the usual way.[1] The thick brownish syrup (15 g) obtained was dissolved in a minimum amount of $CHCl_3$ and left standing overnight. The crude crystals (2.3 g) which formed were filtered and recrystallized from acetone; yield 1.7 g of pure tetraneurin-E (1): mp 200–201°; $[\alpha]^{25}D$ −70.3° (c 0.55, MeOH); λ_{max} MeOH 212 nm (ϵ 10,000); ir bands (Nujol) 3500 (hydroxyl), 1750 and 1730 (carbonyls) cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.90; H, 7.41; O, 29.61. Found: C, 62.65; H, 7.35; O, 29.63.

The mother liquor from the crude crystals was evaporated and resultant residue was dissolved in ethyl acetate–cyclohexane; the solution was then left standing overnight in a refrigerator. A second crop of crystals (1.3 g) was found to be a 4:1 mixture of tetraneurin-A (4) and tetraneurin-E (1) (by nmr). Recrystallization of the crude material from ethyl acetate–cyclohexane yielded 300 mg of pure tetraneurin-A (4).

The tlc analysis (silica gel G) of the mother liquor from the second crop of crystals indicated the presence of a third, less polar substance. The crude syrup (1 g) obtained from the mother liquor was chromatographed over a silica gel (65 g) column packed in benzene. Elution of the column with benzene–acetone (6:1) in 15 ml fractions yielded in fractions 2–4 63 mg of tetraneurin-F (2): mp 135–136°; $[\alpha]^{25}D$ −47.4° (c 0.59, MeOH); λ_{max} (MeOH) 212 nm (ϵ 11,700); ir ($CHCl_3$), 3500 (hydroxyl), 1755 and 1725 (carbonyls), 1240 (acetate) cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.30; H, 7.35; O, 30.60. Found: C, 62.55; H, 7.35; O, 29.73.

Continued elution of the column afforded 100 mg of tetraneurin-E (1).

Isolation of Tetraneurin-E (1) and Tetraneurin-C (3) from *Parthenium integrifolium* L.—Air-dried and ground material (77.4 g) of *Parthenium integrifolium* (collected July 13, 1969, by A. G. Jones along the railroad tracks in Cisco, Piatt County, Ill.) was worked up in the usual manner: yield of crude syrup 1.1 g. The syrup was dissolved in $CHCl_3$ and the resultant solution was left overnight. Crude crystals (30 mg) were collected which yielded after recrystallization from acetone 20 mg of pure tetraneurin-E (1), mp 199–200°. Preparative tlc of the mother liquor yielded a compound which was identified as tetraneurin-C (3) by nmr analysis and cochromatography with an authentic sample.[2]

Tetraneurin-F (2) from Tetraneurin-E (1).—A solution of 200 mg of 1 in 1 ml of pyridine was mixed with 1 ml of acetic anhydride. The solution was kept standing overnight. After work-up of the solution in the usual way, a diacetate was obtained which was identical in all respects with tetraneurin-F (2) by mixture melting point determination and nmr and ir analysis.

Tetraneurin-E Tosylate (6) from Tetraneurin-E (1).—*p*-Toluenesulfonyl chloride (310 mg) was added to a solution of 250 mg of 1 in 2 ml of anhydrous pyridine and the solution was allowed to stand at room temperature for 15 hr. Water was added to the reaction mixture and the product was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, and the solvent was removed. The residue was recrystallized from $CHCl_3$–ether: yield 342 mg (92.4%) of the tosylate 6; mp 170–171°; ir ($CHCl_3$) 3470 (hydroxyl) and 1745 (carbonyl) cm^{-1}.

Anal. Calcd for $C_{24}H_{30}O_8S$: C, 60.20; H, 6.15; O, 26.75; S, 6.47. Found: C, 59.82; H, 6.49; O, 26.81; S, 6.68.

$\Delta^{10(15)}$-Anhydrotetraneurin-E (7) from Tetraneurin-E Tosylate (6).—A solution of 150 mg of 6 in 5 ml of freshly distilled 2,6-lutidine was heated under reflux (N_2 atmosphere) for 17 hr at 150°. The residue obtained on work-up was dissolved in $CHCl_3$ and the resultant solution was washed with 5% aqueous H_2SO_4 and then with aqueous $NaHCO_3$. Evaporation of the $CHCl_3$ and recrystallization of resultant crude crystals from $CHCl_3$–isopropyl ether yielded 84 mg of $\Delta^{10(15)}$-anhydrotetraneurin-E (7): mp 177–179°; ir ($CHCl_3$) 3500 (hydroxyl), 1750 and 1730 (carbonyls), 1250 (acetate) cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.75; H, 7.19; O, 26.18. Found: C, 66.77; H, 7.04; O, 26.44.

$\Delta^{10(15)}$-Deacetylanhydrotetraneurin-E (8) from $\Delta^{10(15)}$-Anhydrotetraneurin-E (7).—Compound 7 (100 mg) was dissolved in freshly distilled dioxane (3 ml) and then 50% aqueous K_2CO_3 (1 ml) and H_2O (3 ml) were added to the solution. The mixture was heated over a steam bath for 2 hr. The mixture was evaporated *in vacuo* and H_2O (3 ml) was added to the residue. The aqueous solution was acidified (10% H_2SO_4) and then saturated with $(NH_4)_2SO_4$. The solution was next extracted three times with ethyl acetate. Evaporation of the ethyl acetate *in vacuo* gave a residue which was preparatively chromatographed on silica gel G plates (ethyl acetate–benzene, 5:3). A major band (R_f 0.49) afforded material which yielded after recrystallization from isopropyl ether–ethyl acetate 28 mg of the pure diol 8: mp 145–147°; ir (Nujol), 3500 (hydroxyl), 1750 (carbonyl), 1656 and 1637 (C=C bonds) cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.58; O, 24.22. Found: C, 67.95; H, 7.43; O, 24.16.

10,15-Dehydrocoronopilin (9) from $\Delta^{10(15)}$-Deacetylanhydrotetraneurin-E (8).—A solution of 8 (15 mg) in 0.3 ml of acetone was treated with 4 drops of the CrO_3–H_2SO_4 reagent[12] at room temperature. After 1 min, the mixture was diluted with 2 ml of water and extracted with three 5-ml portions of $CHCl_3$. Work-up of the $CHCl_3$ solution yielded 12 mg of 9 (recrystallized from $CHCl_3$–ligroin), mp 204–205°, which was identical by nmr and ir with 10,15-dehydrocoronopilin (mp 204–205°) previously prepared from tetraneurin-A.[1]

$\Delta^{1(2)}$-Anhydrotetraneurin-F (10) from Tetraneurin-F (2).—A solution of 2 (50 mg) in 1 ml of anhydrous pyridine was treated at room temperature with 0.5 ml of thionyl chloride. After a few minutes the solution was evaporated *in vacuo* and the resultant residue was dissolved in 5 ml of $CHCl_3$. Work-up of the $CHCl_3$ solution yielded a crude oil (45 mg) whose tlc and nmr analysis indicated that the oil consisted mainly of compound 10. Purification of the oil over tlc (silica gel G; $CHCl_3$–ether, 5:1) afforded, after trituration with ether–cyclohexane, pure $\Delta^{1(2)}$-anhydrotetraneurin-F (10): yield 40 mg; mp 104–105°; ir ($CHCl_3$) 1755 and 1730 (carbonyls), 1240 (acetate), 865 (trisubstituted ethylene group) cm^{-1}.

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.90; O, 27.60. Found: C, 65.31; H, 7.01; O, 27.45.

Asymmetric Esterification of $\Delta^{10(15)}$-Deacetylanhydrotetraneurin-E (8) with (±)-α-Phenylbutyric Acid Anhydride and Pyridine.—A solution of 45 mg of 8 in 189 mg of α-phenylbutyric acid anhydride was mixed with 1.5 ml of pyridine. The solution was allowed to stand overnight at room temperature and was then worked up in the standard manner:[6,7] yield 153 mg of crystalline α-phenylbutyric acid, $[\alpha]^{24}D$ −10.8° (c 1.53, benzene). Fully stereospecific esterification should yield $[\alpha]^{24}D$ −95.6°/[2(3.58) − 1] = −15.6°; therefore, the optical yield is 68%.

Tetraneurin-E Mesylate (11) from Tetraneurin-E (1).—An ice bath cooled solution of 1 (404 mg) in 2 ml of dry pyridine was treated with 0.8 ml of methanesulfonyl chloride. After 10 min the solution was evaporated *in vacuo* and the resultant residue was dissolved in 5 ml of $CHCl_3$. Work-up of the $CHCl_3$ solution yielded a residue which crystallized on trituration with isopropyl ether to give 11: yield 530 mg; mp 164–165° (after recrystallization from $CHCl_3$–benzene); ir ($CHCl_3$) 3450 (hydroxyl), 1745 and 1725 (carbonyls) cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_8S$: C, 53.75; H, 6.46; O, 31.84; S, 7.96. Found: C, 53.68; H, 6.42; O, 31.96; S, 7.95.

Compound (13) from Tetraneurin-E Mesylate (11).—A mixture containing 100 mg of 11 and 350 mg of sodium iodide in 3 ml of acetonitrile was heated under reflux for 21 hr. Work-up of

(9) A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshikantham, R. M. Mirrington, J. Kagan, and W. Herz, *Tetrahedron*, **22**, 3279 (1966); (b) J. Kagan and H. B. Kagan, *J. Org. Chem.*, **33**, 2807 (1968).

(10) Melting points are uncorrected. Analyses were determined by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

(11) This voucher specimen is deposited in the University of Texas at Austin Herbarium.

(12) C. Djerassi, R. R. Engle, and A. Bowers, *ibid.*, **21**, 1548 (1956).

the acetonitrile solution (after filtration) gave an oil which was chromatographed over tlc plates (silica gel G; benzene–ethyl acetate, 4:1). A band (R_f 0.65) afforded **13** as an oil which did not crystallize after long standing: yield 30 mg; ir bands ($CHCl_3$) 3450 (hydroxyl), 1750 (carbonyl), and 1250 (acetate) cm^{-1}. The nmr spectrum (Table I) indicated that the substance was pure and clearly indicated a vinylic methyl group as shown in the formula of **13**.

Registry No.—**1**, 25383-30-6; **2**, 25383-32-8; **6**, 25383-33-9; **7**, 25383-34-0; **8**, 25383-35-1; **9**, 22555-70-0; **10**, 25383-37-3; **11**, 25383-31-7; **13**, 25383-38-4.

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Tumor Inhibitors. LVI.[1a] Cucurbitacins O, P, and Q, the Cytotoxic Principles of *Brandegea bigelovii*[1b]

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An ethanolic extract of *Brandegea bigelovii* Cogn. was found to have significant activity against human carcinoma of the nasopharynx (KB). Systematic fractionation of the extract led to the characterization of the major active principles as the new tetracyclic triterpenes cucurbitacin O (**1a**), cucurbitacin P (**3a**), and cucurbitacin Q (**2**). The structures were deduced from their formulas and spectra, and the relationships were confirmed by conversion of both **1a** and **2** to **3a**. Interrelation of **3a** with the known cucurbitacin B confirmed the structure and stereochemistry of **3a** at all positions but C-3 and C-20. Conversion of **3a** to a 2,3-acetonide showed it to be the 3α-hydroxy isomer of dihydrocucurbitacin F. The mass spectra of these compounds have been studied and are discussed.

In the course of a continuing search for tumor inhibitors of plant origin, an ethanolic extract of *Brandegea bigelovii* Cogn. (*Cucurbitaceae*)[3] was found to show significant activity against human carcinoma of the nasopharynx carried in cell culture (KB).[4] We report herein the systematic fractionation of the crude extract and the characterization of the three major cytotoxic principles as the new tetracyclic triterpenes cucurbitacin O (**1a**), cucurbitacin P (**3a**), and cucurbitacin Q (**2**).

The dried stems, leaves, flowers, and fruit of *B. bigelovii* Cogn. were continuously extracted with ethanol and the crude extract (A) was partitioned into a water-soluble fraction (B) and a chloroform-soluble fraction (C). The activity was concentrated into the latter, which was partitioned between petroleum ether (D) and aqueous methanol (1:9, E). The active fraction E was chromatographed on silica gel and successive elution with chloroform and 3 and 4% methanol in chloroform gave two active fractions (F and G, respectively, Table I).

Further chromatography of fraction G on silica gel gave a fraction which was crystallized from acetone to yield colorless crystals (H), mp 226–227°. A study of the mass spectrum and the elemental analysis suggested that H was a mixture of two similar compounds, $C_{30}H_{46}O_7$ [*m/e* 518 (M^+) and 500 ($M^+ - 18$)] and $C_{30}H_{48}O_7$ [*m/e* 520 (M^+) and 502 ($M^+ - 18$)]. On tlc two overlapping spots were present, the less polar of which absorbed ultraviolet light and thus probably contained a conjugated system. The infrared spectrum, 5.90, 5.94, and 6.14 μ, and ultraviolet spectrum, λ_{max} 230 mμ (ϵ 5500), indicated the presence of an α,β-unsaturated ketone, but the intensity of the ultraviolet absorption was unusually low.

TABLE I
CYTOTOXICITY OF FRACTIONS AND COMPOUNDS FROM *B. Bigelovii* AGAINST EAGLE'S KB STRAIN OF HUMAN CARCINOMA OF THE NASOPHARYNX

Fraction	ED_{50}, μg/ml	Compd	ED_{50}, μg/ml
A	2.70	**1b**	20
B	>100	**2**	0.032
C	0.61	**3a**	0.54
D	>100	**3b**	45
E	0.21	**4**	2.9
F	0.021		
G	0.20		
H	0.24, **1a–3a** (1:1)		
I	0.19, **1a–3a** (3:1)		

Although no work has previously been reported on *Brandegea* species, other members of the family *Cucurbitaceae* have yielded cucurbitacins, a series of highly oxygenated tetracyclic triterpenes which often contain α,β-unsaturated ketones in their side chains. A number of the cucurbitacins have been shown to have cytotoxic properties.[5–7]

(1) (a) Presented at the Southeastern Regional Meeting, American Chemical Society, Richmond, Va., Nov 5–8, 1969. Part LV: S. M. Kupchan in "Plants and the Future of Medicine," T. Swain, Ed., in preparation. (b) This work was supported by grants from the National Institutes of Health (CA-04500 and CA-11718) and the American Cancer Society (T-275), and a contract with Chemotherapy, National Cancer Institute, National Institutes of Health (PH 43-64-551).

(2) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia, Charlottesville, Va. 22901.

(3) Plant collected in California in May 1967. The authors acknowledge receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, under a program developed by the Cancer Chemotherapy National Service Center (CCNSC) with the USDA.

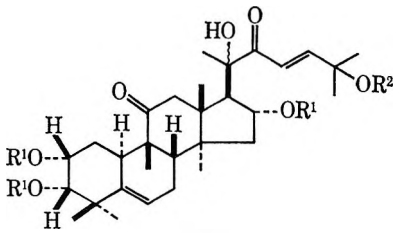
(4) *In vitro* testing was carried out under the auspices of the CCNSC using the techniques described in *Cancer Chemother. Rep.*, **25**, 1 (1962), and also by differential agar diffusion, by Dr. D. Perlman of the School of Pharmacy, University of Wisconsin, Madison, as described in *J. Pharm. Sci.*, **58**, 633 (1969).

(5) S. M. Kupchan, A. H. Grey, and M. D. Grove, *J. Med. Chem.*, **10**, 337 (1967).

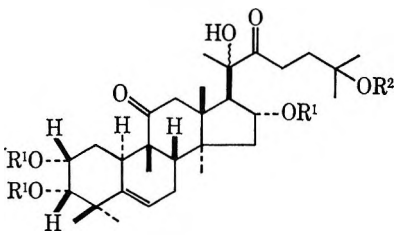
(6) S. Gitter, R Gallily, B. Shohat, and D. Lavie, *Cancer Res.*, **21**, 516 (1961).

(7) R. Gallily, B. Shohat, J. Kalish, S. Gitter, and D. Lavie, *ibid.*, **22**, 1038 (1962).

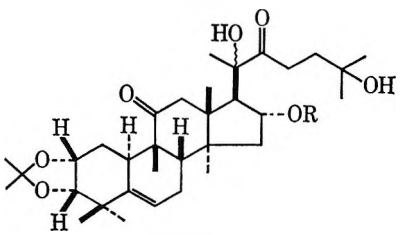
The nmr spectrum of fraction H contained a peak at τ 4.50 typical for a cucurbitacin C-6 vinylic proton.[8] The spectrum also showed a singlet at τ 3.17, which was resolved into an AB quartet (J = 16 Hz) when examined at 100 MHz. However, although this peak could be assigned to the C-23,24 vinylic proton signals of a typical α,β-unsaturated ketone, its integration corresponded to only a single proton. Thus, it appeared that fraction H was a 1:1 mixture of a compound containing a conjugated double bond and its dihydro derivative.



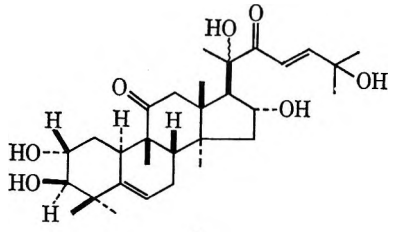
1a, $R^1 = R^2 = H$
b, R^1 = Ac; $R^2 = H$
2, $R^1 = H$; R^2 = Ac



3a, $R^1 = R^2 = H$
b, R^1 = Ac; $R^2 = H$
4, $R^1 = H$; R^2 = Ac



5a, R = H
b, R = Ac



6

Attempts to separate the two compounds by column chromatography on silica gel or on Florisil and by tlc were unsuccessful. Repeated recrystallization from a number of solvents led only to a mixture (I), mp 246–247°, whose nmr spectrum indicated a 1:3 ratio of saturated to α,β-unsaturated ketone. The ultraviolet spectral absorption intensity (ϵ 8250) corresponded to a mixture containing 75% typical α,β-unsaturated carbonyl chromophore [*i.e.*, cucurbitacin B (ϵ 11,000)].[9]

(8) P. R. Enslin, C. W. Holzapfel, K. B. Norton, and S. Rehm, *J. Chem. Soc. C*, 964 (1967).

(9) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

Acetylation of mixture H yielded two amorphous triacetates, which were inseparable on silica gel chromatography but could be separated by chromatography on Florisil. The less polar compound **1b**, λ_{max} 230 mμ (ϵ 12,200), contained, in its nmr spectrum, an AB quartet at τ 2.82 and 3.32 (J = 15 Hz, 2 H) as well as the C-6 proton signal at τ 4.32. The infrared spectrum contained bands at 5.89 and 6.12 μ corresponding also to an α,β-unsaturated ketone. The spectrum of the more polar compound, **3b**, contained only the C-6 vinylic proton (τ 4.32) and the compound showed no ultraviolet absorption bands. The nmr spectra of both compounds contained three singlets at τ 7.9–8.2 (9 H, $COCH_3$) and a multiplet at τ 4.7–5.1 (3 H, –CHOAc). Their mass spectra contained characteristic ions (see later) corresponding to an unsaturated and saturated cucurbitacin side chain, respectively, and to a common tetracyclic nucleus.

Hydrogenation of mixture H over palladium yielded a homogeneous compound, cucurbitacin P (**3a**), $C_{30}H_{48}O_7$ [m/e 520 (M^+)], identical on tlc with the lower portion of mixture H. The compound showed no ultraviolet absorption, and the melting point (157–159°, resolidifying, remelting 211–212°) and infrared spectrum (5.90 μ) suggested that it could be dihydrocucurbitacin F, mp 155–156°. This compound had previously been obtained by Enslin and his coworkers[10] by hydrogenation of cucurbitacin F (**6**), mp 244–245°. However, direct comparison of mixture H and its hydrogenation product by nmr and infrared spectroscopy and tlc with cucurbitacin F[11] and its dihydro derivative showed them to be different. In particular, instead of containing a peak at τ 4.48 for the C-6 proton as in the spectrum of **3a**, the nmr spectrum of cucurbitacin F and its dihydro derivative contained peaks at τ 4.34 and 4.32, respectively. These results suggested that the compounds in hand differed in ring-A stereochemistry from **6** (2α, 3β).

During the work on cucurbitacin F, Enslin found that, if dihydrocucurbitacin D (2α-hydroxy-3-ketone) was reduced with sodium borohydride, dihydrocucurbitacin F was formed. However, if dihydrocucurbitacin D was reduced catalytically, an uncharacterized isomer of dihydrocucurbitacin F was obtained. Cucurbitacin B[5], which is the C-25 acetyl derivative of cucurbitacin D, was therefore catalytically hydrogenated to yield a tetrahydro derivative. Hydrolysis of the acetoxyl group then led directly to a product identical with **3a**. Thus the compounds in hand were considered to differ from cucurbitacin F only at C-3 and thus had a 2α,3α configuration. Confirmation of the *cis* configuration was obtained by treatment of **3a** with acetone and *p*-toluenesulfonic acid, which yielded a mixture of a 2,3-monoacetonide (**5a**) and a diacetonide (probably 2,3:16,25). The structure of **5a** was confirmed by its conversion to only the monoacetate **5b** (τ 8.08, 3 H) on acetylation. The mass and nmr spectra of both acetonides were in agreement with the proposed structures.

Thus mixture H contained a 1:1 mixture of the two new cucurbitacins O (**1a**) and P (**3a**). Cucurbitacin P

(10) K. J. van der Merwe, P. R. Enslin, and K. Pachler, *J. Chem. Soc.*, 4275 (1963).

(11) We cordially thank Professor Enslin, of National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa, for an authentic sample of cucurbitacin F.

appears to be the same as hexahydrocucurbitacin I,[12] mp 156–157°, and tetrahydrocucurbitacin D,[13] mp 152–156°, obtained previously by hydrogenation and shown to be similar to but different from dihydrocucurbitacin F.[10]

The recent work of Barton and coworkers[14] has directly related cucurbitacin A with lanosterol and thus the absolute stereochemistry has been defined for most positions in the cucurbitacins with the exception of C-20. However, there is contradictory evidence in the literature for the relative stereochemistry at C-2. The configurations used in this paper are based on the proposals of Snatzke, *et al.*,[15] and of Barton, *et al.*[14]

The second active fraction (F) from the original separation was repeatedly chromatographed on silica gel but the nmr spectrum showed it still to be a mixture. Finally, after chromatography on Florisil and tlc, cucurbitacin Q (**2**), λ_{max} 229 mμ (ε 9500), was obtained as a single-spot product. The nmr spectrum contained an AB quartet τ 2.94 and 3.56 (J = 15.5 Hz), a vinylic proton signal at τ 4.23 (m), and an acetyl group singlet at τ 8.00. Its mass spectrum contained peaks at m/e 500 ($M^+ - 60$), 482, 405, 387, 113, 112, 111 (strong), and 96 (strong), suggesting that it was the C-25 acetyl derivative of cucurbitacin O (see later). Mild hydrogenation gave a dihydro derivative (**4**, m/e 502 ($M^+ - 60$), τ 4.27, 1 H), which on alkaline hydrolysis yielded cucurbitacin P (**3a**). The dihydro derivative (**4**) was similar to the crude hydrogenation product of cucurbitacin B on examination by tlc and nmr spectroscopy. The nmr spectrum of cucurbitacin Q showed that the side chain was undergoing partial transformation to a 23,24 *cis* form, as the C-25 methyl groups (total 6 H) appeared as two peaks, τ 8.48 (*trans*) and τ 8.37 (*cis*), and the olefinic protons appeared partially as the AB quartet and also as a singlet at τ 3.72 in the same ratio (total 2 H), whereas the remainder of the spectrum was unchanged. On hydrogenation only one compound was formed. The acetyl group was assigned to C-25, the typical substitution position for the cucurbitacins, and the assignment was in agreement with the low-field position of the C-25 methyl group signals in the nmr spectrum (*cf.*, *e.g.*, cucurbitacin B,[5] τ 8.45).

From a study of the mass spectra[16] of the three new compounds and cucurbitacins B and F, a number of correlations were determined. The main fragmentations were those involving the side chain. Loss of the side chain by fission of the 20,22 bond gave a series of peaks unaffected by substitution at C-25 or by the saturation of the 23,24 bond. These peaks appeared at m/e 405, 387, and 369 in the spectra of the 2,3-diols and were shown in the case of **3a** to have the formulas $C_{24}H_{37}O_5$, $C_{24}H_{35}O_4$, and $C_{24}H_{33}O_3$, respectively. In compounds containing a C-3 carbonyl group, peaks appeared instead at m/e 403 and 385. In the spectra of the triacetates **1b** and **3b** there were corresponding peaks at m/e 531, 471, and 411, in the 2,3-acetonide (**5a**) at m/e 445 and 427, and in its acetate (**5b**) at m/e 487 and 427.

The second fragment formed from the 20,22 fission varied markedly. In the case of the Δ-23,24 compounds a very intense and characteristic peak, often the base peak, was found at m/e 96 (C_6H_8O), corresponding to a loss of the C-25 substituent from the side chain to give a vinylic radical. However, when the side chain was reduced, relatively smaller peaks were found. In the case of **3a** these appeared at m/e 115 ($C_6H_{11}O_2$) and m/e 97 (C_6H_9O). Instead a second characteristic fragmentation, by fission of the 17,20 bond, gave a strong peak at m/e 142 ($C_8H_{14}O_2$) corresponding to the entire side chain, minus the C-25 substituent; no corresponding m/e 140 peak was found from the unsaturated compounds.

A second intense peak also occurred in the mass spectra of these compounds, at m/e 111 ($C_7H_{11}O$) if the 23,24 bond was unsaturated or at m/e 113 ($C_7H_{13}O$) if the bond was saturated. Its origin is unclear although it is possibly formed by migration of the C-20 methyl group to C-22 with fission of the 20,22 bond and loss of the C-25 substituent.

As expected the spectrum of mixture H contained peaks at m/e 142, 113, 111, and 96, characteristic of both the saturated and unsaturated side chains. The presence of peaks at m/e 405 and 387 in the spectrum of **2** were strong confirmation of the position of the acetyl group at C-25 rather than C-20. The 20-acetate would be expected to give, instead, peaks at m/e 447 and 429.

Previously,[17] the peaks at m/e 113 and 95 had been assigned to a ring A fragmentation in the C-3 carbonyl compounds tetrahydrocucurbitacin I and dihydrocucurbitacin B, but the present work shows these assumptions to have been incorrect. However, the reported spectra agree with the present arguments as they contain strong m/e 113 and 142 peaks as well as m/e 403 and 385 peaks.

The cytotoxicity of the purified samples (Table I) has been determined and confirmed previous observations that the 23,24 double bond and 25-acetyl groups are important for cytotoxicity. In general, however, the new compounds were much less active than the corresponding cucurbitacin B derivatives,[5] although the only difference was the oxidation level at C-3.

Experimental Section

Melting points were determined on a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-9 spectrometer. Ultraviolet spectra were measured on a Beckman DK-2A spectrometer. Nmr spectra were determined on Varian A-60A and HR-100 spectrometers, using deuteriochloroform as solvent, except for fraction H, **3a**, and **6**, which were measured in DMSO-d_6. Analytical and preparative tlc were carried out on silica gel plates, using ethyl acetate as solvent unless otherwise stated. Petroleum ether refers to the fraction, bp 60–68°. Evaporations were carried out at reduced pressure below 40°. Analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Extraction and Fractionation.—The dried ground stems, leaves, flowers, and fruits of *Brandegea bigelovii* Cogn. (1.6 kg) were continuously extracted with 95% ethanol for 15 hr. Evaporation gave the crude extract (A, 250 g). A portion of fraction A (200 g) was partitioned between water (500 ml) and chloroform (1.5 l.). The chloroform was washed with water (200 ml) and evaporated to give a brown foam (C, 138 g). The combined

(12) D. Lavie and D. Willner, *J. Amer. Chem. Soc.*, **80**, 710 (1958).

(13) D. Lavie and Y. Shvo, *ibid.*, **81**, 3058 (1959).

(14) D. H. R. Barton, C. F. Garbers, D. Giacopello, R. G. Harvey, J. Lessard, and D. R. Taylor, *J. Chem. Soc. C*, 1050 (1969).

(15) G. Snatzke, P. R. Enslin, C. W. Holzapfel, and K. B. Norton, *ibid.*, 972 (1967).

(16) We cordially thank Dr. D. Rosenthal, Research Triangle Institute, N. C., and Dr. W. E. Baitinger and Dr. W. L. Budde, Department of Chemistry, Purdue University, for the high- and low-resolution mass spectra.

(17) G. R. Duncan, D. D. Levi, and R. Pyttel, *Planta Med.*, **16**, 224 (1968).

aqueous solutions were evaporated to yield fraction B (62 g). Fraction C (138 g) was partitioned between aqueous methanol (1:9, 1 l.) and petroleum ether (four 400-ml portions). Evaporation of the aqueous methanol yielded a brown foam (E, 36 g) and the combined petroleum ether extracts yielded a residue (D, 100 g).

Isolation of Active Principles.—Repeating the separation yielded a larger aqueous methanol-soluble fraction E (250 g), which was fractionated by chromatography on silicAR (3 kg). Elution with chloroform followed by 3% methanol in chloroform yielded the first active fraction (F, 15.2 g); further elution with 4% methanol in chloroform yielded a second active fraction (G, 27 g).

Fraction F was repeatedly rechromatographed on silicic acid and silica gel to give a fraction apparently homogeneous by tlc but which was found to be a mixture on examination by nmr spectroscopy. Further chromatography using Florisil, on elution with ether–ethyl acetate (2:1), gave a fraction, which on preparative tlc yielded a single-spot gum, cucurbitacin Q (**2**, 48 mg): R_f 0.6; mp 118–135°; uv λ_{max}^{MeOH} 229 mμ (ε 9000); ir $\lambda_{max}^{CHCl_3}$ 2.9, 5.82, 5.95, and 6.17 μ; mass spectrum, *m/e* 500 (M^+ − 60), 405, 387, 369, 111.0800 ($C_7H_{11}O$), and 96.0575 (C_6H_8O).

Chromatography of fraction G on silica gel, on elution with 5% methanol in chloroform and crystallization from acetone, yielded the major component as a crystalline solid (H), which was a mixture of **1a** and **3a** (1:1): R_f 0.46–0.40 (upper part absorbed uv light); mp 226–227°; uv λ_{max}^{MeOH} 230 (ε 5500) and 292 mμ (ε 25); ir λ_{max}^{KBr} 2.9, 5.90, 5.94, and 6.14 μ; mass spectrum, *m/e* 520 (M^+), 518 (M^+), 500 (M^+ − 18), 502 (M^+ − 18).

Anal. Calcd for $C_{30}H_{46}O_7$: C, 69.47; H, 9.94; mol wt, 518. Calcd for $C_{30}H_{48}O_7$: C, 69.30; H, 9.29; mol wt, 520. Found: C, 69.61; H, 9.17.

Rechromatography of fraction H on silica gel or Florisil failed to achieve any resolution into its two components. Recrystallization of fraction H (98 mg) from chloroform gave crystals (45 mg): mp 238–240°; λ_{max}^{MeOH} 231 mμ (ε 8400). On recrystallization from aqueous methanol and then from ethyl acetate, crystals (I, 18 mg) were obtained [mp 247–248°; uv λ_{max}^{MeOH} 230 mμ (ε 8250); ir $\lambda_{max}^{CHCl_3}$ 2.9, 5.89, 5.93 (sh), and 6.12 μ; nmr τ 3.19 and 4.44 (3:2)], which thus consisted of a mixture of cucurbitacin P (**3a**)–cucurbitacin O (**1a**) (1:3). Fraction I was unchanged on further recrystallization.

Cucurbitacin P. a. From Fraction H.—A solution of fraction H (95 mg) in ethanol was hydrogenated using 10% Pd–C catalyst to give a white solid. Recrystallization twice from ethyl acetate–petroleum ether yielded crystals, mp 190–191°, and further recrystallization from aqueous methanol and then ethyl acetate–petroleum ether gave cucurbitacin P (**3a**, 22 mg): R_f 0.40; mp 157–159°, then resolidifying, mp 211–212° dec; ir λ_{max}^{KBr} 2.9, 5.90, and 6.13 μ; mass spectrum, *m/e* 502.3305 (M^+ − 18, $C_{30}H_{46}O_6$), 405.2633 ($C_{24}H_{37}O_5$), 387.2526 ($C_{24}H_{35}O_4$), 369.2419 ($C_{24}H_{33}O_3$), 142.0985 ($C_8H_{14}O_2$), and 113.0961 ($C_7H_{13}O$).

Anal. Calcd for $C_{30}H_{48}O_7$: C, 69.20; H, 9.29. Found: C, 68.81; H, 9.23.

b. From Dihydrocucurbitacin Q.—A solution of dihydrocucurbitacin Q (**4**, 20 mg) in methanol (3 ml) and 2 *N* aqueous sodium hydroxide (1 ml) was stirred at 25° for 6 hr. The solution was partially evaporated, then diluted with water (4 ml), and extracted with ethyl acetate (three 10-ml portions). The extract on drying ($MgSO_4$) and evaporation gave a white solid, which was separated by tlc to give the major component (10 mg). Recrystallization from ethyl acetate–ether–petroleum ether gave cucurbitacin P (**3a**, 5 mg) [mp 220–221°, mmp 215–217° dec] the infrared spectrum (KBr) was identical with that of **3a** obtained by method a.

c. From Cucurbitacin B.—A solution of cucurbitacin B (30 mg) in acetic acid was hydrogenated using platinum as catalyst. The product was twice separated by tlc to yield crude dihydrocucurbitacin Q (16 mg). This material was hydrolyzed as in method b. Separation by tlc and recrystallization twice from ethyl acetate–petroleum ether gave cucurbitacin P (1 mg) identical by infrared spectroscopy (KBr) and tlc with **3a** from method a.

Dihydrocucurbitacin Q (4).—A solution of cucurbitacin Q (**2**, 37 mg) in methanol (5 ml) was hydrogenated using 10% Pd–C as catalyst. The product was centrifuged and the supernatant liquid was evaporated to give a homogeneous (tlc) oil (**4**, 37 mg): ir $\lambda_{max}^{CHCl_3}$ 2.75, 2.9, 5.81, and 5.90 μ; mass spectrum, *m/e* 502 (M^+ − 60), 405, 387, 369, 142, 113, and 97.

Triacetates 1b and 3b.—A solution of fraction H (110 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was left overnight at room temperature. Working up in the normal way gave a solid, which was separated by chromatography on silica gel to give a mixture of two triacetates (99 mg) and an unidentified less polar product. Repeating the acetylation gave a mixture of two triacetates (174 mg), which was separated by chromatography on Florisil (100 g). Elution with ether and then 3% ethyl acetate in ether yielded first the acetate **1b** as a homogeneous (tlc) amorphous solid (40 mg): R_f 0.6, absorbed uv light [ether–ethyl acetate (4:1)]; uv λ_{max}^{MeOH} 230 mμ (ε 12,200); ir $\lambda_{max}^{CHCl_3}$ 2.9, 5.74, 5.89, and 6.12 μ; mass spectrum, *m/e* 644 (M^+), 531, 471, 411, 111, and 96.

Further elution yielded a second amorphous homogeneous (tlc) triacetate **3b** (146 mg): R_f 0.5 [ether–ethyl acetate (4:1)]; uv end absorption; ir $\lambda_{max}^{CHCl_3}$ 2.8, 5.74, 5.90, and 6.10 μ; mass spectrum, *m/e* 531, 471, 411, 142, and 113.

Acetonide of Cucurbitacin P (5a).—A solution of cucurbitacin P (**3a**, 1.1 g) and *p*-toluenesulfonic acid (91 mg) in acetone (40 ml) was stirred overnight with anhydrous Na_2SO_4 (1.5 g). The solution was filtered through silica gel and evaporated to give a brown solid (1.3 g), which was fractionated by chromatography on silica gel (120 g). Elution successively with chloroform, 2% methanol in chloroform, and 7% methanol in chloroform yielded first a crude diacetonide (152 mg), R_f 0.8, and then a crude monoacetonide (544 mg), R_f 0.7. The diacetonide was chromatographed on Florisil and on elution with ether gave a homogeneous (tlc) oil: $\lambda_{max}^{CHCl_3}$ 2.8, 5.91 μ; mass spectrum, *m/e* 600 (M^+), 567, 142, and 113. The crude monoacetonide was twice recrystallized from ether–petroleum ether to give crystals of the monoacetonide (**5a**, 80 mg): mp 181–182°; ir $\lambda_{max}^{CHCl_3}$ 2.67, 2.90, 5.90, and 5.91 μ; mass spectrum, *m/e* 542 (M^+ − 18), 524.3516 ($C_{33}H_{48}O_5$), 445, 142, and 113.

Anal. Calcd for $C_{33}H_{52}O_7$: C, 70.68; H, 9.35; mol wt, 560. Found: C, 71.14; H, 9.45.

Acetate of Acetonide 5a.—Acetylation of the acetonide (**5a**, 30 mg) with acetic anhydride in pyridine yielded a mixture. Separation by tlc gave a homogeneous (tlc) amorphous compound (**5b**, 11 mg): R_f 0.7; ir $\lambda_{max}^{CHCl_3}$ 2.78, 2.90, 5.72, and 5.90 μ; nmr τ 8.08 (acetyl CH_3CO); mass spectrum, *m/e* 602 (M^+), 487, 427, 115, and 113.

Registry No.—**1a**, 25383-23-7; **1b**, 25383-24-8; **2**, 25383-25-9; **3a**, 25383-26-0; **3b**, 25383-27-1; **4**, 25383-28-2; **5a**, 25383-29-3; **5b**, 25383-31-7.

Bufadienolides. 11. Bufalin and Resibufogenin[1]

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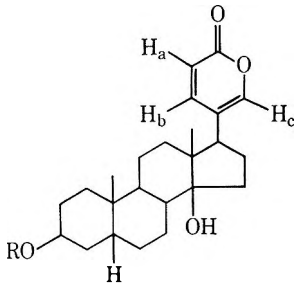
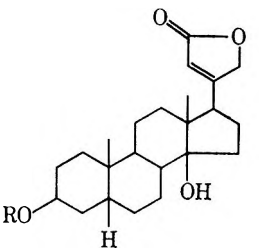
Received January 16, 1970

A total synthesis of resibufogenin (**12b**) and bufalin (**1a**) has been summarized. Digitoxigenin (**2a**) was employed as relay and converted to 14-dehydrobufalin acetate (**11**). The latter substance was transformed to resibufogenin (**12b**) and bufalin (**1a**). The synthesis represents a new approach to the bufadienolides and constitutes the first synthetic route from a cardenolide to a bufadienolide.

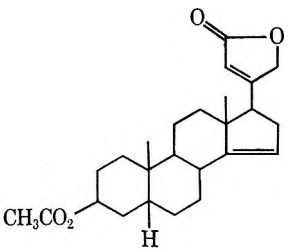
One of the principal objectives in our study of bufadienolide-type steroids was to complete a useful total synthesis of bufalin.[2] Once conversion of digitoxigenin (**2a**) to isobufalin[3] was at hand, total synthesis of bufalin seemed secure but no reproducible technique for the superficially uncomplicated rearrangement isobufalin → **6**. The latter substance was selected as an intermediate which could be utilized to circumvent practical limitations encountered in our assaults on a bufalin synthesis from digitoxigenin. A disadvantage seemingly inherent in using olefin **6a** would lie in having to reintroduce oxygen at the 14β position. However, a number of



1a, R = H
b, R = $COCH_3$



2a, R = H
b, R = 3(D-digitoxose)
c, R = $COCH_3$



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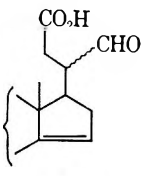

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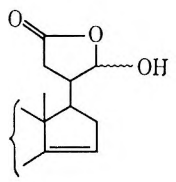

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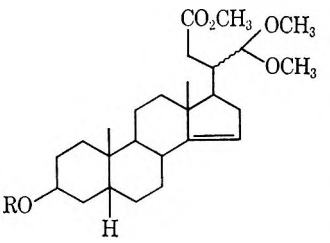
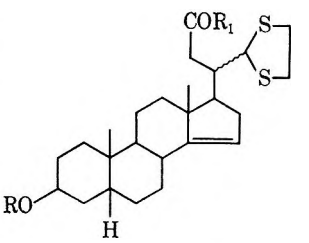
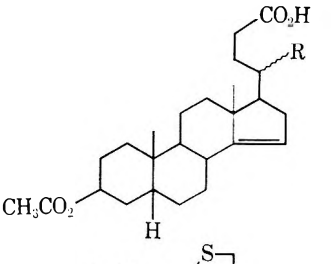
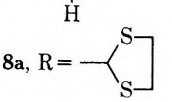


6a, R = H
b, R = $COCH_3$



7a, R = $COCH_3$; R_1 = CH
b, R = $COCH_3$; R_1 = CCH_2
c, R = H; R_1 = OH
d, R = $COCH_3$; R_1 = Cl
e, R = $COCH_3$; R_1 = CHN_2



8a, R = 
b, R = —CHO

bufalin was discovered.[4] Meanwhile the total synthesis of bufalin herein summarized immerged as a practical and reproducible method.

From a series of accessory experiments[5] performed with digitoxigenin, it appeared possible to convert digitoxigenin (**2a**) *via* aldehyde **4** and lactol **5** to acetal **6**. The latter substance was selected as an intermediate which could be utilized to circumvent practical limitations encountered in our assaults on a bufalin synthesis from digitoxigenin. A disadvantage seemingly inherent in using olefin **6a** would lie in having to reintroduce oxygen at the 14β position. However, a number of recent advances in experimental manipulation of the Δ^{14} system suggested this would no longer be a problem and indeed key steps in the transformation of 14-dehydrobufalin to bufalin had already been noted in the patent literature.[6] Therefore a synthesis of bufalin based on acetal **6a** seemed promising and was undertaken as follows.

Digitoxigenin (**2a**) prepared by hydrolysis of digitoxin (**2b**) was acetylated (**2c**) and dehydrated to 14-dehydrodigitoxigenin acetate (**3**). Upon treatment with sodium methoxide in methanol (followed by acidification) cardenolide **3** was transformed, presumably *via* alde-

(1) This investigation was supported by Public Health Service Research Grants CA-10115-01 to CA-10115-04 from the National Cancer Institute. (a) For paper 10 in the series, refer to J. C. Knight, G. R. Pettit, and P. Brown, *J. Org. Chem.*, **35**, 1415 (1970). (b) The present contribution also represents Steroids and Related Natural Products. LXII (part LXI, G. R. Pettit and B. Green, *Can. J. Chem.*, **48**, in press). A preliminary report has been summarized by G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *Chem. Commun.*, 93 (1969).

(2) The naturally occurring bufadienolides until 1969 remained the last classic category of steroids in which no member had yielded to total synthesis. For a brief review of this subject and outline of potential biological importance, consult references in 1b and G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(3) G. R. Pettit, T. R. Kasturi, J. C. Knight, and K. A. Jaeggi, *ibid.*, **35**, 1410 (1970).

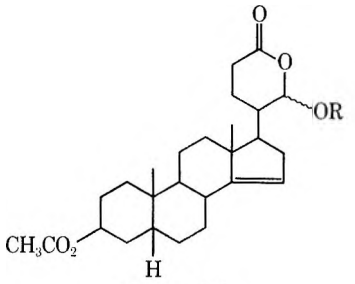
(4) On one occasion 14-dehydrobufalin was obtained from isobufalin, but the method proved unreliable and was abandoned. At that time Professor Sondheimer kindly informed us of preparing bufalin in his laboratory *via* 14-dehydrobufalin and resibufogenin; see F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969). Remainder of the same year witnessed three new synthetic routes to the bufadienolides and a total synthesis of scillarenin: (a) G. R. Pettit, D. C. Fessler, K. D. Paull, P. Hofer, and J. C. Knight, *Can. J. Chem.*, **47**, 2511 (1969); (b) U. Stache, K. Radscheit, W. Fritsch, H. Kohl, W. Haede, and H. Ruschig, *Tetrahedron Lett.*, 3033 (1969); and (c) C. R. Engel, R. Bouchard, A. F. deKrassny, L. Ruest, and J. Lessard, *Steroids*, 637 (1969). We wish to thank Professor C. R. Engel for informing us of his contribution prior to publication.

(5) G. R. Pettit, T. R. Kasturi, J. C. Knight, and J. Occolowitz, *J. Org. Chem.*, **35**, 1404 (1970).

(6) H. Kondo and S. Ohno, U. S. Patent 3,134,772 [*Chem. Abstr.*, **61**, 5736 (1964)].

hyde **4**, to lactol **5**. Preparation of oily lactol **5** from digitoxigenin proved efficient (79% overall) and the assigned structure was entirely consistent with spectral data. Methanolysis of lactone **5** using methanol containing *p*-toluenesulfonic acid readily afforded acetal methyl ester **6a**. Of several methods explored for homologation of methyl ester **6a** an Arndt–Eistert sequence seemed best for detailed study, but this choice did necessitate reprotecting the aldehyde as an ethylene-thioacetal. Necessary protection was achieved by first acetylating alcohol **6a** and then treatment with ethanedithiol containing 70% perchloric acid. Simply washing the crude product with aqueous base resulted in extensive saponification of the methyl ester. Following acidification, carboxylic acid **7a** was obtained. The yield of acid **7a** was increased by saponifying (and acetylating the product) remaining methyl ester **7b**. The pronounced sensitivity of methyl ester **7b** to base hydrolysis suggests a neighboring-group-type participation by sulfur. A pmr study of intermediates **6** and **7** indicated that the acid reagents did not cause any detectable shift of the Δ^{14} double bond to the $\Delta^{8(14)}$ position.

Homologation of acid **7a** *via* acid chloride **7d** and diazo ketone **7e** led to carboxylic acid **8a**. Cleavage of the ethylene thioacetal was accomplished using a mercuric oxide–mercuric chloride–aqueous acetic acid procedure. Substitution of aqueous acetone resulted in reduced yields and under prolonged reaction conditions led to migration ($\Delta^{14} \rightarrow \Delta^{8}$) of the olefin. Also, the more commonly employed cadmium carbonate–mercuric chloride–aqueous acetone technique for cleavage of ethylene thioacetal **8a** did not give good results. With methanol as solvent, the major product appeared (spectral evidence) to be methyl acetal **9a**. While the

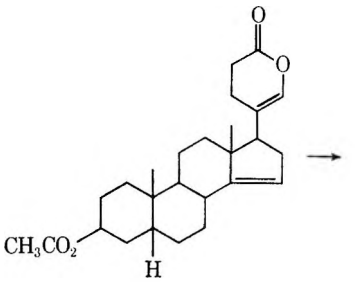


9a, R = CH_3
b, R = H

acetal **9a** was readily converted using aqueous acetic acid to lactol **9b** elimination of water to provide enol lactone **10** was not easily realized.

Enol cyclization of aldehyde **8b** was achieved using *p*-toluenesulfonic acid as catalyst.[7] The amount of *p*-toluenesulfonic acid and reaction time for cyclization were important factors in obtaining good conversion to enol lactone **10**. Excess catalyst and prolonged treatment led to extensive migration of the Δ^{14} olefin. Other methods such as iodine in benzene gave poor yields while dicyclohexylcarbodiimide in pyridine gave only lactol **9b**.

Dehydrogenation of enol lactone **10** was easily realized using the sulfur procedure developed in part 7 of this series. The product, 14-dehydrobufalin acetate (**11**), was identical with an authetic specimen prepared from natural bufalin. Early in our appraisal of synthetic routes to the natural bufadienolides, we considered a possibility that the pyrone ring did not freely rotate. A serious consequence of such restricted rotation in bufalin would be a good possibility of synthesizing the wrong isomer.[8] We assume from being able to obtain routinely 14-dehydrobufalin by enol lactonization of aldehyde carboxylic acid **8b** and subsequent dehydrogenation that restricted rotation if present must be negligible in the temperature ranges employed.



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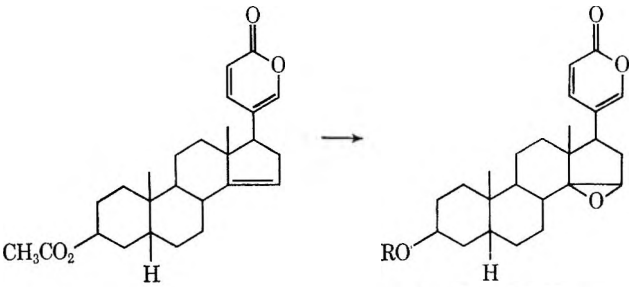

11 **12a**, R = $COCH_3$
b, R = H

The remaining steps to bufalin were completed as follows. Treatment of 14-dehydrobufalin acetate (**11**) with *m*-chloroperoxybenzoic acid was used to prepare resibufogenin acetate (**12a**). Selective saponification of acetate **12a** was achieved using basic alumina. The product, resibufogenin (**12b**), was completely identical with a natural specimen thus completing a total synthesis of this clinically useful bufadienolide.[2] Careful (−50°) and selective reduction of resibufogenin was employed to obtain bufalin (**1a**).[9] The synthetic specimen of bufalin and a natural sample were identical by all the usual criteria.

The total syntheses of bufalin and resibufogenin herein described also correspond to the first cardenolide → bufadienolide conversions. Extension of the new bufadienolide synthesis to preparation of newly discovered bufadienolides with cell growth inhibitory properties such as 3β-acetoxyhellebrigenin[10] and 3β-acetoxybersaldeginin[11] are now under investigation in our laboratory.

(7) G. R. Pettit, D. C. Fessler, K. D. Paull, P. Hofer, and J. C. Knight *J. Org. Chem.*, **35**, 1398 (1970).

(8) Recently an example of asymmetry due to restricted rotation about the C-17,20 bond has actually been noted: F. Kohen, R. A. Mallory, and I. Scheer, *Chem. Commun.*, 580 (1969).

(9) An analogous route from 14-dehydrobufalin acetate *via* resibufogenin to bufalin has already been reported in a patent[6] and a preliminary communication (*cf.* Sondheimer[4]). The present work provides further confirmation for these important interconversions.

(10) S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *Tetrahedron Lett.*, 149 (1968).

(11) S. M. Kupchan and I. Ognyanov, *ibid.*, 1709 (1969).

Experimental Section

All solvent extracts of aqueous solutions were dried over magnesium sulfate. Silica gel HF_{254} (E. Merck, Darmstadt) on microscope slides was employed for analytical thin layer chromatography and at a thickness of 1 mm was utilized for preparative layer chromatography. The plates were observed using ultraviolet light or developed with 2% ceric sulfate in 2 *N* sulfuric acid.

Unless noted differently, introduction to the Experimental Sections of Bufadienolides papers 7, 8, and 10 outlines other general information for the experiments now described.

Methyl 3β-Hydroxy-20ξ-formyl-21-nor-5β-norchol-14-enate 20-Ethylene Thioacetal (7b).—To a solution of sodium methoxide prepared from methanol (600 ml) and sodium (17.5 g) was added 14-dehydrodigitoxigenin acetate (19 g)[12] as a suspension in methanol (600 ml). The resulting solution was stirred in a nitrogen atmosphere for 3 hr at room temperature. Upon cooling the solution was acidified with 2 *N* hydrochloric acid (500 ml), diluted with water (800 ml), and extracted (4 times) with ether. Washing the combined ethereal extract with water and concentration under reduced pressure yielded a colorless oil (19 g). A pmr spectrum of the product was consistent with lactol structure **5**.

A solution of lactol **5** (19.0 g) in methanol (600 ml) containing *p*-toluenesulfonic acid (0.8 g) was heated at reflux for 3.5 hr. Water (600 ml) was added to the solution and the resulting mixture was extracted with chloroform (three 200-ml portions). The chloroform extract was washed with water and concentrated to an oil (20.2 g). A 0.22-g aliquot of the oil was purified by preparative layer chromatography (4:1 chloroform–ethyl acetate mobile phase). The principal zone was separated and eluted with ethyl acetate to afford 0.15 g of oily acetal **6a**: pmr δ 0.98 (18 and 19 methyls), 3.34–3.42 (for closely spaced signals corresponding to the acetal methoxyl in each of the C-20 epimers), 3.68 (methyl ester), 4.14 (3α proton), 4.28 (acetal proton), and 5.18 (olefinic proton at C-15). The remaining product was predominantly **methyl 3β-acetoxy-20ξ-formyl-21-nor-5β-norchol-14-enate 20-dimethyl acetal (6b)**. Larger scale separation of the products was achieved employing column chromatography on silica gel. The crude product was chromatographed in 1:19 ligroin–ethyl acetate and alcohol **6a** eluted by 2:1 ligroin–ethyl acetate. However, it was more efficient to simply acetylate (acetic anhydride–pyridine) the crude product and proceed to the next step (**7b**) without further purification.

A solution of acetal **6b** (20 g) in ethanedithiol (25 ml) containing 70% perchloric acid (0.2 ml) was allowed to remain at room temperature for 3 hr. The mixture was diluted with ether (120 ml) and washed with 2 *N* sodium hydroxide (two 50-ml portions). The sodium salt of acid **7a** separated and was collected, washed with water, suspended in chloroform, and acidified. After washing the chloroform phase with water and removal of solvent, thioacetal **7a** was obtained as a colorless solid (12.5 g). Several recrystallizations from ethyl acetate–hexane provided an analytical sample as crystals melting at 126–129°: ν_{max} 3425–2550, 1740, and 1700 cm^{-1}; pmr δ 0.98 (18 and 19 methyls), 2.05 (acetate methyl), 3.20 (thioacetal methylene), 4.91 (thioacetal proton), 5.05 (3α proton), 5.17 (olefinic C-15 proton), and 9.20 (carboxylic acid proton).

Anal. Calcd for $C_{27}H_{40}O_4S_2$: C, 65.66; H, 8.18; S, 13.02. Found: C, 65.46; H, 8.01; S, 13.16.

The ethereal extract obtained as noted in the preceding paragraph was concentrated to a colorless oil (7 g) which was saponified employing 2 *N* sodium hydroxide–methanol (1:1, 50 ml). Alcohol **7c** was obtained as an oil (5.2 g) but acetylation (acetic anhydride–pyridine) provided an additional 5.2 g of crystalline acid **7b**.

3β-Acetoxy-20ξ-formyl-21-nor-5β-chol-14-enic Acid 20-Ethylene Thioacetal (8a).—A solution composed of benzene (250 ml), oxalyl chloride (7 ml), and acid **7a** (7.0 g) was heated at reflux for 2 hr. Solvent was removed under reduced pressure, dry benzene was added, and the solution was again concentrated to a pale yellow oil: ν_{max}^{neat} 1800, 1735, and 1680 cm^{-1}. The diazomethane prepared from 7 g of nitrosomethylurea was distilled with ether from 50% aqueous potassium hydroxide (at ice-bath temperature) and treated (dropwise) with an ether (100 ml) solution of crude acid chloride **7d** (7.2 g). Before cautious solvent removal, cooling was continued for 14 hr. The benzene solution of the yellow oily residue was chromatographed on silica gel. Elution with 93:7 hexane–ethyl acetate led to diazo ketone **7e** (4.0 g) as a pale yellow oil: ν_{max}^{neat} 2100, 1735, and 1640 cm^{-1}; pmr δ 0.97 (18 and 19 methyls), 2.02 (acetate methyl), 3.17 (thioacetal methylenes), 4.92 (thioacetal proton), 5.04 (3α proton), 5.16 (C-15 olefinic proton), and 5.29 (diazo ketone proton); mass spectrum *m/e* 488 (M − 28, loss of nitrogen).

A solution of the diazo ketone (4.0 g) in dioxane (20 ml) was added (dropwise) to a stirred suspension of freshly prepared silver oxide (from 4.0 g of silver nitrate) in dioxane (40 ml) containing 10% aqueous sodium thiosulfate (15 ml) and 3% potassium carbonate (0.5 ml). The reaction temperature was maintained at 60° and 1 hr later 90% of the theoretical amount of nitrogen had been evolved. Upon cooling the black mixture was filtered (twice) using Celite and 10% potassium carbonate (50 ml) was added to the filtrate. The aqueous mixture was extracted with hexane–ether (1:1, 50 ml) and the organic solvent was washed with 10% potassium carbonate (three 25-ml portions). The combined carbonate extract was acidified with 2 *N* hydrochloric acid and the solution was extracted with chloroform (three 50-ml portions). The combined chloroform extract was washed with water and concentrated (reduced pressure) to afford the homologous acid **8a** (3.2 g) as a pale yellow solid. Three recrystallizations from ethyl acetate–hexane yielded the analytical sample as colorless crystal clusters melting at 176–180°: ν_{max} 3500, 2700, 1740, and 1700 cm^{-1}; pmr δ 0.90 and 0.98 (18 and 19 methyls), 2.02 (acetate methyl), 3.20 (thioacetal methylenes), 4.90 (thioacetal proton), 5.04 (3α proton), 5.18 (olefinic C-15 proton), and 8.55 (carboxylic acid proton).

Anal. Calcd for $C_{28}H_{42}O_4S_2$: C, 66.34; H, 8.35. Found: C, 65.87; H, 8.39.

3β-Acetoxy-20ξ-formyl-21-nor-5β-chol-14-enic Acid (8b).—A mixture made from 90% acetic acid (10 ml), thioacetal **8a** (0.5 g), mercuric chloride (0.5 g), and red mercuric oxide (0.25 g) was heated (steam bath) for 25 min. On cooling, the solution was filtered through Celite. The filtrate was diluted with water and extracted with $CHCl_3$ (three 15-ml portions). The combined chloroform extract was washed with water and concentrated to a colorless oil (0.45 g). A pure sample of 3β-acetoxy-20ξ-formyl-21-nor-5β-chol-14-enic acid (**8b**) was obtained by preparative thin layer chromatography using 7:3:0.1 ethyl acetate–ligroin–acetic acid as mobile phase. The oily specimen of aldehyde **8b** exhibited $\nu_{max}^{CHCl_3}$ 3500–2400 and 1730–1690 cm^{-1}; pmr δ 0.90 and 0.98 (18 and 19 methyls), 2.07 (acetate methyl), 5.06 (3α proton), 5.18 (olefinic C-15 proton), 7.86 (carboxylic acid proton), and 9.55 (aldehyde proton).

14-Dehydrobufalin Acetate (11). Method A.—Using a Dean–Stark apparatus a solution composed of dry benzene (50 ml), aldehyde acid **8b** (0.2 g), and *p*-toluenesulfonic acid (0.025 g) was heated at reflux for 16 hr. The yellow oil obtained by evaporation of solvent was subjected to preparative layer chromatography (4:1 hexane–ethyl acetate mobile phase). Elution of the major zone with chloroform led to enol lactone **10** (0.05 g) which crystallized from hexane as needles: mp 165–167°; ν_{max} 1780, 1735, and 1675 cm^{-1}; pmr δ 0.83 and 1.0 (18 and 19 methyls), 2.06 (acetate methyl), 5.07 (3α proton), 5.18 (C-15 olefinic proton), and 6.40 (C-21 olefinic proton).

An intimate mixture prepared by evaporating a solution of enol lactone **10** (0.04 g) and sulfur (0.12 g) in carbon disulfide was heated (metal bath) at 208° for 24 min. The time and temperature variables for this dehydrogenation reaction were determined by a series of thin layer chromatographic appraisals. After cooling, the principal product, bufadienolide **11**, was isolated by preparative layer chromatography (4:1 hexane–ethyl acetate). The product (0.009 g) was eluted by chloroform and crystallized from hexane to afford colorless prisms of 14-dehydrobufalin acetate melting at 170–172° (mass spectrum M^+ 410). The synthetic specimen of 14-dehydrobufalin was identical[13] with an authentic sample prepared from natural bufalin.[14]

Method B.—A 0.10-g specimen of natural bufalin[2] in pyridine (2.5 ml)–acetic anhydride (2.2 ml) was maintained at approximately 25° for 14 hr. The solution was evaporated (reduced pressure) and a solution of the residue in methanol was washed (3 times) with *n*-heptane. After each washing the upper layer

(12) G. Bach, J. Capitaine, and C. R. Engel, *Can. J. Chem.*, **46**, 733 (1968).

(13) The identical composition of both specimens was confirmed by results of thin layer chromatographic, proton magnetic resonance, and infrared spectral (in potassium bromide) comparison.

(14) We are indebted to Professor K. Meyer and Dr. Y. Kamano for generous specimens of natural bufalin.

(heptane) was removed in a current of carbon dioxide. The methanol solution was concentrated and the residue crystallized from methanol–ether to provide 98 mg of bufalin acetate (**1b**) as plates which melted at 228–231° (lit.[15] mp 236–247°). To a cooled (ice bath) solution of acetate **1b** (98 mg) in pyridine (6 ml) was added (dropwise over 60 min) thionyl chloride (2 ml) in dry pyridine (4 ml). Stirring was continued with cooling for a total of 2 hr. At that point the mixture was placed in a refrigerator for 4 hr and then diluted with ice water. Following extraction with chloroform, washing the solution, and concentration to dryness, a solution of the residue in methanol was washed (3 times) with *n*-heptane as noted for preparation of bufalin acetate. The product 11 was crystallized from methanol–ether to yield 40.8 mg of plates melting at 173–178°. The second recrystallization provided 40.0 mg melting at 172–176° (lit.[4] mp 144–161°).

Resibufogenin Acetate (12a).—A solution prepared from chloroform (1 ml), 14-dehydrobufalin acetate (10 mg), and *m*-chloroperoxybenzoic acid (9.5 mg, 86% pure) was stirred at room temperature 4.5 hr. The mixture was diluted with ether and washed with 5% aqueous sodium hydroxide and water. Removal of solvent gave 9.8 mg of colorless solid. Resibufogenin acetate was isolated by preparative thin layer chromatography (1:1 ligroin–ethyl acetate mobile phase). Following elution from the silica gel with chloroform, the product was washed with 10% sodium bicarbonate, 1 *N* hydrochloric acid, and water. Evaporation of solvent and crystallization of the residue from methanol–chloroform yielded 4.0 mg of plates and needles melting at 222–227°. The product **12a** was identical[13] with an authentic specimen of resibufogenin acetate[16] prepared as noted with bufalin acetate. The synthetic resibufogenin acetate displayed ν_{max} 3020 (epoxide), 2970, 1730, 1340 (epoxide) cm^{-1}; mass spectrum M$^+$ 426, 408 (M − 18), 366 (M − 60).

Resibufogenin (12b).—An ether solution of resibufogenin acetate (12 mg) was mixed with activated alumina (Woelm, basic, activity III, pH *ca.* 8–9) and placed in a small column. Following a 24-hr period resibufogenin was eluted by ether and chloroform. The crude product weighed 9.2 mg. Recrystallization from chloroform–methanol gave 6.2 mg of plates with a double melting point 110–121° and 148–168° (natural resibufogenin melts at 104–122° and 146–170°). The synthetic resibufogenin was identical[13] with the natural counterpart and exhibited ν_{max} 3070, 2950, 1735, 1640, 1545 cm^{-1} and mass spectrum M$^+$ 384, 366 (100%), M$^+$ − 18.

Bufalin (1a).—The following reduction experiment was performed using dry reagents and equipment. To a solution of resibufogenin (0.105 g) in ether (22 ml) was added (dropwise) an ethereal (20 ml) solution of lithium aluminum hydride (0.275 g). Stirring and cooling at −50° was continued for 4 hr. The mixture was carefully treated with wet ether and then diluted with water. The ethereal phase was washed with 10% sodium bicarbonate, 1 *N* hydrochloric acid, and water (3 times). Removal of solvent gave 78 mg of crude (5 component mixture by thin layer using 95:5 chloroform–methanol) bufalin. A pure specimen of bufalin (18 mg) was obtained by preparative layer chromatography (95:5 chloroform–methanol mobile phase). Recrystallization from methanol–chloroform gave 12.4 mg of needles melting at 242–243° (natural bufalin from Japan melted at 221–242° and from Switzerland at 212–240°): mass spectrum M$^+$ 386, 368, 350, 325, 250, 232, 214, 207, 203, and 147; ir ν_{max} 3080, 2945, 1725, 1640, and 1545 cm^{-1}; pmr δ (at 100 MHz) 0.71 and 0.96 (18 and 19 methyls), 4.14 (3α proton), 6.25 (doublet, H$_a$, J = 10 Hz), 7.28 (partially masked doublet, H$_c$, J = 2 Hz), and 8.85 (quartet, H$_b$, J = 10 and 2 Hz).[17] The synthetic specimen of bufalin was completely identical[13] with a natural sample.[2]

Registry No.—**1a**, 465-21-4; **7a**, 25090-22-6; **8a**, 25090-23-7; **8b**, 25090-24-8; **10**, 25090-25-9; **12b**, 465-39-4.

(15) M. Barbier, H. Schröter, K. Meyer, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 2486 (1959).

(16) We are grateful to Dr. Y. Kamano for providing resibufogenin.

(17) We wish to thank Dr. George Smythe and Professor W. Caughey, for providing this spectrum.

The Photochemical Conversion of Phenyl Epoxycinnamate to Flavonoids and the Synthesis of 2′-Hydroxyepoxychalcone[1]

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Phenyl epoxycinnamate (**1**) undergoes photochemical cleavage to phenylcarbene, as well as Fries rearrangement. The resulting 2′-hydroxyepoxychalcone (**4**) partially photolyzed further into the diketone **5**, which is easily converted into flavone. It also cyclized during work-up to 3-hydroxyflavanone (**6**), which partially oxidized to flavonol (**7**). Peracid oxidation of the chalcone **9** provided the first authentic sample of 2′-hydroxyepoxychalcone, a controversial intermediate in the AFO reaction. Its chemical and photochemical properties were consistent with those required from an intermediate in the photolysis of **1**, as well as in the AFO reaction.

Chalcones are precursors *in vivo* for all the different classes of flavonoid and isoflavonoid pigments,[3] but they may not be the only entities containing 15 carbon atoms to have that distinction. In particular, the immediate biosynthetic precursor to chalcones has not been characterized.[4] We have been engaged in a study of chemical models for the biosynthesis of chalcones and we now wish to describe one observation which is also relevant to the problem of synthesizing flavonoid pigments in general.

Phenyl epoxycinnamate (**1**) was prepared by refluxing phenyl cinnamate with *m*-chloroperoxybenzoic acid in chloroform. Upon irradiation in benzene at 253.7 nm under nitrogen, it yielded products which could be accounted for by the intervention of two competing pathways, the carbene formation from phenyloxiranes[5] and the photo-Fries rearrangement of aromatic esters.[6] The reaction products were isolated by column chromatography over silica gel, and they were *trans*-stilbene (**2**) (from phenyl carbene), phenol (**3**), *o*-hydroxybenzoylacetophenone (**5**), 3-hydroxydihydroflavone (**6**), and 3-hydroxyflavone (**7**). Analysis of the crude photolysis mixture by tlc indicated that one prominent spot had not been accounted for and there were no spots corresponding to **6** and **7**, which must have been artifacts. Although we failed in our attempts to isolate it, we believe that the formation of **6** and **7**

(1) This work was outlined at the Meeting of the Phytochemical Society of North America, Banff, Canada, Aug 1969.

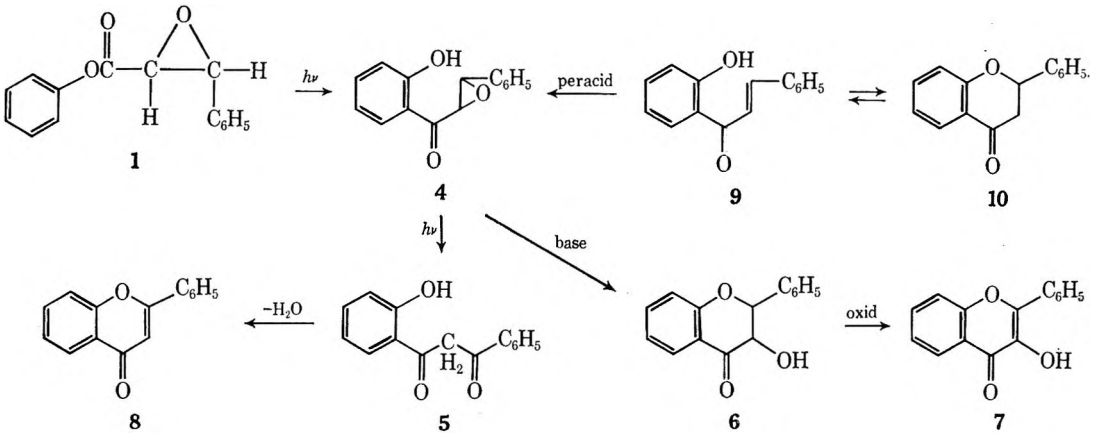
(2) To whom inquiries should be directed.

(3) H. Grisebach in "Recent Advances in Phytochemistry," T. J. Mabry, V. C. Runeckles, and R. E. Alston, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, p 379.

(4) The accepted precursor is a cinnamoyl derivative of a polyketide, but attempts to synthesize it enzymatically have been fruitless.[3]

(5) A. Padwa, "Organic Photochemistry," O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 112.

(6) D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967).



revealed the generation of the hitherto unknown 2′-hydroxyepoxychalcone **4**, which underwent intramolecular nucleophilic displacement at the epoxide to yield **6**, from which **7** was derived by air oxidation. In support of this view, we found that spraying the tlc plate with dilute alkali immediately converted the unknown spot into flavonol, recognized by its characteristic fluorescence under ultraviolet light.[7]

We believe that **5** is formed by photolysis of **4**, the product of Fries rearrangement of **1**, in accord with the well-known behavior of epoxy ketones.[8] It could, of course, have occurred after initial isomerization of **1** to a β-keto ester, followed by Fries rearrangement. This pathway is much less attractive, since photolysis of simple glycidic esters does not lead to β-keto esters.[9] Regardless of the actual mechanism, the isolation of **5** has more than a theoretical interest, since its dehydration is known to yield flavone (**8**) in excellent yield, as in the classical Baker–Vankataraman and Allan–Robinson procedures.[10]

Three of the most common types of flavonoid pigments, flavone, flavonol, and flavanonol,[11] were secured from the irradiation of a simple derivative of phenyl cinnamate under mild conditions, but we have thus far failed in our attempts to widen the scope of the photochemical reaction since we could not convert substituted phenyl cinnamates into their epoxides by peracid or hydrogen peroxide oxidation,[13] or *via* their bromo- or chlorohydrins.

The Algar–Flynn–Oyamada (AFO) reaction converts flavanone (**10**) into **7** by alkaline hydrogen peroxide oxidation.[15] The matter of the intermediacy of the hitherto unknown 2′-hydroxyepoxychalcone **4** (formed by epoxidation of the chalcone **9**, which is in equilibrium with **10**) has long been controversial.[15,16] Since we had circumstantial evidence indicating that **4** was formed photochemically and that it had an appreciable stability, we were encouraged to seek an alternate synthesis for that elusive compound. When **9** was refluxed in chloroform with *m*-chloroperoxybenzoic acid, it yielded the desired epoxychalcone **4**, along with 2-hydroxyphenyl cinnamate formed by Baeyer–Villiger oxidation.[17] Several unidentified products were also formed. The isolation of **4** proved quite difficult because of the facile cyclization to **6**, which took place during the required purification by chromatography. This undesired reaction was minimized by using a silica gel which had been thoroughly washed with acetic acid followed by ethyl acetate, and which was then dried at 100°. A pure sample of **4** was thus secured in about 20% yield. It melted at 78° and its nmr ($CDCl_3$) clearly showed the two epoxide protons at 4.15 and 4.3 ppm (each a doublet, J = 2 Hz),[18] nine aromatic protons from 7.0 to 8.0 ppm, and the hydroxyl at 11.9 ppm. Upon treatment with alkali in deoxygenated solution, **4** instantaneously isomerized into the 3-hydroxyflavanone (**6**). Alkali treatment of **4** without removal of oxygen, on the other hand, converted **4** first into **6** and then into **7**, as reported in the AFO reaction.[15]

The above chemical behavior of **4** leaves no doubt that the intermediacy of a 2′-hydroxyepoxychalcone would satisfactorily account for the products of the AFO reaction. Our synthesis of **4**, however, took place in acidic rather than alkaline medium, and the question of whether 2′-hydroxyepoxychalcones are formed in the AFO reaction is still formally open for debate.

The photolysis of **4** gave **5** in very good yield. Since, furthermore, the tlc properties of **4** matched those of the labile product in the photolysis of **1**, we may feel confident that the photo-Fries rearrangement to **4** represents a major pathway in the photochemistry of **1**. Finally, the isolation of **5**, **6**, and **7** in our original experiment is in complete accord with the photochemical and chemical behavior of the authentic sample of epoxychalcone **4**.

(7) M. Seikel, "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y. 1962, p 51.

(8) D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold, New York, N. Y., 1967, p 208.

(9) S. P. Singh and J. Kagan, unpublished results; T. I. Temnikova and I. P. Stepanov, *J. Org. Chem. USSR*, **3**, 2203 (1967); P. C. Petrellis and G. W. Griffin, *Chem. Commun.*, 691 (1967).

(10) J. Gripenberg, ref 7, p 410.

(11) The acid treatment of O-protected *o*-hydroxyepoxychalcones has been discussed by S. C. Bhrara, A. C. Jain, and T. R. Seshadri, *Tetrahedron*, **20**, 1141 (1964). These authors found that, whereas the O-benzylated form of **4** yielded only **6**, its congeners substituted in the cinnamoyl moiety also yielded isoflavones, in a synthetically useful method.[12] Therefore, this fourth class of flavonoid pigments should also be available in our procedure from the proper cinnamic esters.

(12) A. C. Jain, P. Lal, and T. R. Seshadri, *Indian J. Chem.*, **7**, 305 (1969).

(13) A similar situation was found in the α,β-unsaturated ketone series, which required initial reduction to the allylic alcohols, epoxidation, and, finally, oxidation to the epoxy ketone.[14]

(14) H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **79**, 6491 (1957).

(15) F. M. Dean, "Naturally Occuring Oxygen Ring Compounds," Butterworths, London, 1963, p 345.

(16) F. M. Dean and V. Podimuang, *J. Chem. Soc.*, 3978 (1965).

(17) Surprisingly, identical treatment of the isomer **10** did not lead to **4**, **5**, **6**, **7**, or 2-hydroxyphenyl cinnamate. We thank Dr. V. K. Bhatia for carrying out the experiment.

(18) The nmr of *trans*-epoxychalcone itself, in the same solvent, shows the epoxide protons at 4.16 and 4.31 (J = 2 Hz).

Experimental Section

The nmr spectra were recorded with internal TMS on Varian A-60A spectrometer and are reported on the δ scale with coupling constants in hertz. The uv spectra were obtained with a Hitachi–Coleman-12 spectrometer, and the mass spectra with a Perkin-Elmer 270 gc–mass spectrometer, equipped with a direct solid inlet. The melting points are not corrected. The irradiation were performed in a Rayonet apparatus, after bubbling nitrogen through the solution for 30 min. All the tlc analyses were performed on silica gel with benzene.

Phenyl *trans*-Epoxycinnamate (1).—A mixture of *trans*-cinnamoyl chloride (from 10 g of acid) and phenol (10 g) was refluxed in 150 ml of benzene in presence of 1.2 g of Mg turnings for 2.5 hr.[19] After washing with dilute base and with water, drying over $MgSO_4$, removing the solvent, and crystallizing the residue from benzene–hexane, there was obtained 14.5 g (97%) of phenyl cinnamate: mp 76° (lit.[20] 75–76°); mol wt 224 (mass spectrum); nmr (in $CDCl_3$) 6.63 and 7.9 (each a d, J = 12 Hz, vinyl protons) and 7.1–7.9 (10 aromatic protons).

A solution of 4.5 g of phenyl cinnamate and 5.0 g of *m*-chloroperoxybenzoic acid in 150 ml of CCl_4 was refluxed for 25 hr. The mixture was washed with dilute $NaHCO_3$ and with water, and was dried over $MgSO_4$. Evaporation of the solvent gave 4.4 g of residue which crystallized on standing and was recrystallized from benzene–hexane to yield 3.0 g of 1: mol wt 240 (mass spectrum); mp 88–90°; uv max at 220 nm; nmr ($CDCl_3$) at 3.7 and 4.3 (each a d, J = 2 Hz, *trans*-epoxide protons) and 7.2–7.4 (10 aromatic protons).

Photolysis of 1.—A solution of 3 g of 1 in 300 ml of benzene was irradiated at 253.7 nm under nitrogen for 30 hr. The solvent was evaporated and the residue was chromatographed over silica gel. Elution with hexane gave 120 mg of *trans*-stilbene, identified by direct comparison (melting point, uv, nmr, and mass spectra) with an authentic sample. Elution with CCl_4 gave 1.5 g of a mixture from which 1.32 g of unreacted 1 crystallized out; the mother liquor yielded *o*-hydroxybenzoylacetophenone (5). Elution with CCl_4–C_6H_6 (3:1) yielded 0.12 g of phenol, identified by direct comparison with an authentic sample. Elution with 1:1 benzene–CCl_4 yielded a mixture of 100 mg of flavanonol (6) and 20 mg of flavonol (7) which were separated by fractional crystallization.

The diketone 5, mp 118–120° (lit.[21] 120–121°), was characterized by the ir at 1605, 1565, and 1560 cm^{-1}, by the nmr at 6.8–8.0 (10 aromatic H's), 12.16 (s, phenolic OH), and 15.66 (s, enolic OH), and by the mass spectrum, which, in addition to the mass peak at m/e 240, showed major peaks at m/e 222, 163, 135, 120, 119, 93, and 77. The structure of 6, mp 186–188° (lit.[22] 188°), was deduced from the uv at 250 and 320 nm and the nmr (DMSO-d_6) at 4.66 (q, J = 12 and 6 Hz, H-3), 5.3 (d, J = 12 Hz, H-2), 5.75 (d, J = 6 Hz, 3-OH), and 7.0–8.0 (9 aromatic H's). After D_2O was added, the H-3 signal became a doublet (J = 12 Hz) and the OH signal disappeared.

The structure of 7, mp 170° (lit.[23] 169.5–170.5°), was deduced from the uv at 238, 304, and 344 nm (this last band shifting to 405 nm in presence of $AlCl_3$[24]), and from the nmr (DMSO-d_6) at 7.2–7.8 (aromatic H's). The samples of 6, 7, and 8 were also found to be identical with authentic samples by direct comparison.

Conversion of 5 into Flavone (8).—A mixture of 50 mg of 5 and 200 mg of sodium acetate in 2 ml of acetic acid was refluxed for 1.5 hr.[25] Flavone (8), isolated by preparative tlc, had mp 93–95° (lit.[23] 97–99), λ_{max} at 250 and 294 nm, and nmr ($CDCl_3$) at 6.8 (s, H-3) and 7.2–8.2 (9 aromatic protons).

Epoxidation of 9.—A solution of 4.5 g of 9 and 10.0 g of *m*-chloroperoxybenzoic acid in 150 ml of CCl_4 was refluxed for 15 hr. After washing with dilute $NaHCO_3$ and with water, drying with $MgSO_4$, and evaporating the solvent, the residue was chromatographed over a silica gel which had been previously washed with acetic acid and ethyl acetate, followed by drying at 100°. Benzene first eluted 1.0 g of 4: mass spectrum main peaks at m/e 240, 211, 133, 122, 121, 120, 105, 93, 92, 91, and 77; mp 78° (C_6H_6–hexane); nmr ($CDCl_3$) 4.15 and 4.30 (each a d, J = 2 Hz, 1 H), 7.0–8.0 (m, 9 H's), and 11.9 (s, OH). Further elution yielded 200 mg of 6, identical with an authentic sample, and 200 mg of *o*-hydroxyphenylcinnamate: mp 139–141° (lit.[26] mp 140–141°); nmr ($CDCl_3$) 6.66 and 7.93 (each a d, J = 16 Hz, 1 H), 7.0–7.8 (m, 9 H's), and 5.8 (s, OH); mass spectrum main peaks at m/e 240, 147, 131, 103, and 77.

Photolysis of 4.—A solution of 100 mg of 4 in 15 ml of benzene was irradiated under N_2 for 2 hr at 253.7 nm. The diketone 5 was isolated by silica gel chromatography in 75% yield. It had mp 118–120°, and was identical with the sample isolated in the photolysis of 1.

Base Treatment of 4.—A small amount of 4 was dissolved in methanol. One-half of the solution was treated with 1 drop of 1 *N* aqueous NaOH and was immediately analyzed by tlc. A mixture of 6 and 7 was found, and the concentration of the latter increased with time at the expense of the former until it became the only product. The other half was deoxygenated by boiling and was cooled to room temperature under nitrogen. It was treated with 1 drop of 1 *N* aqueous NaOH which had been similarly deoxygenated. Immediate tlc analysis showed that 6 was the only component.

Registry No.—1, 25518-21-2; 4, 25518-22-3; 5, 1469-94-9; 6, 1621-55-2; 7, 577-85-5; 8, 525-82-6.

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The Photochemical Synthesis of 2′-Hydroxychalcones from Phenyl Cinnamates[1]

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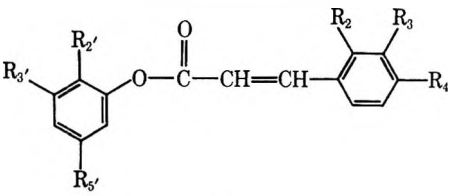
The photolysis of substituted phenyl cinnamates leads to *o*-hydroxychalcones. The examples reported utilized phenol, resorcinol, guaiacol, or phloroflucinol esterified with cinnamic acid or its 2-hydroxy, 4-hydroxy, 4-methoxy, 3,4-dihydroxy, 3-methoxy-4-hydroxy, and 3,4-dimethoxy derivatives. Some 2′,6′-dihydroxychalcones cyclized to the flavanones.

Substituted 2′-hydroxychalcones are widely distributed in plants[3] and they also serve as biosynthetic precursors to all the other classes of flavonoid and isoflavonoid pigments.[4] They can undergo a reversible cyclization to flavanones, and they can also be converted enzymatically into optically active flavanones.[5] Although the conversion of chalcones into the other classes of flavonoids is well understood, their own biosynthesis is still obscure, especially with respect to the origin of the A ring.[4] Our interest in the biosynthetic problem led us to investigate the photochemical conversion of substituted phenyl cinnamates to 2′-hydroxychalcones as a possible model for the biological reaction.[6]

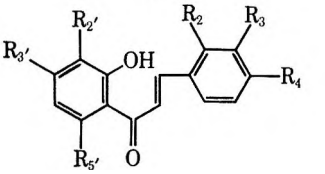
Discussion

The Friedel–Crafts acylation of protected phenols with cinnamoyl chlorides in presence of aluminum chloride has been reported.[8] When the hydroxyls were not protected prior to the reaction with the acid chloride, acylation did proceed, probably *via* Fries rearrangement of the initially formed ester,[9,10] but the hydroxychalcones were not stable under the reaction conditions, and the isomeric flavanones were actually isolated. The photochemical equivalent of the Fries rearrangement is now a well-known reaction,[11] which was recently utilized by Obara, *et al.*,[12,13] in the synthesis of simple 2′-hydroxychalcones from phenyl cinnamates. We independently studied the photochemical reaction, with the goal of obtaining chalcones having the complex substitution patterns usually found in plants.

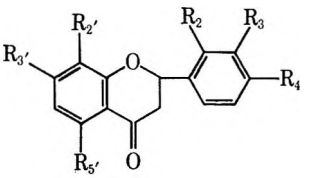
After confirming that the photo-Fries reaction proceeded with the simple ester **1a**, which yielded **2a** as



1



2



3

a, $R_{2'} = R_{3'} = R_{5'} = R_2 = R_3 = R_4 = H$
b, $R_{2'} = OCH_3$; $R_{3'} = R_{5'} = R_2 = R_3 = R_4 = H$
c, $R_{3'} = OH$; $R_{2'} = R_{5'} = R_2 = R_3 = R_4 = H$
d, $R_{5'} = OH$; $R_{2'} = R_{3'} = R_2 = R_3 = R_4 = H$
e, $R_{3'} = R_{5'} = OH$; $R_{2'} = R_2 = R_3 = R_4 = H$
f, $R_{3'} = R_{5'} = R_2 = OH$; $R_{2'} = R_3 = R_4 = H$
g, $R_{3'} = R_{5'} = R_4 = OH$; $R_{2'} = R_2 = R_3 = H$
h, $R_{3'} = R_{5'} = OH$; $R_4 = OCH_3$; $R_{2'} = R_2 = R_3 = H$
i, $R_{3'} = R_{5'} = R_3 = R_4 = OH$; $R_{2'} = R_2 = H$
j, $R_{3'} = R_{5'} = R_4 = OH$; $R_3 = OCH_3$; $R_{2'} = R_2 = H$
k, $R_{3'} = R_{5'} = OH$; $R_3 = R_4 = OCH_3$; $R_{2'} = R_2 = H$

the major rearranged products,[12] we introduced substituents in the A ring and found that the 2-methoxy- (**1b**) and 3-hydroxy- (**1c**) phenyl cinnamates yielded the products of *ortho* migration, namely **2b** from **1b** and a mixture of **2c** and **2d** from **1c**.[14] Most flavonoid pigments are formally derived from chalcones having hydroxyls at the 2′, 4′, and 6′ positions, and phloro-

(1) This work was presented at the meeting of the Phytochemial Society of North America, Banff, Canada, Aug 1969.

(2) Author to whom inquiries should be directed.

(3) J. B. Harborne in "Comparative Biochemistry of the Flavonoids," Academic Press, New York, N. Y., 1967, p 78.

(4) H. Grisebach in "Recent Advances in Phytochemistry," T. J. Mabry, R. E. Alston, and V. C. Runeckles, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, p 379.

(5) M. Shimokoriyama, *J. Amer. Chem. Soc.*, **79**, 4199 (1957).

(6) The view that phloroglucinol is not a precursor to chalcones *in vivo* is based on short-term competitive feeding experiments between phloroglucinol and carbon dioxide in cut plants.[7a] While the rate of absorption of phloroglucinol through damaged cells and its translocation to the sites of chalcone biosynthesis may not compete efficiently with direct synthesis from carbon dioxide *via* photosynthesis, the intermediacy of the phenol is not necessarily eliminated. We have secured preliminary evidences (M. A. Ali and J. Kagan, unpublished results) that labeled phloroglucinol was indeed absorbed through the stems of buckwheat cuttings, yielding radioactive flavonoids. This result contrasts with the often quoted but still unpublished work by Watkin and Neish.[7b]

(7) (a) J. E. Watkin, E. W. Underhill, and A. C. Neish, *Canad. J. Biochem. Physiol.*, **35**, 230 (1957); (b) A. C. Neish in "Biochemistry of Phenolic Compounds," H. B. Harborne, Ed., Academic Press, New York, N. Y., 1964, p 341.

(8) H. Simonis and C. Lear, *Chem. Ber.*, **59**, 2908, 2914 (1926).

(9) (a) J. Shinoda and S. Sato, *J. Pharm. Soc. Jap.*, **48**, 791 (1928); (b) *ibid.*, **48**, 791 (1928); (c) *ibid.*, **49**, 64 (1929); (d) *ibid.*, **49**, 71 (1929).

(10) J. Shinoda and Kawagoye, *ibid.*, **48**, 938 (1928).

(11) (a) D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967); (b) J. W. Meyer and G. S. Hammond, *J. Amer. Chem. Soc.*, **92**, 2187 (1970), and references therein cited.

(12) H. Obara and H. Takahashi, *Bull. Chem. Soc. Jap.*, **40**, 1012 (1967).

(13) H. Obara, H. Takahashi, and H. Hirano, *ibid.*, **42**, 560 (1969).

(14) The irradiation of **1c** in benzene yielded only **2c**.[13]

glucinol cinnamates, therefore, were required. Since many flavonoids also bear hydroxyls in the B ring, it was necessary to obtain the monoester without forming polyesters and products of selfcondensation from the hydroxycinnamoyl moiety.

Phloroglucinol could not be directly esterified[15] with hydroxycinnamic acids in acceptable yield and we used the following approach. First, the required cinnamic acid was treated with an excess of chloromethyl methyl ether in the presence of base.[16] After saponification, the O-protected cinnamic acid was treated with thionyl chloride, and the acid chloride was allowed to react with phloroglucinol in excess. There is a practical limit to the size of the excess, but we observed that even a sixfold molar excess did not completely eliminate the formation of di- and triesters. The monoester was isolated after column chromatography.

Finally, the protecting groups in the B ring of the phloroglucinol monocinnamate were removed in presence of acid, yielding the esters **1e–k**, which were photolyzed at 253.7 or 300 nm in benzene or methanol solution. The yield of chalcone was usually higher in methanol. The photo-Fries reaction of phloroglucinol monoesters is particularly simple since, for reasons of symmetry, the two products of *ortho* migration and that of *para* migration are identical.

Using the procedure outlined above, we synthesized 2′,4′,6′-trihydroxychalcones having either no substituent (**2e**), a 2-hydroxyl (**2f**), 4-hydroxyl (**2g**), 4-methoxyl (**2h**), 3,4-dihydroxyl (**2i**), 3-methoxyl-4-hydroxyl (**2j**), or 3,4-dimethoxyl (**2k**) substitution in the B ring. These substitution patterns correspond to some of the most common natural flavonoid pigments. The procedure, therefore, appears to be equally suited for the synthesis of other polyhydroxylated chalcones and flavanones and their glycosides.

In contrast to the acid-catalyzed acylation reaction, the isomerization of the initially formed chalcones into flavanones did not occur immediately. It took place occasionally during work-up and we thus synthesized the naturally occurring flavanones, pinocembrin (**3e**), isosakuranetin (**3g**), and eriodictyol (**3i**).

The photochemical *cis–trans* equilibration of olefins is well known,[17] but we did not isolate any *cis*-chalcones as judged by the coupling constant between the vinyl protons in the nmr, even though the unreacted cinnamic esters had partially isomerized. Isomerization had also occurred in the methyl cinnamates obtained by fragmentation during photolysis in methanol. Coumarin, for example, which was isolated along with **2f** in the photolysis of **1f** must have been formed by intramolecular transesterification of methyl *cis*-*o*-hydroxycinnamate.

The yield of the chalcones isolated in this work was between 20 and 50% based on the reacted esters. In the related acid-catalyzed acylation reaction, Shinoda, *et al.*, obtained similar products (only as the flavanones) but did not report the yields.[9,10] In a more recent application of Shinoda's method,[18] the synthesis of **3e** was performed with a yield of about 20%, whereas we secured it in about 46% photochemically. The photolysis of phenyl cinnamates, however, does not always proceed with high conversion, probably because their specific absorption is smaller than that of the chalcones, which therefore act as internal filters. Alternatively, the products may quench the reactive triplet state of **1**.[19]

Experimental Section

All uv spectra were recorded in methanol on a Hitachi–Coleman Model 124 spectrophotometer. The nmr spectra were recorded with TMS as internal standard on a Varian A-60A or T-60 spectrometer in DMSO-d_6 except where indicated. They are reported in parts per million on the δ scale. The mass spectra were obtained at 70 eV and at the appearance potential by direct injection into the ion source of a Perkin-Elmer 270 gc-mass spectrometer. The melting points are uncorrected and were determined with a Kofler microscope–hot stage. All the irradiation experiments were carried out under nitrogen in a Rayonet apparatus. The nylon powder chromatography was performed on short column by introducing the sample coated over some powder at the top of a column packed in water and by eluting the components with methanol solutions of increasing concentrations. The structural assignments of flavonoid products derived from spectral shifts is based on Jurd's work.[20]

Phenyl Cinnamate (**1a**).—Cinnamoyl chloride was prepared by refluxing the acid (10 g) and an excess of thionyl chloride in $CHCl_3$. It was treated with phenol (10 g) in refluxing benzene in presence of Mg. After work-up there was obtained 14.5 g (98%) of ester, mol wt 224 (mass spectrum), mp 75–76° (lit.[21] 75–76°). A solution of 640 mg of ester in 150 ml of methanol or chloroform was irradiated at 253.7 nm for 20 hr. After solvent removal and silica gel chromatography there was obtained 150 mg of chalcone **2a** eluted with benzene, mp 86–88° (lit.[12] 87–88°), with complex nmr signals between 6.77 and 8.05, identical with those of an authentic sample. A lower yield was observed upon irradiation in benzene. Unreacted starting material, phenol, methyl cinnamate, and 4′-OH chalcone were also isolated.

2-Methoxyphenyl Cinnamate (**1b**).—The ester was obtained from cinnamic acid (7 g) by treatment with $SOCl_2$ in $CHCl_3$ at reflux followed by reflux with guaiacol in benzene in the presence of Mg. After work-up, the ester (11.9 g) had mp 139–140° (lit.[22] 130°); mol wt 254 (mass spectrum); nmr 3.81 (s, OCH_3), 6.63 and 7.88 (each a d, J = 16 cps, 1 H), and 6.9–7.6 (m, 9 aromatic H's).

The ester (5 g) was irradiated at 300 nm in $CHCl_3$ under nitrogen for 40 hr. Chromatography over silica gel yielded 1.7 g of starting material and 1.4 g of its *cis* isomer, an oil in which the vinyl protons appeared at 6.09 and 7.07 ppm (J = 13 cps). These, as well as guaiacol (160 mg), were eluted with benzene–hexane (1:3). Elution with benzene–hexane (1:1) yielded 700 mg of chalcone **2b**, mp 120–122°, which showed nmr absorption at 3.87 (s, OCH_3), 6.6-7.9 (m, 10 aromatic and vinyl H's), and 13.0 (s, OH). It showed no tendency to isomerize to **3b** in solution.

3,5-Dihydroxyphenyl Cinnamate (**1e**).—A mixture of cinnamoyl chloride (from 6 g of acid) in 100 ml of benzene, and phloroglucinol (18 g) in 20 ml of pyridine was stirred with cooling for 5 hr. After work-up and chromatography to separate it from some diester, there was obtained 4 g of phloroglucinol monocinnamate: mp 199–200°; mol wt 256 (mass spectrum); nmr 6.25 (s, 3 A ring H's), 7.6 broad s, 5 aromatic H's), 6.71 and 7.95 (each a d, J = 16 cps, vinyl H's), and 9.61 (s, OH). Acetylation with Ac_2O–pyridine yielded a diacetate: mp 76° (hexane); mol wt 340 (mass spectrum); nmr 2.25 (s, 6 H's), 6.53 and 7.84

(15) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965); A. R. Bader and A. D. Kontowicz, *J. Amer. Chem. Soc.*, **75**, 5416 (1953); Y. Yanaoka, D. Yonemitsu, K. Tanizama, K. Matsuzaki, and Y. Ban, *Chem. Ind. (London)*, 2102 (1964).

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(20) L. Jurd in "Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 107.

(21) "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 714.

(22) German Patent 62,176; Beilstein, Vol. 9, 1926, p 585.

(each a d, J = 16 cps, 1 H), 6.90 (3 H's), and 7.2–7.6 (m, 5 H's).

A solution of 3.5 g of ester in 300 ml of MeOH was irradiated at 253.7 nm under nitrogen for 22 hr. Silica gel chromatography yielded 0.9 g of methyl cinnamate (*cis* and *trans*), 0.3 g of starting material, 0.85 g of phloroglucinol, as well as the chalcone–flavanone fraction (1.5 g) which was eluted with EtOAc–$CHCl_3$ (1:19). Careful silica gel chromatography of this last fraction with C_6H_6–$CHCl_3$ (1:1) eluted successively a pure sample (150 mg) of 5,7-dihydroxyflavanone (pinocembrin, **3e**) [mp 198–200° (lit.[9a] 203–204°); λ_{max} 288 nm (log ϵ 4.44); and nmr absorption at 2.85 (q, H-3 *cis* to H-2), 3.55 (q, H-3 *trans* to H-2), and 5.67 (q, H-2) with J_{gem} = 17, J_{cis} = 4, and J_{trans} = 12 cps, 6.05 (s, H-6 and H-8), 7.55 (s, B ring H's), and 12.23 (s, 2 OH's)], and 1.15 g of chalcone **2e** [mp 181–183° (lit.[9a] 189–190°); λ_{max} 341 nm (log ϵ 4.6)]. The latter product partially isomerized into the flavanone upon standing in solution.

3,5-Dihydroxyphenyl *p*-Methoxycinnamate (1h).—A benzene solution of the acid chloride, obtained from 5.35 g of 4-methoxycinnamic acid, was treated with 15 g of phloroglucinol in 15 ml of pyridine at 0° for 5 hr. After work-up and silica gel column chromatography, there was obtained 2 g of pure **1h**: mp 161–163°; nmr 3.82 (s, OCH_3), 6.08 (s, 3 H's), 6.6 and 7.8 (each a d, J = 16 cps, 1 H), 6.98 and 7.72 (each a d, J = 8.5 cps, 2 H), and 9.5 (OH). Acetic anhydride in pyridine treatment yielded a diacetate: mp 78–80°; nmr 2.25 (s, 6 H's), 3.6 (s, OCH_3), 6.38 and 7.78 (each a d, J = 16 cps, 1 H), 6.88 (s, 3 H's), 6.88 and 7.49 (each a d, J = 8.5 cps, 2 H's).

A solution of 1.5 g of **1h** in 300 ml of MeOH was irradiated at 300 nm for 22 hr. Silica gel chromatography yielded 70 mg of 5,7-dihydroxy-4′-methoxyflavanone (**3h**) eluted with benzene–hexane (3:1), 500 mg of 2′,4′,6′-trihydroxy-4-methoxychalcone (**2h**) eluted with EtOAc–$CHCl_3$ (1:19), as well as methyl 4-methoxycinnamate (350 mg, *cis* and *trans*), 50 mg of starting material, and 300 mg of phloroglucinol. The isolated flavanone (isosakuranetin) had mp 190–192° (lit.[5] 190°), and λ_{max} 289 nm (log ϵ 4.37). Its nmr showed absorption at 2.63 (q, H-3 *cis* to H-2), 3.41 (q, H-3 *trans* to H-2), and 5.43 (q, H-2, with J_{gem} = 17, J_{cis} = 3.5, and J_{trans} = 12 cps), 3.71 (s, OCH_3), 5.86 (s, H-6 and H-8), 6.9 (d, J = 8 cps, H-2′ and H-6′), 7.37 (d, J = 8 cps, H-3′ and H-5′), and 12.06 (OH). The chalcone **2h** isomerized very readily into **3h** in solution and could not be obtained in pure state.

Resorcinol Monocinnamate (1c).—A solution of cinnamoyl chloride (from 9 g of acid) in 50 ml of benzene was added dropwise to a solution of 20 g of resorcinol in 165 ml of benzene–pyridine (10:1). After overnight stirring and work-up of the upper layer, which was washed with dilute HCl and $NaHCO_3$, the residue was chromatographed over silica gel to yield 7 g of **1c**: mol wt 240 (mass spectrum); mp 102–103° (lit. 112–113°,[13] 129–130°[23]); nmr ($CDCl_3$) 7.83 and 6.53 (each a d, J = 16 cps, vinyl H's), 7.5–6.5 (m, 9 aromatic H's), and 6.06 (OH). A solution of 4 g of **1c** in 500 ml of ethanol was irradiated under nitrogen at 253.7 nm for 45 hr. After removal of the solvent and silica gel chromatography, there was obtained 1.2 g of methyl cinnamate (*cis* and *trans*), 140 mg of **2d**, 600 mg of **2c**, and 1.2 g of starting material and resorcinol. The sample of **2d** had mp 171°; nmr complex signals at 7.8–7.0 (8 H's) and 6.45–6.3 (2 H's); λ_{max} 323 (log ϵ 4.44), shifting to 329 in presence of NaOAc and to 362 nm in presence of $AlCl_3$. The sample of **2c** had mp 145° (lit.[13] 146–147°); complex nmr signals at 8.25–7.3 (8 H's) and 6.5–6.3 (2 H's); λ_{max} 320 (log ϵ 4.34) and 343 (log ϵ 4.32), shifting to 376 in presence of NaOAc and to 352 and 420 nm in presence of $AlCl_3$.

Phloroglucinol Hydroxycinnamates. General Procedure.—The hydroxycinnamic acid was added in small portions to a stirred and cooled suspension of sodium hydride in THF–DMF (5:1). After 2 hr, chloromethyl methyl ether was added dropwise with cooling, and the mixture was stirred overnight at room temperature. After filtering off the precipitate, the filtrate was concentrated under vacuum and gave a residue which was refluxed in 3% sodium hydroxide for 2 hr. After ethyl acetate washing, the aqueous layer was acidified with cold dilute HCl and gave the protected acid, which was filtered and dried. The yield was better than 95%.

The acid chloride was prepared in benzene solution by treatment with thionyl chloride and pyridine for 2 hr at room temperature. After removal of the unreacted thionyl chloride under vacuum, the crude chloride was treated with 18 equiv of phloroglucinol in cold benzene–pyridine (4:1). After stirring overnight at room temperature, the mixture was decanted. The lower layer was washed with benzene, which was added to the upper layer. The upper layer was diluted with ethyl acetate, washed with dilute HCl and dilute $NaHCO_3$, dried over $MgSO_4$, and concentrated to yield the esters, contaminated with some phloroglucinol. That mixture was chromatographed over silica gel. $CHCl_3$ eluted the tri- and diesters, whereas $CHCl_3$–MeOH (19:1) eluted the protected monoester which was crystallized from ethyl acetate–hexane. The protecting group was removed by refluxing 1 g of ester in 40 ml of a mixture of trifluoroacetic acid, methanol, and water (1:2:1). The reaction took from 1 to 4 hr and its course was followed by tlc. After work-up, the free ester was purified by silica gel chromatography.

Phlorogulcinol 2-Hydroxycinnamate (1f).—Protection of 2-hydroxycinnamic acid and reaction with phloroglucinol yielded **1f**: mol wt 272; mp 228–230°; nmr spectrum, 10.1 (2 phloroglucinol OH's), 9.25 (OH), 8.05 and 6.78 (each a d, J = 16 cps, vinyl H's), 7.8–6.9 (4 B ring H's), and 6.08 (s, 3 A ring H's). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 110–112°; nmr ($CDCl_3$) 7.4–7.8 (4 B ring H's), 7.0 (s, 3 A ring H's), 6.67 and 8.03 (each a d, J = 16 cps, 1 H), 2.43 (s, 3 H's), and 2.3 (s, 6 H's).

A solution of 350 mg of **1f** in 100 ml of methanol was irradiated at 253.7 nm for a period of 16 hr. After evaporation of the solvent, the residue was chromatographed over silica gel. There was obtained 120 mg of coumarin, mp 70°, identical with an authentic sample, 20 mg of methyl *trans*-2-hydroxycinnamate, and 100 mg of **2f**, in addition to phloroglucinol and starting material. The chalcone **2f** had mp 165–167° (lit.[24] 172–174°); nmr 5.9 (s, 2 A ring H's), 6.7–7.2 (complex, 4 H's), 7.96 and 8.3 (each a d, J = 16 cps, 1 H); λ_{max} 363 (log ϵ 4.25), shifted to 370 with NaOAc, and to 390 nm with $AlCl_3$.

Phloroglucinol 4-Hydroxycinnamate (1g).—The *p*-coumaric acid was converted into the 4-methoxymethyleneoxycinnamic acid, mp 154°. The preparation of the acid chloride often resulted in polymeric products; in order to minimize them, the chloride from 4.5 g of acid was immediately treated with phloroglucinol in excess without removing the excess of thionyl chloride. After removal of the protecting group and chromatography, there was obtained 1.0 g of **1g**: mp 220–222° (lit.[25] ~200°); nmr 6.05 (s, 3 A ring H's), 6.53 and 7.73 (each a d, J = 16 cps, 1 vinyl H), 6.83 and 7.62 (each a d, J = 8.5 cps, 2 B ring H's), and OH's at 9.4 (2 H's) and 10.0 (1 H). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 107–108°, nmr 2.28 (s, 6 H's), 2.32 (s, 3 H's), 6.5 and 7.87 (each a d, J = 16 cps, 1 H), 6.8–7.0 (3 H's), 7.18 and 7.62 (each a d, J = 8.5 cps, 2 H's). A solution of 0.8 g of **1g** in 200 ml of methanol was irradiated at 253.7 nm for a period of 22 hr. Following chromatography over silica gel and nylon powder, there was obtained 300 mg of methyl *cis*- and *trans*-*p*-coumarate, 50 mg of starting material, 120 mg of phloroglucinol, and 260 mg of **2g**. The chalcone was purified by paper chromatography and recrystallized from MeOH. It had mp 184° (lit.[26] 173–174°); nmr 5.9 (s, 2 H's), 6.9 and 7.6 (each a d, J = 8.5 cps, 2 H's), 7.7 and 8.1 (each a d, J = 16 cps, 1 H); λ_{max} 362 (log ϵ 4.44) shifted to 373 with NaOAc, to 400 nm with $AlCl_3$. The chalcone isosalipurpol (**2g**) did not isomerize to the flavanone naringenin (**3g**) during work-up, even when it was placed in acetic acid solution.

Phloroglucinol 3,4-Dihydroxycinnamate (1i).—Caffeic acid was converted into the dimethoxymethyleneoxy derivative, mp 127–129°. The protected acid (7.0 g) was converted into 4.0 g of pure phloroglucinol ester: mp 169–171°; nmr spectrum, 3.5 (s, 6 H's), 5.33 (s, 4 H's), 6.18 (s, 3 H's), 6.75 and 7.83 (each a d, J = 16 cps, 1 H), 7.0–7.6 (m, H's), and 9.56 (2 H's). Removal of the protecting group yielded **1i** in 50% yield: mp 218–220°; nmr spectrum, 6.1 (s, 3 H's), 6.43 and 7.67 (each a d, J = 16 cps, 1 H), 6.7–7.2 (m, 3 H's), and 9.4 (4 H's). Treatment with acetic anhydride–pyridine yielded a tetraacetate: mp 110–111°; nmr 2.27 (s, 6 H's), 2.3 (s, 6 H's), 6.5 and 7.83 (each a d, J = 16 cps, 1 H), 6.91 (s, 3 H's), 7.2–7.5 (m, 3 H's).

A solution of 1.0 g of **1i** in 200 ml of methanol was irradiated at 253.7 nm under nitrogen for 36 hr. Following chromatography

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(24) British Patent 914,248; *Chem. Abstr.*, **58**, 124,723 (1963).

(25) A. Sonn, *Chem. Ber.*, **46**, 4050 (1913).

(26) L. Falcao de Fonseca, *Rev. Port. Farm.*, **15**, 322 (1965); *Chem. Abstr.*, **64**, 11,161 (1966).

over silica gel and nylon, there was obtained 250 mg of methyl caffeate (*cis* and *trans*), 200 mg of phloroglucinol, 100 mg of starting material, and 300 mg of eriodictyol (**3i**): mp 264–266° (lit.[27] 267°); nmr 2.8–3.6 (m, H-3's), 5.6 (qu, H-2) 5.9 (s, H-6 and H-8), and 6.6–6.8 (m, 3 B-ring H's); λ_{max} 289 and 330, identical with that of an authentic sample. The chalcone was originally present but it isomerized completely during the nylon powder chromatography.

Phloroglucinol 3-Methoxy-4-hydroxycinnamate (1j).—Protection of 3-methoxy-4-hydroxycinnamic acid yielded the 3-methoxy-4-methoxymethyleneoxycinnamic acid, mp 137–139°. The protected acid (5 g) was converted into the phloroglucinol monoester (2.3 g): mp 166–168°; nmr spectrum, 3.4 (s, 3 H's), 3.85 (s, 3 H's), 5.22 (s, 2 H's), 6.07 (s, 3 H's), 6.72 and 7.75 (each a d, J = 16 cps, 1 H), 7.0–7.5 (3 H's), and 9.47 (2 H's). Removal of the protecting group yielded the free ester **1j**: mp 234–236; 3.83 (s, 3 H's), 6.07 (s, 3 H's), 6.63 and 7.75 (each a d, J = 16 cps, 1 H), 6.9–7.4 (3 H's), 9.4 (2 OH's), and 9.6 (1 OH). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 111–112°; nmr ($CDCl_3$) 2.18 (s, 6 H's), 2.23 (s, 3 H's), 3.75 (s, 3 H's), 6.32 and 7.6 (each a d, J = 16 cps, 1 H), 6.73 (3 H's), and 6.9–7.1 (3 H's). A solution of 1.5 g of **1j** in 200 ml of methanol was irradiated for a period of 17 hr at 253.7 nm. Chromatography over silica gel yielded 250 mg of methyl 3-methoxy-4-hydroxycinnamate (*cis* and *trans*). The remainder was chromatographed over nylon powder, and yielded 500 mg of starting material, 200 mg of phloroglucinol, and 400 mg of chalcone **2j**, which was further purified by paper chromatography. It had mp 205–208° (lit.[28] 210–212°); nmr 3.8 (s, 3 H's), 5.8 (s, 2 H's), 6.6–7.1 (3 H's), and 7.5 and 7.9 (each a d, J = 16 cps, 1 H); λ_{max} 373 (log ϵ 4.52), shifted to 384 with NaOAc, to 406 with $AlCl_3$.

Phloroglucinol 3,4-Dimethoxycinnamate (1k).—The acid chloride from 10.0 g of 3,4-dimethoxycinnamic acid in 100 ml of benzene was added dropwise with stirring and cooling to a solution of 30.0 g of phloroglucinol in benzene–pyridine (10:3). After 4 hr, the upper layer was worked up as above, and it yielded a mixture which was chromatographed over silica gel. The di- and triesters were eluted with $CHCl_3$, while elution with ethyl acetate–chloroform (1:9) gave 6.0 g of monoester **1k**: mp 204–205; nmr 3.83 (s, 6 H's), 6.0 (3 H's), 6.67 and 7.73 (each a d, J = 16 cps, 1 H), 6.9–7.4 (m, 3 H's), and 9.47 (2 OH's). Acetic anhydride–pyridine treatment yielded a diacetate: mp 146–147°; nmr ($CDCl_3$) 2.3 (s, 6 H's), 3.93 (s, 6 H's), 6.47 and 7.85 (each a d, J = 16 cps, 1 H), and 6.9–7.3 (m, 6 H's). Irradiation of a solution of 2.0 g of **1k** in 300 ml of methanol for 36 hr at 253.7 nm gave, after chromatography over silica gel and nylon, 550 mg of methyl 3,4-dimethoxycinnamate (*cis* and *trans*), 400 mg of starting material, 400 mg of phloroglucinol, and 450 mg of chalcone **2k**, which was recrystallized from methanol and had mp 173: nmr 3.8 (s, 6 H's), 5.9 (s, 2 H's), 7.0–7.3 (3 H's), and 7.65 and 8.1 (each a d, J = 16 cps, 1 H); λ_{max} 366 (log ϵ 4.51), shifted to 378 with NaOAc, and to 400 nm with $AlCl_3$.

(27) F. B. Power and F. Tutin, *J. Chem. Soc.*, **91**, 887 (1907).

(28) M. Swaleh, W. Rahman, and M. O. Farooq, *Indian J. Chem.*, **2**, 375 (1964).

Registry No.—**1b**, 531-40-8; **1c**, 22129-63-1; **1f**, 25518-27-8; **1f** (triacetate), 25518-28-9; **1g**, 25568-73-4; **1g** (triacetate) 25518-29-0; **1h**, 25528-10-3; **1i**, 25528-11-4; **1i** (tetraacetate), 25528-12-5; **1j**, 25528-13-6; **1j** (triacetate), 25528-14-7; **1k**, 25528-15-8; **1k** (diacetate), 25528-16-9; **2b**, 25515-42-8; **2c**, 25515-43-9; **2d**, 25515-44-0; **2f**, 25515-45-1; **2g**, 25515-46-2; **2j**, 25515-47-3; **2k**, 25515-48-4; **3e**, 6307-93-3; **3h**, 480-43-3; **3i**, 4049-38-1; phloroglucinol monocinnamate, 28867-41-0; phloroglucinol (diacetate), 25528-21-6; 3-methoxy-4-methoxymethyleneoxycinnamic acid, 25528-22-7.

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A New Preparation of Coumarans

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A new reaction for the formation of 2,2-dialkylcoumarans has been discovered. When phenols are allowed to react with 2,2-disubstituted aldehydes in the presence of an acid catalyst, 2,2-dialkylcoumarans are formed in one step.

As part of an investigation of the reaction of various aldehydes with phenol and substituted phenols, the sulfuric acid catalyzed interaction of isobutyraldehyde with phenol in refluxing toluene was observed to give a substantial amount of 2,2-dimethylcoumaran (**3**), which was identified by infrared and nuclear magnetic resonance spectral parameters, elemental analysis, and conversion of the courmaran into the reported[1] solid 5,7-dinitro derivative. In addition an authentic sample of the coumaran (**3**) was prepared from β-methylallyl phenyl ether by the method of Franko-Filipasic.[2]

A number of other aldehydes and substituted phenols were allowed to interact under these same conditions in order to establish the limitations of the method. Isobutyraldehyde reacted with *o*-cresol, *m*-cresol, *p*-cresol, 2,4-xylenol, 4-(1,1,3,3-tetramethylbutyl)phenol, and α-naphthol to give coumarans in yields of 10–62% (Table I). Likewise, 2-ethylhexanal reacted with *m*-cresol to give 2-butyl-2-ethyl-6-methylcoumaran (**6**), but under the same conditions the following aldehydes failed to yield coumarans by reaction with *m*-cresol: acetaldehyde, propionaldehyde, butanal, pentanal, 3-methylbutanal, 2-methyl-2-butenal, and 2-phenylpropionaldehyde. In our hands, the only aldehydes which have produced a coumaran by interaction with a phenol are those which have only one hydrogen atom attached to the second carbon atom of the aldehyde molecule (a 2,2-disubstituted aldehyde).

Each reaction, whether it yielded a coumaran or not, produced varying amounts of resinous materials whose infrared spectra displayed a strong phenolic hydroxyl stretching absorption near 3500 cm^{-1}. Considering the reactants and the reaction conditions, these resins probably have a Novolak-type structure.[3]

The infrared spectra of all the coumarans and of the naphthofuran prepared in this work show a strong ab-

(1) C. D. Hurd and R. Dowbenko, *J. Amer. Chem. Soc.*, **80**, 4711 (1958).

(2) B. R. Franko-Filipasic (to FMC Corp.), U. S. Patent 3,320,286 (May 16, 1967).

(3) L. F. Fieser and M. Fieser, "Organic Chemistry," Reinhold, New York, N. Y., 1956, pp 866–869.

Table I
Coumarans Formed from Various Phenols and Isobutyraldehyde

Phenol	Coumaran[a]	Density, d^{20}_4	$n^{20}D$	Yield, %	Calcd, % C	Calcd, % H	Calcd, % O	Found, % C	Found, % H	Found, % O	Bp, °C (mm)	Ref[b]
Phenol	2,2-Dimethylcoumaran	0.9956	1.51234	35	81.04	8.16	10.79	81.04	8.06	10.92	109 (50)	1, c
o-Cresol	2,2,7-Trimethylcoumaran	0.9807	1.51598	46	81.43	8.69	9.86	81.78	8.60	9.92	123 (50)	*c*
m-Cresol	2,2,6-Trimethylcoumaran	0.9763	1.51405	62	81.43	8.69	9.86	81.59	8.29	9.76	131 (50)	*c*, *d*
p-Cresol	2,2,5-Trimethylcoumaran	0.9812	1.51327	22	81.43	8.69	9.86	81.34	8.64	10.23	123 (50)	*c*
2,4-Xylenol	2,2,5,7-Tetramethylcoumaran	0.9667	1.51303	54	81.77	9.14	9.07	81.72	9.01	9.19	116 (19)	
4-(1,1,3,3-Tetramethylbutyl phenol	2,2-Dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran		1.50680	10	83.02	10.84	6.14	83.16	10.17	6.99	153 (10)	
α-Naphthol	2,3-Dihydro-2,2-dimethylnaphtho[1,2-*b*]furan	1.0176	1.60465	40	84.81	7.11	8.07	84.82	7.01	8.20	138 (1)	

[a] All of the coumarans listed in this table are liquids at room temperature. [b] A reference indicates an alternate and previously reported synthesis of the coumaran. When no reference given, the coumaran is apparently new or has not been previously reported. [c] Q. R. Bartz, R. F. Miller, and R. Adams, *J. Amer. Chem. Soc.*, **57**, 371 (1935). [d] F. Bohlmann and C. Zdero, *Tetrahedron Lett.*, No. 33, 3683 (1968).

sorption band near 1260 cm^{-1}, assignable to aromatic ether absorption. Absorption bands assignable to carbonyl and hydroxyl stretching frequencies are absent. The nuclear magnetic resonance spectra display no unusual features.[4]

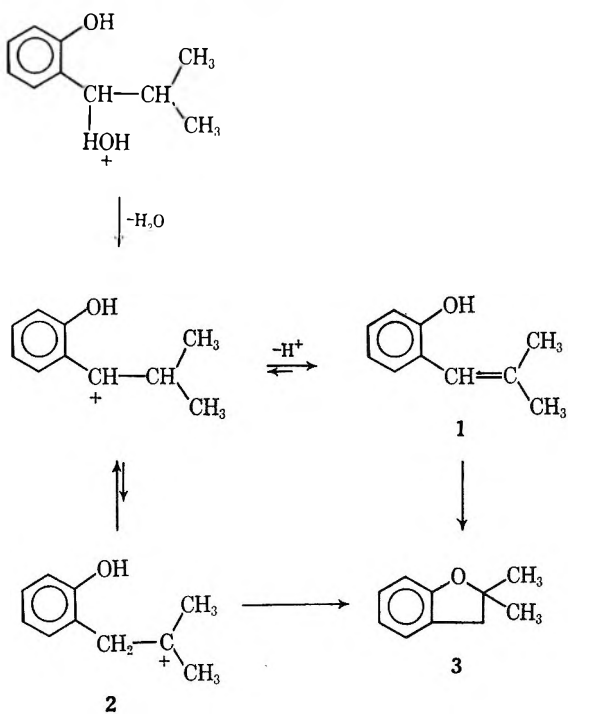
While a detailed study of the mechanism of this reaction was not made, we have observed several general aspects of the reaction which point to a carbonium ion pathway. First, the reaction is catalyzed by strong acids, including sulfuric, phosphoric, hydrochloric, and chlorosulfonic acids and a sulfonic acid type of ion-exchange resin. Nitric acid did not catalyze the production of coumarans, possibly because of its ability to act as an oxidizing agent. Sodium hydroxide was also ineffective as a catalyst.

A second aspect of the reaction is that refluxing benzene, toluene, and xylene are all successful solvents for the reaction, but water is not. This is reasonable because the reactants have limited solubility in water, and because the strong acid catalyst would protonate water in preference to a reactant species.

Finally, in several of the acid-catalyzed reactions of phenols with isobutyraldehyde a small amount of product, up to 5%, was identified as a phenol bearing an isobutenyl substituent. Because of this, equimolar amounts of *m*-cresol and isobutyraldehyde were heated in refluxing toluene solution for 27 days in the absence of any catalyst to give recovered starting materials, 12% 2-isobutenyl-5-methylphenol, and a trace of 2,2,6-trimethylcoumaran (**4**). The 2-isobutenyl-5-methylphenol was then smoothly cyclized to **4** by heating it in the presence of a catalytic amount of anhydrous magnesium chloride.

A reaction path which is consistent with these observations is illustrated by the reaction of phenol with isobutyraldehyde to give 2,2-dimethylcoumaran (**3**) (Scheme I). Our data are insufficient to comment upon the relative importance of 2-isobutenylphenol (**1**) and the ion (**2**).

Scheme I

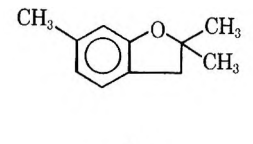


This mechanism helps to explain why aldehydes such as butanal or 3-methylbutanal which have secondary hydrogen atoms at the 2 position fail to form coumarans upon reaction with *m*-cresol, especially if the reaction path is predominantly through **2**. In such cases, the reaction would require formation of a secondary rather than a tertiary carbonium ion from the much more stable benzylic carbonium ion. We are unable to explain the failure of the reaction of 2-phenylpropionaldehyde with *m*-cresol to give a coumaran on this basis.

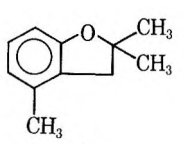
Two isomeric coumarans may result from the reaction of *m*-cresol with aldehydes. Thus, isobutyraldehyde and *m*-cresol produced a coumaran which might be 2,2,6-trimethylcoumaran (**4**) or 2,2,4-trimethylcoumaran (**5**). The coumaran from 2-ethylhexanal

(4) All of the coumarans listed in Table I, including the naphthofuran, are 2,2-dimethyl derivatives. These two methyl groups appear in all cases at 1.3 ppm (δ) in the nuclear magnetic resonance spectra as a single absorption line when observed in carbon tetrachloride solution. The adjacent two hydrogen atoms at the C-3 position appear as a singlet at 2.8–2.9 ppm. The aromatic protons appear in all of the coumarans in Table I as a multiplet at 6.2–7.1 ppm except those of 2,2,5,7-tetramethylcoumaran where the two aromatic protons appear as a single line at 6.7 ppm. The aromatic protons of the naphthofuran appear as a multiplet at 7.0–7.8 ppm. The methyl groups attached to the aromatic ring in those coumarans derived from *o*-cresol *m*-cresol, *p*-cresol, and 2,4-xylenol all appear as a singlet at 2.2 ppm. The 1,1,3,3-tetramethylbutyl group of 2,2-dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran shows additional absorption at 0.7 ppm due to its terminal *t*-butyl moiety, a singlet at 1.6 ppm due to the single methylene group in this chain, and a single line at 1.3 ppm assignable to the two methyl groups which are attached to the carbon atom which is joined to the aromatic ring.

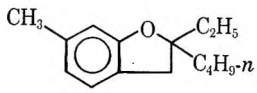
and *m*-cresol could be 2-butyl-2-ethyl-6-methylcoumaran (**6**) or 2-butyl-2-ethyl-4-methylcoumaran (**7**).



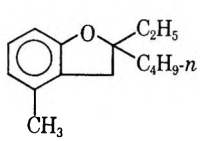
4



5



6



7

The nuclear magnetic resonance spectra showed that the pattern of the aromatic multiplets at 6.2–6.9 ppm (δ) is identical for both reaction products. This is conclusive evidence that the position of the aromatic methyl group in the coumaran from each reaction is the same. That is, the products are either **4** and **6** or **5** and **7**. The aromatic multiplet consists of a doublet centered at 6.8 ppm which integrates for 1 proton, a second doublet centered at 6.4 ppm, and a singlet at 6.3 ppm which nearly superimposes one peak of this latter doublet; this combination of the doublet at 6.4 and singlet at 6.3 integrates for 2 protons. Such a pattern indicates that the coumaran obtained from *m*-cresol and isobutyraldehyde is **4** and that the coumaran obtained from *m*-cresol and 2-ethylhexanal is **6**.

Further evidence for this conclusion is provided by the infrared spectra of **4** and **6**, which display bands and patterns characteristic of a 1,2,4-trisubstituted benzene.[5]

To show more conclusively that the product of the reaction of *m*-cresol with isobutyraldehyde is the coumaran (**4**), this coumaran was converted in a four-step sequence to 2,2,6-trimethyl-3-coumaranone by following a published procedure in which 2,2-dimethylcoumaran was converted to 2,2-dimethyl-3-coumaranone.[6] The 2,2,6-trimethyl-3-coumaranone is a known compound with a reported[7] melting point of 52°; it gives a semicarbazone derivative reported[7] to melt at 250°. The coumaranone which we prepared from the product of *m*-cresol and isobutyraldehyde melts at 51.5–52.5°; it gave a semicarbazone derivative which melts at 244–246°.

Experimental Section

Melting and boiling points are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 221 spectrometer. All nmr spectra were recorded in carbon tetrachloride solution on a Varian HA 60-IL spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane: s = singlet, d = doublet, t = triplet, and m = multiplet.

General Preparation of Coumarans. 2,2,6-Trimethylcoumaran (4).—This reaction will serve as an example for the preparation of all the coumarans and the naphthofuran listed in Table I, since each of these compounds is prepared in the same manner as 2,2,6-trimethylcourmaran.

A solution of 216 g (2.0 mol) of *m*-cresol, 144 g (2.0 mol) of isobutyraldehyde, 120 ml of toluene, and 6.5 g of concentrated sulfuric acid was refluxed for 3 hr, water being removed azeotropically as it was formed through use of a Barrett trap. The reaction mass was then distilled at 20° (4 mm), collecting the total distillate in a single receiver. The distillate was washed with 20% sodium hydroxide solution to remove unreacted *m*-cresol, then with water, and dried over calcium sulfate. It was then distilled again to give 200 g (62%) of 2,2,6-trimethylcourmaran (**4**), bp 131° (50 mm).

Preparation of 2-Isobutenyl-5-methylphenol.—A solution of 570 g (5.0 mol) of *m*-cresol, 360 g (5.0 mol) of isobutyraldehyde, and 250 ml of toluene was allowed to reflux for 27 days in the absence of a catalyst and was then distilled to give recovered starting materials, 121 g (12%) of 2-isobutenyl-5-methylphenol [bp 150° (50 mm)], and 5.0 g of 2,2,6-trimethylcoumaran (**4**) which was identified by its ir spectrum. The mass spectrum of 2-isobutenyl-5-methylphenol showed a parent ion at *m/e* 162 which corresponds to a molecular formula of $C_{11}H_{14}O$; nmr spectrum (CCl_4) δ 1.7 (s, 3, CH_3 group on double bond), 1.9 (s, 3, CH_3 group on double bond), 2.2 (s, 3, C_5 CH_3), 5.4 (s, 1, C_1 OH), 6.1 (s, 1, H on double bond), 6.5–7.0 (m, 3, aromatic); ir spectrum (NaCl) 3500 and 1180 cm^{-1} (phenolic OH), 795 and 1580 cm^{-1} (trisubstituted olefin where the double bond is conjugated with the aromatic ring). On high dilution (CCl_4) the band at 3500 cm^{-1} was observed as two bands, one at 3608 cm^{-1} ("free" OH stretching frequency) and another at 3540 cm^{-1} (intra hydrogen bonding to the π bond of the 2-isobutenyl substituent).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.47; H, 9.00. Found: C, 81.44; H, 8.70.

Cyclization of 2-Isobutenyl-5-methylphenol.—A mixture of 50 g of 2-isobutenyl-5-methylphenol from the previous reaction and 0.5 g of anhydrous magnesium chloride was heated at 184–194° for 8.5 hr and then distilled *in vacuo* to give 84% 2,2,6-trimethylcoumaran (**4**), identified by vpc retention time and by comparison of its ir spectrum with that of **6** prepared in one step from *m*-cresol and isobutyraldehyde (Table I).

Conversion of β-Methylallyl Phenyl Ether to 2,2-Dimethylcoumaran.—According to an established procedure,[2] a mixture of β-methylallyl phenyl ether (76.5 g, 0.5 mol) and 0.76 g of anhydrous magnesium chloride was purged with nitrogen and then stirred and heated at 180–186° for 6 hr under a nitrogen atmosphere. The reaction mass was distilled to give a 70% yield of 2,2-dimethylcoumaran, identified by vpc retention time and by comparison of its ir spectrum with that of the coumaran prepared from phenol and isobutyraldehyde (Table I).

Nitration of 2,2-Dimethylcoumaran.—Following the exact procedure of Hurd and Dowbenko,[1] a solution of 10 ml of concentrated sulfuric acid and 10 ml of concentrated nitric acid was employed to convert 1.5 g of 2,2-dimethylcoumaran, which had been prepared from phenol and isobutyraldehyde (Table I), into 2,2-dimethyl-5,7-dinitrocoumaran, yellow crystals, mp 150–151° from ethanol (lit.[2] 149–150°). This same dinitrocoumaran was then prepared as just described from the 2,2-dimethylcoumaran which had been obtained by cyclization of β-methylallyl phenyl ether. A mixture melting point of the dinitrocoumaran prepared by both methods showed no depression.

Preparation of 2-Butyl-2-ethyl-6-methylcoumaran (6).—A solution of 216 g (2.0 mol) of *m*-cresol, 256 g (2.0 mol) of 2-ethylhexanal, 108 ml of toluene, and 6.6 g of concentrated sulfuric acid was refluxed for 70 min, water being removed azeotropically as it was formed through use of a Barrett trap. The reaction mass was then distilled until a temperature of 200° at 2 mm had been obtained, collecting all of the distillate in a single receiver. The distillate was washed with 20% sodium hydroxide solution, then water, dried over calcium sulfate, and distilled again to give 172 g (39%) of 2-butyl-2-ethyl-6-methylcoumaran (**6**): bp 160° (22 mm); nmr spectrum (CCl_4) δ 0.9 (t, 6, ethyl- and butyl CH_3), 1.0–1.8 (m, 8, ethyl and butyl CH_2), 2.2 (s, 3, C_6 CH_3), 2.8 (s, 2, C_3 H), 6.8 (d, 1, aromatic), 6.4 (d, 1, aromatic), 6.3 (s, 1, aromatic).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16; O, 7.33. Found: C, 82.68; H, 9.90, O, 7.51.

2,2,6-Trimethyl-3-coumaranone.—This sequence of reactions

(5) 2,2,5-Trimethylcoumaran is a 1,2,4-trisubstituted benzene. Its infrared spectrum shows strong bands at 810 and 880 cm^{-1} (out-of-plane CH deformation vibrations) and a weak absorption pattern of three bands (overtone and combination bands) in the 2000–1650-cm^{-1} range, all of which are characteristic of a 1,2,4-trisubstituted benzene (L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 67, 78, 90). The spectra of **4** and **6** in these regions are essentially identical.

(6) C. D. Hurd and R. Dowbenko, *J. Amer. Chem. Soc.*, **82**, 3662 (1960).

(7) K. v. Auwers, *Justus Liebigs Ann. Chem.*, **439**, 132 (1924).

was carried out in a manner very similar to that used by Hurd and Dowbenko[6] to convert 2,2-dimethylcoumaran to 2,2-dimethyl-3-coumaranone. Thus a mixture of 8.1 g (0.05 mol) of 2,2,6-trimethylcoumaran (4), 8.9 g (0.05 mol) of N-bromosuccinimide, 0.05 g of benzoyl peroxide, and 150 ml of dry carbon tetrachloride was refluxed for 2 hr and processed in the manner of Hurd and Dowbenko to give 7.6 g (63%) of 3-bromo-2,2,6-trimethylcoumaran as a colorless liquid: bp 80–81° (1.5 mm); nmr spectrum (CCl_4) δ 1.3 (s, 3, C_2 CH_3), 1.5 (s, 3, C_2 CH_3), 2.2 (s, 3, C_6 CH_3), 4.9 (s, 1, C_3 H), and 6.3–7.2 (m, 3, aromatic).

The entire amount of 3-bromo-2,2,6-trimethylcoumaran was dissolved in a mixture of 12 ml of glacial acetic acid and 7.5 g of freshly fused potassium acetate. The mixture was heated at 120° for 10 min, allowed to stand at room temperature overnight, and then heated on a steam bath for 3 hr. The crude product, 3-acetoxy-2,2,6-trimethylcoumaran, was isolated in the same way that Hurd and Dowbenko isolated 3-acetoxy-2,2-dimethylcourmaran except that the product was not distilled. Instead, the crude acetoxycoumaran was dissolved in a solution of 50 ml of methanol and 5.0 g of potassium hydroxide, and the solution was refluxed for 1 hr. It was then diluted with 100 ml of water, saturated with sodium chloride, and extracted with ether. After drying the ethereal extract, solvent was removed and the crude product, 3-hydroxy-2,2,6-trimethylcoumaran (3.1 g), solidified spontaneously. After recrystallization from hexane, the hydroxycoumaran appeared as colorless crystals, mp 66–66.5°; its ir spectrum (NaCl) showed the expected hydroxyl stretching vibration at 3370 cm^{-1} and a band at 1280 cm^{-1} assignable to the ether stretching vibration.

The 3-hydroxy-2,2,6-trimethylcoumaran (2.5 g) in 20 ml of pyridine was added to a slurry of chromium trioxide (4.5 g) in 45 ml of pyridine at 20°. The reaction mixture was allowed to stand overnight at 20–25° and was then diluted with 200 ml of water. The mixture was extracted with ether. The ethereal extract was washed with dilute aqueous hydrochloric acid, then water, and dried over calcium sulfate. Evaporation of the ether gave 2.1 g of 2,2,6-trimethyl-3-coumaranone as colorless needles, mp 51.5–52.5° from hexane (lit.[7] 52°), whose ir spectrum showed a strong carbonyl stretching vibration at 1725 cm^{-1}. The coumaranone formed a semicarbazone derivative, mp 244–246° from ethanol (lit.[7] 250°).

Registry No.—6, 25594-08-5; 2-isobutenyl-5-methylphenol, 25594-09-6; 3-bromo-2,2,6-trimethylcoumaran, 25594-10-9; 3-hydroxy-2,2,6-trimethylcoumaran, 25594-11-0; 2,2,5,7-tetramethylcoumaran, 25594-12-1; 2,2-dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran, 25594-13-2; 2,3-dihydro-2,2-dimethylnaphtho[1,2-*b*]-furan, 25594-14-3.

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Synthesis and Characterization of C_3 and C_{17} Steroidal Amines

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The synthesis and characterization of 5α-androstane C_3 and C_{17} amines are reported. Primary, tertiary, and quaternary mono- and diammonium salts of 5α-androstane have been synthesized. The salts are found to interact selectively with nucleic acids.[3]

For the past three years, considerable work has been devoted in our laboratory to the elucidation of the interaction specificity of nucleic acid systems with mono- and polyammonium salts.[2] It is well known that these compounds interact very strongly with polynucleotides. This paper reports the synthesis and characterization of steroidal amines, of 5α-androstane, *i.e.*, primary, tertiary, and quaternary ammonium salts as well as various epimers (3α, 3β, 17α, and 17β). The interaction specificity of these salts with various nucleic acids has been studied by proton magnetic resonance, ultraviolet, circular dichroism, viscometry, and T_m of helix–coil transitions. While this is reported elsewhere,[3] the results indicate that the steroidal amines selectively stabilize the DNA helical structure, while causing the ribose-containing acids to unravel and denature. The temperature-dependent pmr experiments show that single-stranded random coils interact with the steroidal amines *via* electrostatic and hydrogen- and hydrophobic-type bonding. The capacity to form H bonding in the random coils is shown to be greater than that of the helix.[3]

Results and Discussion

The synthetic scheme for the preparation of the steroidal amines is straightforward and is outlined in Schemes I and II. The 3-amino-17-oxo-(5α)-androstane derivatives, **1** and **2**, were synthesized by an SN2 reaction of dimethylamine with the appropriate 3-tosylate 17-oxo-(5α)-androstane precursor. For example, the 3β-tosylate 17-oxo intermediate was allowed to react with dimethylamine in a sealed tube to give the 3α-dimethylamino-17-oxo-(5α)-androstane product as the tosylate salt. Conversion to the free base and acidification with HCl afforded the salt **2**. In a similar manner, the 3β epimer was obtained. The stereochem-

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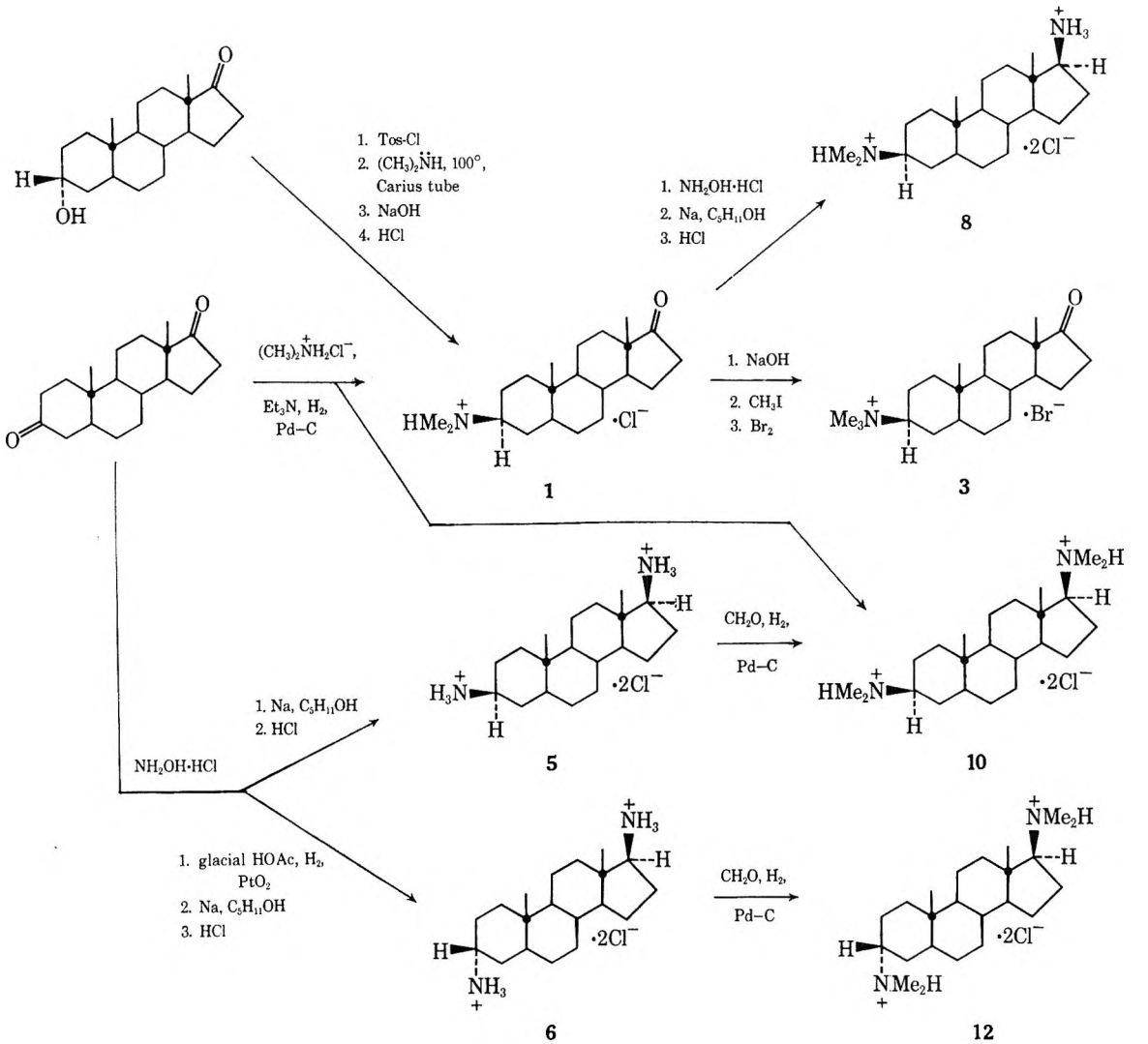
SCHEME I



istry at the 3 position on the steroid nucleus was consistent with pmr spectra.[4]

The identical 3β-dimethylamino-17-oxo-(5α)-androstane salt (**1**) was prepared in greater yield by selective reductive amination of the 3-keto group in 3,17-dioxo-(5α)-androstane by condensation under hydrogen atmosphere with dimethylamine hydrochloride in the presence of triethylamine and palladized charcoal. A by-product of this reaction afforded the 3β,17β-bis(dimethylamino)-(5α)-androstane salt (**10**) in approximately 1% yield. The bisdimethylamino derivative **10** was synthesized by another route, and this will be described later.

The 3-(tertiary amino)-17-oxo derivatives, **1** and **2**, were converted to the corresponding 3-(quaternary amino)-17-oxo compounds, **3** and **4**, by conversion to the free base and alkylation with methyl iodide. However, the resulting iodide salt always turned from light yellow to black on exposure to light, even after repeated purification. It was therefore decided to convert the iodide salt into the bromide salt by addition of excess bromine. The bromide salt of the 3-(quaternary amino)-17-oxo compounds, **3** and **4**, were found to be stable upon exposure to light.

The 3β,17β-bis(dimethylamino)-(5α)-androstane salt (**10**), previously mentioned, was prepared in larger yields by the following route. The 3,17-dioxo-(5α)-androstane starting material was converted to the bisoxime and then stereoselectively reduced with sodium in *n*-amyl alcohol according to the method of Dodgson and Haworth[5] to give the bis(primary amino) salt **5**. It was shown by Shoppee, *et al.*,[6] that the 3-oxime in 5α steroids is stereoselectively reduced with sodium in alcohol to give the 3β-amine, whereas the epimeric 3α-amine is stereoselectively obtained by platinum oxide

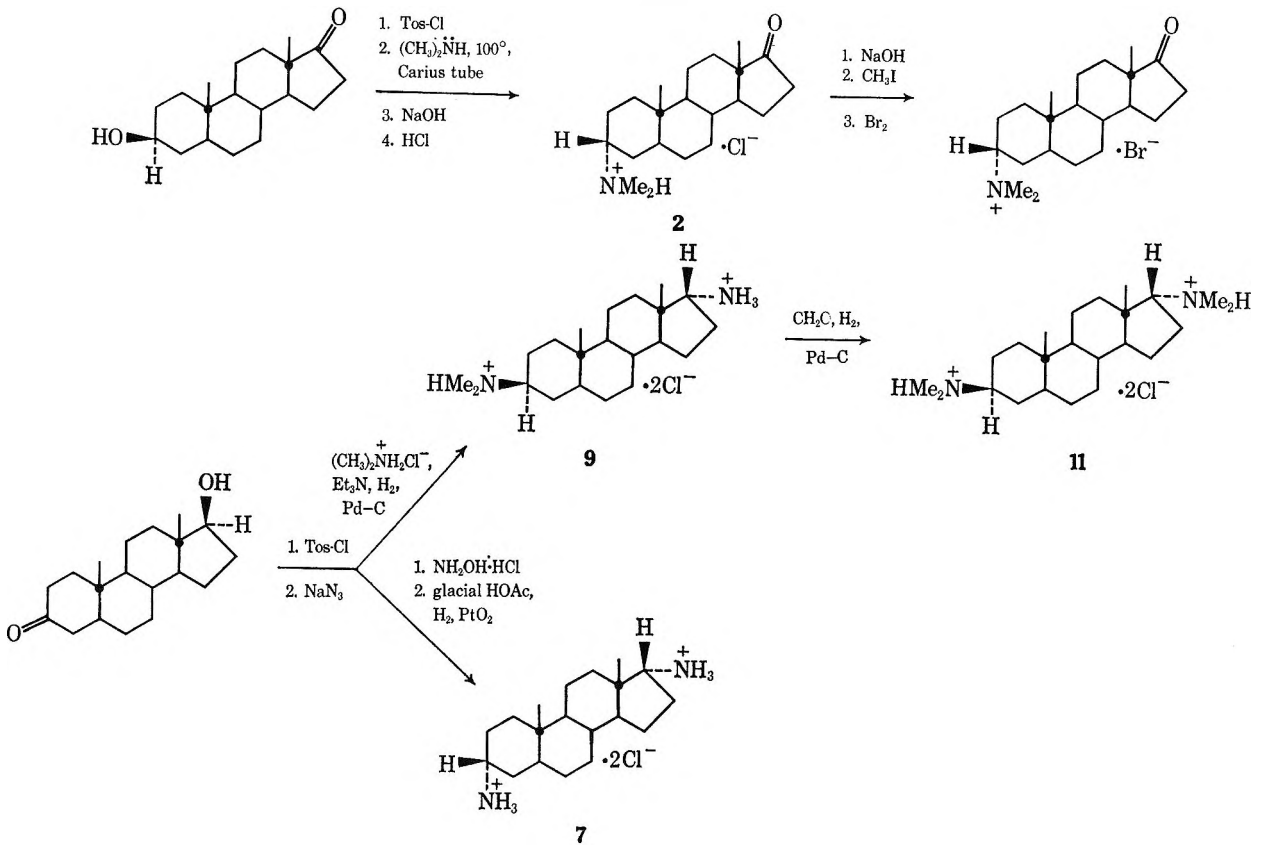
(4) The following pmr empirical formula which relates the width at half height ($\Delta\nu_{1/2}$) of a complex multiplet in a rigid system was utilized to determine whether or not the pmr assignment for the steroidal $\overset{+}{N}$-methyne protons was consistent with the proposed structure. Using this relationship, the α-methyne proton would have a relatively broader width at half height ($\Delta\nu_{1/2}$ = 9–21 cps) compared with that for the β-methine proton ($\Delta\nu_{1/2}$ = 2–14 cps). The pmr spectra of the 3β-dimethylamino derivative, **1**, showed a complex multiplet at 6.90 ± 0.33 τ ($\Delta\nu_{1/2}$ = 25 cps), and the 3α-dimethylamino derivative, **2**, showed a complex multiplet at 6.70 ± 0.15 τ ($\Delta\nu_{1/2}$ = 8 cps). Thus, the pmr assignments for the $\overset{+}{N}$-methyne protons were found to be consistent with the proposed structure. See (a) J. N. Shoolery and M. J. Rogers, *J. Amer. Chem. Soc.*, **80**, 5121 (1958); (b) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958); C. A. Grob and R. A. Whol, *Helv. Chim. Acta*, **48**, 1610 (1965).

$$\Delta\nu_{1/2} = J_{AX} + J_{BX}$$

(5) D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.*, 67 (1952).

(6) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *ibid.*, 1649 (1956).

SCHEME II



catalyzed hydrogenation in glacial acetic acid.[7] In addition, Shoppee, *et al.*,[6] found sterically hindered C-17 oximes were stereoselectively reduced to give the amine arising from approach of the reducing agent to the least hindered side of the steroid.[8] The 3β,17β-bis(primary amino) salt **5** was converted to the corresponding bis(tertiary amino) salt **10** by reductive condensation with formaldehyde. This product was found to be identical in all respects (melting point and infrared and nmr spectra) with the material produced in low yield by reductive amination of 3,17-dioxo-(5α)-androstane with dimethylamine hydrochloride, as discussed earlier.

The 3-oxime of the 3,17-bisoxime intermediate was selectively reduced to the 3α-amino-17-hydroxyamino intermediate by platinum oxide catalyzed hydrogenation in glacial acetic acid, and the infrared spectrum was consistent with the proposed structure. The 3α,17β-bis(primary amino) derivative **6** was then obtained by sodium reduction in *n*-amyl alcohol followed by acidification with hydrochloric acid. The nmr spectrum in deuterium oxide (DSS standard) showed a complex multiplet at τ 6.44 ± 0.16 ($\Delta\nu_{1/2}$ = 8 cps) and 6.94 ± 0.28 ($\Delta\nu_{1/2}$ = 16 cps) corresponding to the 3β-$\overset{+}{\text{N}}$-methyne and 17α-$\overset{+}{\text{N}}$-methyne protons, respectively. The corresponding 3α,17β-bis(tertiary amino) compound **12** was then obtained by reductive condensation of the 3α,17β-bis(primary amino) compound **6** with formaldehyde.

(7) Reduction of the 3-oxime with lithium aluminum hydride afforded an epimeric mixture of amines.

(8) Shoppee, *et al.*,[6] found this to occur when the oxime was reduced by sodium in alcohol, platinum oxide catalyzed hydrogenation in glacial acetic acid, or lithium aluminum hydride.

3-Oxo-17β-hydroxy-(5α)-androstane was converted to the tosylate and then reacted with sodium azide to give the 3-oxo-17α-azido intermediate. The 3-keto function underwent reductive amination with dimethylamine hydrochloride under hydrogen atmosphere while the 17α-azide function was simultaneously reduced to yield the 3β-dimethylamino-17α-amino-(5α)-androstane salt (**9**).

The 3-oxo-17α-azide intermediate was also utilized to form the 3α,17α-bis(primary amino) salt **7**. This was accomplished by forming the 3-oxime, and then platinum oxide catalyzed hydrogenation in glacial acetic acid to reduce the 3-oxime and 17α-azido functions.

The 3β-dimethylamino-17β-amino-(5α)-androstane salt (**8**) was obtained by conversion of the tertiary amino keto salt **1** to the oxime, followed by reduction of the oxime by sodium in *n*-amyl alcohol.

All derivatives of the steroidal amines I and II were characterized by infrared, pmr, ORD, and elemental analysis, and the results were found to be consistent with the proposed structures.

Experimental Section

Melting points were determined on Mel-Temp apparatus and are uncorrected. Unless otherwise stated, pmr spectra of the neutral compounds were taken in $CDCl_3$ with TMS acting as internal standard and in D_2O with DSS as internal standard for the polar ammonium salts. The spectra were recorded on a Varian A-60 spectrometer. The infrared spectra were run in KBr pellets unless specified, and the group frequencies listed are unlabeled for stretch frequencies, and labeled b for bending frequencies. The ORD and CD spectra of the steroidal amines were recorded on a Cary 60 spectropolarimeter. Analyses were performed by George Robertson, Florham Park, N. J.

3β-Dimethylamino-17-oxo-(5α)-androstane Hydrochloride Hemihydrate (**1**).—To 2.00 g (6.9 mmol) of 3α-hydroxy-17-

oxo-(5α)-androstane, 6.0 g (32 mmol) of *p*-toluenesulfonyl chloride and 40 cc of dry pyridine were added. The reaction mixture was heated for 4 days at 48°. Upon cooling of the reaction mixture and addition of 25 cc of water, a solid separated which was washed successively with water, 1 *N* hydrochloric acid, and water. After the solid was dissolved in 1 cc of chloroform, excess *n*-hexane was added, and a solid separated which was recrystallized from acetone–water to give 0.51 g (16.5% yield) of the intermediate compound, 3α-*p*-toluenesulfonyl-17-oxo-(5α)-androstane as needles, mp 137.5–138.5° dec. The infrared spectrum showed absorptions at 2910 (C–H), 1735 (five-membered cyclic C=O), 1345 and 1180 (S=O), and 897 cm^{-1} (S–O–C). The nmr spectrum showed a two-proton doublet at τ 2.28 (J = 8 cps, aromatic 3′ protons), a two-proton doublet at τ 2.75 (J = 8 cps, aromatic 2′ protons), a one-proton complex multiplet at τ 5.29 ± 0.10 ($\Delta\nu_{1/2}$ = 7 cps, 3β-methyne proton), a three-proton singlet at τ 7.58 (aromatic methyl protons), a 22-proton complex multiplet at τ 8.50 ± 0.98 (methylene and methyne protons), a three-proton singlet at τ 9.17 (C-19 methyl protons), and a three-proton singlet at τ 9.25 (C-18 methyl protons).

The intermediate tosylate compound (0.460 g) was allowed to react with 5 cc of dimethylamine. The reaction mixture was heated in a sealed tube at 100° for 48 hr. Upon evaporation of the excess dimethylamine, a solid separated. After the solid was dissolved in 1 cc of chloroform, excess *n*-hexane was added and a solid separated. The solid was dissolved in hot water and excess aqueous sodium hydroxide was added. The solid which separated was extracted with chloroform. After evaporation of the chloroform layer, the free amine was obtained as an oil. After addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–ether to give 0.040 g (10.7% yield) of 3β-dimethylamino-17-oxo-(5α)-androstane hydrochloride hemihydrate (**1**), mp 271–273° dec. The ORD of the sample (2.5 × 10^{-3} *M* in water) showed a positive Cotton effect, with a molecular rotation for the first extremum of $[\Phi]_{306}$ +9200, λ_0 290 mμ, and $[\Phi]_{271}$ −8280 for the second extremum. The infrared spectrum showed absorptions at 2920 (C–H), 2570 and 2440 (tertiary $\overset{+}{N}$–H), 1740 (five-membered cyclic C=O), 1640 (N–H, b), and 1475 cm^{-1} (C–H, b). The nmr spectrum showed a one-proton complex multiplet at τ 6.90 ± 0.33 ($\Delta\nu_{1/2}$ = 25 cps, 3α-methyne proton), a six-proton singlet at τ 7.19 (N-methyl protons), a 22-proton complex multiplet at τ 8.54 ± 0.95 (methylene and methyne protons), a three-proton singlet at τ 9.12 (C-19 methyl protons), and a three-proton singlet at τ 9.17 (C-18 methyl protons).

Anal. Calcd for $C_{21}H_{36}NOCl \cdot {}^1/_2H_2O$: C, 69.48; H, 10.28. Found: C, 69.45; H, 10.40.

Compound **1** was prepared in greater yield by another route. To 5.00 g (17.3 mmol) of 3,17-dioxo-(5α)-androstane, 100 cc of ethanol, 2 cc of triethylamine, 10 g of dimethylamine hydrochloride, and 1.0 g of 10% palladized charcoal were added. The reductive condensation reaction was carried out in a Parr shaker under a hydrogen atmosphere for a period of 25 hr at 36-psi pressure. After filtration of the catalyst and evaporation of the solvent, a solid separated which was dissolved in a blend of 50:50 chloroform–1 *M* hydrochloric acid. The aqueous layer was saved for subsequent work-up. Upon separation of the organic layer and evaporation of the solvent, a solid separated which was recrystallized out of chloroform–hexane to give 4.90 g of solid, mp 260–262° dec. Further recrystallization of 3.40 g of solid from water gave 1.14 g (19.0% yield) of 3β-dimethylamino-17-oxo-(5α)-androstane hydrochloride hemihydrate (**8**), mp 271–274° dec. The melting point and infrared and nmr spectra were found to be identical with those of the material prepared by the method described above.

3α-Dimethylamino-17-oxo-(5α)-androstane Hydrochloride Sesquihydrate (2).—To 2.00 g (6.9 mmol) of 3β-hydroxy-17-oxo-(5α)-androstane, 6.0 g (32 mmol) of *p*-toluenesulfonyl chloride and 40 cc of dry pyridine were added. The reaction mixture was heated for 4 days at 48°. Upon cooling of the reaction mixture and addition of 25 cc of water, an oil separated. Purification of the oil by trituration yielded a solid which was washed successively with water, 1 *N* hydrochloric acid, and water and then recrystallized from acetone–water to give 2.04 g (66.0% yield) of the intermediate compound, 3β-*p*-toluenesulfonyl-17-oxo-(5α)-androstane as needles, mp 151–152° (lit.[9] 160–161°). The infrared spectrum showed absorptions at 2860 (C–H), 1725 (five-membered cyclic C=O), 1340 and 1170 (S=O), and 925 cm^{-1} (S–O–C). The nmr spectrum showed a two-proton crude doublet at τ 2.19 (J = 8 cps, aromatic 3′ protons), a two-proton crude doublet at τ 2.66 (J = 8 cps, aromatic 2′ protons), a one-proton complex multiplet at τ 5.69 ± 0.28 (3α-methyne proton), a three-proton singlet at τ 7.55 (aromatic methyl protons), a 22-proton complex multiplet at τ 8.45 ± 1.18 (methylene and methyne protons), a three-proton singlet at τ 9.18 (C-19 methyl protons), and a three-proton singlet at τ 9.20 (C-18 methyl protons).

The tosylate (1.66 g) was allowed to react with 10 cc of dimethylamine. The reaction mixture was heated in a sealed tube at 100° for 48 hr. Upon evaporation of the excess dimethylamine, a solid separated. The solid was dissolved in hot water and excess aqueous sodium hydroxide was added; the solid which separated was extracted with chloroform. Upon evaporation of the chloroform layer, the free amine was obtained as an oil. After addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–ether to give 0.57 g (40.3% yield) of 3α-dimethylamino-17-oxo-(5α)-androstane hydrochloride sesquihydrate (**2**), mp 202–205° dec. The ORD of the sample (2.5 × 10^{-3} *M* in water) showed a positive Cotton effect with a molecular rotation for the first extremum of $(\Phi)_{306}$ +8200, λ_0 290 mμ, and $[\Phi]_{270}$ −7960 for the second extremum. The infrared spectrum showed absorptions at 2930 (C–H), 2700 and 2480 (tertiary $\overset{+}{N}$–H), 1735 (five-membered cyclic C=O), 1635 (N–H, b), and 1460 cm^{-1} (C–H, b). The nmr spectrum showed a one-proton complex multiplet at τ 6.70 ± 0.15 ($\Delta\nu_{1/2}$ = 8 cps, 3β-methyne proton), a six-proton at τ 7.14 (N-methyl protons), a 22-proton complex multiplet at τ 8.42 ± 0.93 (methylene and methyne protons), and a six-proton singlet at τ 9.13 (C-18, C-19 methyl protons).

Anal. Calcd for $C_{21}H_{36}NOCl \cdot 1{}^1/_2H_2O$: C, 66.20; H, 10.32. Found: C, 66.05; H, 10.50.

3β-Trimethylammonium-17-oxo-(5α)-androstane Bromide Hemihydrate (3).—To 0.150 g (0.41 mmol) of **1**, excess aqueous sodium hydroxide was added, and the solid which separated was extracted with chloroform. Upon evaporation of the chloroform layer, the free amine was obtained as a solid. To the free amine, 1 cc of ethanol and 2.5 cc of methyl iodide were added. The reaction mixture was heated in a sealed tube for 18 hr at 100°. Upon evaporation of the solvent, a black solid separated. After the solid was recrystallized from ethanol–ether, a yellow solid separated which became black upon exposure to light. The solid was dissolved in ethanol and 0.3 cc of bromine was added, which caused the solution to change color from black to orange. After addition of excess ether, a solid separated which was recrystallized from ethanol–ether to give 0.041 g (23.8% yield) of 3β-trimethylammonium-17-oxo-(5α)-androstane bromide hemihydrate (**3**), mp 287° dec. The ORD of the sample (2.5 × 10^{-3} *M* in water) showed a positive Cotton effect with a molecular rotation for the first extremum of $[\Phi]_{306}$ +8040, λ_0 290 mμ, and $[\Phi]_{271}$ −6920 for the second extremum. The infrared spectrum showed absorptions at 2920 (C–H), 1740 (five-membered cyclic C=O), and 1470 cm^{-1} (C–H, b). The nmr spectrum showed a one-proton complex multiplet at τ 6.47 ± 0.16 (3α-methyne proton), a nine-proton singlet at τ 6.90 (N-methyl protons), a 22-proton complex multiplet at τ 8.43 ± 1.04 (methylene and methyne protons), a three-proton singlet at τ 9.10 (C-19 methyl protons), and a three-proton singlet at τ 9.13 (C-18 methyl protons).

Anal. Calcd for $C_{22}H_{38}NOBr \cdot {}^1/_2H_2O$: C, 62.69; H, 9.33. Found: C, 62.79; H, 9.38.

3α-Trimethylammonium-17-oxo-(5α)-androstane Bromide Hemihydrate (4).—Using the method described for **3**, 0.150 g (0.39 mmol) of **2** was allowed to react to give 0.031 g (18.9% yield) of 3α-trimethylammonium-17-oxo-(5α)-androstane bromide hemihydrate (**4**), mp 277° dec. The ORD of the sample (2.5 × 10^{-3} *M* in water) showed a positive Cotton effect with a molecular rotation for the first extremum of $[\Phi]_{306}$ +9760, λ_0 291 mμ, and $[\Phi]_{271}$ −7960 for the second extremum. The infrared spectrum showed absorptions at 2920 (C–H) and 1735 (five-membered cyclic C=O), and 1475 cm^{-1} (C–H, b). The nmr spectrum showed a one-proton complex multiplet at τ 6.72 ± 0.10 (3β-methyne proton), a nine-proton singlet at τ 6.97 (N-methyl protons), a 22-proton complex multiplet at τ 8.51 ± 0.89 (methylene and methyne protons), a three-proton singlet at τ 9.12 (C-19 methyl protons), and a three-proton singlet at τ 9.16 (C-18 methyl protons).

(9) J. Iriarte, G. Rosenkranz, and R. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955).

Anal. Calcd for $C_{22}H_{38}NOBr \cdot {}^1/_2H_2O$: C, 62.69; H, 9.33. Found: C, 62.55; H, 9.41.

3β,17β-Diamino-(5α)-androstane Dihydrochloride Hemihydrate (5).—To 3,17-dioxo-(5α)-androstane, 8.3 g (120 mmol) of hydroxylamine hydrochloride, 8.3 cc of pyridine, and 100 cc of ethanol were added. The reaction mixture was refluxed for 1 hr, during which time a white solid separated. After evaporation of the solvent and washing with water, the solid was recrystallized out of ethanol to give 3.36 g (73.4% yield) of 3,17-bis(hydroxyamino)-(5α)-androstane, mp 267–270° (lit. 260–261° [10] and 271–273° [5]). The infrared spectrum showed absorptions at 3270 (O–H), 1670 (C=N), and 940 cm^{-1} (N–OH).

The bisoxime (3.96 g) was added to 450 cc of *n*-amyl alcohol and reduced with 25 g of sodium according to the method of Dodgson and Haworth.[5] After acidification of the solution with hydrochloric acid and evaporation of the solvent, a solid separated. The solid was dissolved in hot water and excess sodium hydroxide was added; the solid which separated was extracted with chloroform. After evaporation of the chloroform layer, the free amine was obtained as an oil. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 4.04 g (88.0% yield) of 3β,17β-diamino-(5α)-androstane dihydrochloride hemihydrate (5), mp >370° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 3440 (primary $\overset{+}{N}$–H), 2910 (C–H), 1985 ($\overset{+}{N}H_3$, b), 1590 (N–H, b), 1490 (N–H, b), and 1445 cm^{-1} (C–H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.92 ± 0.33 (N-methyne protons), a 22-proton complex multiplet at τ 8.62 ± 1.07 (methylene and methyne protons), a three-proton singlet at τ 9.18 (C-19 methyl protons), and a three-proton singlet at τ 9.20 (C-18 methyl protons).

Anal. Calcd for $C_{19}H_{36}N_2Cl_2 \cdot {}^1/_2H_2O$: C, 61.28; H, 10.02. Found: C, 61.34; H, 10.09.

3α,17β-Diamino-(5α)-androstane Dihydrochloride Dihydrate (6).—The intermediate bisoxime (3.2 g) described in the preparation of 12 was added to 120 cc of glacial acetic acid, and 0.60 g of platinum oxide was added. The sterically less hindered 3-oxime was stereoselectively reduced to the 3α-amine under a hydrogen atmosphere in a Parr shaker for 15 hr at 36 psi according to the method of Shoppee, *et al.*[6] After filtration of the catalyst and evaporation of the solvent, an oil separated. Upon addition of hot water, followed by filtration of the water-insoluble residue, excess sodium hydroxide was added, and the solid which separated was extracted with chloroform and then ether. Upon evaporation of the combined organic layers, 2.4 g (78.5% yield) of the solid crude 3α-amino-17-hydroxyamino-(5α)-androstane was obtained and used without further purification. The infrared spectrum showed absorptions at 3310 (N–H and O–H), 2910 (C–H), 1660 (C=N), 1580 (N–H, b), 1440 (C–H, b), and 940 cm^{-1} (N–OH).

The above intermediate (2.4 g) was added to 350 cc of *n*-amyl alcohol. The oxime was reduced to the β-amine with 21 g of sodium in boiling *n*-amyl alcohol according to the method of Dodgson and Haworth.[5] After acidification with hydrochloric acid and evaporation of the solvent, a solid separated. The solid was dissolved in hot water and excess sodium hydroxide was added; the solid which separated was extracted with chloroform. After evaporation of the chloroform layer, the free amine was obtained as an oil. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 1.6 g (51.0% yield) of 3α,17β-diamino-(5α)-androstane dihydrochloride dihydrate (6), mp >370° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 3460 (primary $\overset{+}{N}$–H), 2940 (C–H), 2000 ($\overset{+}{N}H_3$, b), 1615 (N–H, b), 1505 (N–H, b), and 1450 cm^{-1} (C–H, b). The nmr spectrum showed a one-proton complex multiplet at τ 6.44 ± 0.16 ($\Delta\nu_{1/2}$ = 8 cps, 3β-methyne proton), a one-proton complex multiplet at τ 6.94 ± 0.28 ($\Delta\nu_{1/2}$ = 16 cps, 17α-methyne proton), a 22-proton complex multiplet at τ 8.52 ± 0.88 (methylene and methyne protons), a three-proton singlet at τ 9.18 (C-19 methyl protons), and a three-proton singlet at τ 9.22 (C-18 methyl protons).

Anal. Calcd for $C_{19}H_{36}N_2Cl_2 \cdot 2H_2O$: C, 57.13; H, 10.09. Found: C, 57.35; H, 10.14.

3α,17α-Diamino-(5α)-androstane Dihydrochloride Monohydrate (7).—To 2.0 g (6.9 mmol) of 3-oxo-17β-hydroxy-(5α)-androstane, 6.0 g (32 mmol) of *p*-toluenesulfonyl chloride and 40 cc of dry pyridine were added. The reaction mixture was heated for 4 days at 48°, according to the method of Elks and Shoppee.[11] Upon cooling of the reaction mixture and addition of 15 cc of water, a solid separated which was washed successively with water, 1 *N* hydrochloric acid, and water and then recrystallized from acetone to give 2.8 g (90.9% yield) of the intermediate compound, 3-oxo-17β-*p*-toluenesulfonyl-(5α)-androstane as needles, mp 180–181°. The infrared spectrum showed absorptions at 2910 and 2860 (C–H), 1700 (six-membered cyclic C=O), 1340 and 1165 (S=O), and 960 cm^{-1} (S–O–C). The nmr spectrum showed a two-proton crude doublet at τ 2.24 (J = 8 cps, aromatic 3′ protons), a two-proton crude doublet at τ 2.70 (J = 8 cps, aromatic 2′ protons), a one-proton triplet at τ 5.75 (J = 8 cps, 17α-methyne proton), a three-proton singlet at τ 7.56 (aromatic methyl protons), a 22-proton complex multiplet at τ 8.53 ± 1.09 (methylene and methyne protons), a three-proton singlet at τ 9.01 (C-19 methyl protons), and a three-proton singlet at τ 9.19 (C-18 methyl protons).

The intermediate tosylate (1.8 g) was allowed to react with 2.1 g (32 mmol) of sodium azide in 25 cc of absolute ethanol and 2 cc of water. The reaction mixture was heated in a sealed tube for 18 hr at 130°. Upon cooling of the reaction mixture, 25 cc of water and 100 cc of chloroform were added. After evaporation of the chloroform layer, an oil was obtained. Upon addition of *n*-hexane to the oil, a solid separated which was shown to be unreacted starting material by comparison of its infrared spectrum with that of the starting material. Evaporation of the hexane filtrate gave an oil of 1.2 g (95.5% yield) of the crude intermediate compound, 3-oxo-17α-azido-(5α)-androstane, which was used without further purification. The infrared spectrum (thin film on sodium chloride) showed absorptions at 2930 and 2870 (C–H), 2100 (N=N), 1710 (six-membered cyclic C=O), and 1440 cm^{-1} (C–H, b).

The crude intermediate compound, 3-oxo-17α-azido-(5α)-androstane (1.25 g), was allowed to react with 1.6 g (22.8 mmol) of hydroxylamine hydrochloride in 25 cc of ethanol and 2 cc of pyridine. The reaction mixture was heated under reflux for 4 hr. Upon evaporation of the solvent, a solid separated. After washing of the solid with 20 cc of water, 1.24 g (94.1% yield) of the crude intermediate compound, 3-hydroxyamino-17α-azido-(5α)-androstane, was obtained and was utilized without further purification. The infrared spectrum showed absorptions at 3280 (O–H), 2920 (C–H), 2110 (N=N), 1650 (C=N), 1440 (C–H, b), and 960 cm^{-1} (N–OH).

The crude intermediate compound, 3-hydroxyamino-17α-azido-(5α)-androstane (1.24 g), was added to 50 cc of glacial acetic acid, and 0.25 g of platinum oxide was added. The reduction of the 3-oxime to the 3α-amine and the corresponding reduction of the azide to the amine were carried out under a hydrogen atmosphere in a Parr shaker for 20 hr at 36 psi. After filtration of the catalyst and evaporation of the solvent, an oil separated which was dissolved in a blend of 50:50 chloroform–1 *N* hydrochloric acid. Upon separation of the aqueous layer and addition of excess sodium hydroxide, a solid separated which was extracted with chloroform. After evaporation of the chloroform layer, the free amine was obtained as an oil. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 0.07 g (5.0% yield) of 3α,17α-diamino-(5α)-androstane dihydrochloride monohydrate (7), mp 370° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 3460 (primary $\overset{+}{N}$–H), 2920 (C–H), 2040 ($\overset{+}{N}H_3$, b), 1600 (N–H, b), 1510 (N–H, b), and 1440 cm^{-1} (C–H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.66 ± 0.28 (N-methyne protons), a 22-proton complex multiplet at τ 8.42 ± 1.05 (methylene and methyne protons), and a six-proton singlet at τ 9.11 (C-18, C-19 methyl protons).

Anal. Calcd for $C_{19}H_{36}N_2Cl_2 \cdot H_2O$: C, 59.82; H, 10.04. Found: C, 59.67; H, 10.27.

(10) (a) L. Ruzicka, P. Meister, and V. Prelog, *Helv. Chim. Acta*, **30**, 867 (1947); (b) P. Crabbe, M. J. Durazo, R. M. Salama, and P. G. Holton, *Bull. Soc. Chim. Belg.*, **71**, 203 (1962).

(11) J. Elks and C. W. Shoppee, *J. Chem. Soc.*, 241 (1953).

3β-N,N-Dimethylamino-17β-amino-(5α)-androstane Dihydrochloride Monohydrate (8).—To 1.5 g (4.1 mmol) of **1**, 1.5 g (22 mmol) of hydroxylamine hydrochloride, 2 cc of pyridine, and 60 cc of ethanol were added. The reaction mixture was refluxed for 1 hr, during which time a white solid separated. After evaporation of the solvent and washing with water, the solid was dried to give 1.2 g (78% yield) of the crude intermediate compound, 3β-dimethylamino-17-hydroxyamino-(5α)-androstane hydrochloride, which was used without further purification. The infrared spectrum (Nujol mull) showed absorptions at 3280 (O-H), 2620 (tertiary $\overset{+}{N}$-H, b), 1670 (C=N), and 930 cm^{-1} (N-OH).

The crude intermediate compound (1.12 g) was added to 200 cc of *n*-amyl alcohol. The oxime was reduced with 12 g of sodium in boiling *n*-amyl alcohol according to the method of Dodgson and Haworth.[5] After acidification with hydrochloric acid and evaporation of the solvent, a solid separated. The solid was dissolved in hot water and excess sodium hydroxide was added; the solid which separated was extracted with chloroform. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 0.62 g (50.1% yield) of 3β-N,N-dimethylamino-17β-amino-(5α)-androstane dihydrochloride monohydrate (**8**), mp 360° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 3400 (primary $\overset{+}{N}$-H), 2870 (C-H), 2690 (tertiary $\overset{+}{N}$-H), 2070 ($\overset{+}{N}H_3$, b), 1610 (N-H, b), 1515 (N-H, b), and 1460 cm^{-1} (C-H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.87 ± 0.37 (N-methyne protons), a six-proton singlet at τ 7.18 (N-methyl protons), a 22-proton complex multiplet at τ 8.51 ± 0.76 (methylene and methyne protons), a three-proton singlet at τ 9.17 (C-19 methyl protons), and a three-proton singlet at τ 9.20 (C-18 methyl protons).

Anal. Calcd for $C_{21}H_{40}N_2Cl_2 \cdot H_2O$: C, 61.59; H, 10.34. Found: C, 61.64; H, 10.43.

3β-N,N-Dimethylamino-17α-amino-(5α)-androstane Dihydrochloride Monohydrate (9).—The crude intermediate compound (1.30 g), 3-oxo-17α-azido-(5α)-androstane, described in the preparation of **7** was allowed to react with 3.35 g (41 mmol) of dimethylamine hydrochloride, 1 cc of triethylamine, 1.0 g of 10% palladized charcoal, and 125 cc of ethanol. The reductive condensation and azide reduction was carried out in a Parr shaker under hydrogen atmosphere for 42 hr at 36 psi. After filtration of the catalyst and evaporation of the solvent, a solid separated. The solid was dissolved in hot water and excess sodium hydroxide was added; the solid which separated was extracted with ether. After evaporation of the ether layer, the free amine was obtained as an oil. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 0.20 g (11.9% yield) of 3β-N,N-dimethylamino-17α-amino-(5α)-androstane dihydrochloride monohydrate (**9**), mp 316° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region from 200–300 mμ. The infrared spectrum showed absorptions at 3480 (primary $\overset{+}{N}$-H), 2940 (C-H), 2680 (tertiary $\overset{+}{N}$-H, b), 2110 ($\overset{+}{N}H_3$, b), 1640 (N-H, b), 1510 (N-H, b), and 1440 cm^{-1} (C-H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.81 ± 0.40 (N-methyne protons), a six-proton singlet at τ 7.18 (N-methyl protons), a 22-proton complex multiplet at τ 8.43 ± 0.94 (methylene and methyne protons), and a six-proton singlet at τ 9.17 (C-18, C-29 methyl protons).

Anal. Calcd for $C_{21}H_{40}N_2Cl_2 \cdot H_2O$: C, 61.59; H, 10.34. Found: C, 61.47; H, 10.16.

3β,17β-Bis(dimethylamino)-(5α)-androstane Dihydrochloride (10).—To 3.86 g (10.4 mmol) of **5**, 50 cc of water was added, and the pH was adjusted to 7.0 with aqueous sodium hydroxide. The methylation was accomplished by reductive condensation with 71 g (850 mmol) of 37% formaldehyde solution and hydrogen in the presence of 1.0 g of 10% palladized charcoal in a total volume of 150 cc. The reaction was carried out in a Parr shaker for 40 hr at 36 psi. After filtration of the catalyst and evaporation of the solvent, a solid separated. The solid was dissolved in hot water and excess sodium hydroxide was added; the solid which separated was extracted with ether. After evaporation of the ether layer, the free amine was obtained as an oil. Upon addition of hydrochloric acid, a solid separated which was recrystallized from ethanol–acetone to give 2.54 g (58.5% yield) of 3β,17β-bis(dimethylamino)-(5α)-androstane dihydrochloride (**10**), mp >370° dec (lit.[4] >360° dec). The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region from 200–300 mμ. The infrared spectrum showed absorptions at 2930 (C-H), 2560 and 2460 (tertiary $\overset{+}{N}$-H 1470 (N-H, b), and 1440 cm^{-1} (C-H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.93 ± 0.33 (N-methyne protons), a six-proton singlet at τ 7.19 (17 N-methyl protons), a 22-proton complex multiplet at τ 8.40 ± 0.92 (methylene and methyne protons), a three-proton singlet at τ 9.10 (C-19 methyl protons), and a three-proton singlet at τ 9.19 (C-18 methyl protons).

Anal. Calcd for $C_{23}H_{44}N_2Cl_2$: C, 65.86; H, 10.57. Found: C, 65.89; H, 10.63.

Compound **10** was also prepared by another route. To 5.00 g (17.3 mmol) of 3,17-dioxo-(5α)-androstane, 100 cc of ethanol, 2 cc of triethylamine, and 1.0 g of palladized charcoal were added. The reductive condensation reaction was carried out in a Parr shaker under hydrogen atmosphere for 25 hr at 36 psi. After filtration of the catalyst and evaporation of the solvent, a solid separated which was dissolved in a blend of 50:50 chloroform–1 hydrochloric acid. The organic layer was saved for subsequent work-up, and yielded **1**. Upon separation of the aqueous layer and addition of excess sodium hydroxide, the basic solution was extracted with ether. After evaporation of the ether layer, the free amine was obtained as an oil. The oil was dissolved in acetone and excess hydrochloric acid was added. A solid separated which was recrystallized from ethanol–acetone to give 0.10 g (1.4% yield) of 3β,17β-bis(dimethylamino)-(5α)-androstane dihydrochloride (**10**), mp >370° dec. The melting point and infrared and nmr spectra were found to be identical with those of the material prepared by the method described above.

3β,17α-Bis(dimethylamino)-(5α)-androstane Dihydrochloride (11).—Using the method described for **10**, 0.125 g (0.30 mmol) of **9** was allowed to react to give 0.047 g (42.3% yield) of 3β,17α-bis(dimethylamino)-(5α)-androstane dichloride (**11**), mp 313° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 2940 (C-H), 2580 and 2470 (tertiary $\overset{+}{N}$-H, b), 1710 (N-H, b), 1640 (N-H, b), and 1470 cm^{-1} (C-H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.77 ± 0.33 (N-methyne protons), a 12-proton singlet at τ 7.12 (N-methyl protons), a 22-proton complex multiplet at τ 8.57 ± 1.02 (methylene and methyne protons), a three-proton singlet at τ 9.11 (C-19 methyl protons), and a three-proton singlet at τ 9.16 (C-18 methyl protons).

Anal. Calcd for $C_{23}H_{44}N_2Cl_2$: C, 65.86; H, 10.57. Found: C, 65.96; H, 10.62.

3α,17β-Bis(dimethylamino)-(5α)-androstane Dihydrochloride Monohydrate (12).—Using the method described for **10**, 1.40 g (3.5 mmol) of **6** was allowed to react to give 0.56 g (36.6% yield) of 3α,17β-bis(dimethylamino)-(5α)-androstane dihydrochloride monohydrate (**12**), mp 287° dec. The ORD of the sample (2.5×10^{-3} *M* in water) gave a very slight positive plain curve in the region of 200–300 mμ. The infrared spectrum showed absorptions at 2930 (C-H), 2650 and 2480 (tertiary $\overset{+}{N}$-H), 1630 (N-H, b), and 1450 cm^{-1} (C-H, b). The nmr spectrum showed a two-proton complex multiplet at τ 6.90 ± 0.37 (N-methyne protons), a 12-proton singlet at τ 7.07 (N-methyl protons), a 22-proton complex multiplet at τ 8.42 ± 0.95 (methylene and methyne protons), a three-proton singlet at τ 9.08 (C-19 methyl protons), and a three-proton singlet at τ 9.12 (C-18 methyl protons).

Anal. Calcd for $C_{23}H_{44}N_2Cl_2 \cdot H_2O$: C, 63.14; H, 10.60. Found: C, 63.07; H, 10.79.

Registry No.—**1**, 25383-09-9; **2**, 25383-11-3; **3**, 25383-12-4; **4**, 25383-13-5; **5**, 14968-31-1; **6**, 25383-15-7; **7**, 25383-16-8; **8**, 25383-18-0; **9**, 25383-19-1; **10**, 14967-50-1; **11**, 25383-21-5; **12**, 25383-22-6; 3α-*p*-toluenesulfonyl-17-oxo-5α-androstane, 25383-10-2; 3-oxo-17β-*p*-toluenesulfonyl-5α-androstane, 25383-17-9.

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Structures and Reactions of Condensation Products of Benzaldehyde and Acetoacetic Ester

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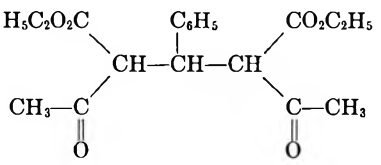
The configurations of the three known isomers of 1-methyl-3-phenyl-1-cyclohexanol-5-one-2,4-dicarboxylate esters are assigned on the basis of nmr spectra. The predominant condensation product has all equatorial substituents except hydroxyl. The next highest yield product has an axial 2-carbomethoxy and an axial hydroxyl group; other groups are equatorial. The minor product has an axial 1-methyl and an axial 2-carbomethoxy group. In the nmr spectrum of the first product, long-range coupling to the hydroxyl proton is observed. The large magnitude of this four-bond coupling to the hydroxy proton is considered the result of a preferential hydrogen-bonded conformation which holds the coupled protons in the W conformation. A mechanism is proposed for the unusual base-catalyzed loss of the 4-carbomethoxy and 1-hydroxyl functions which accounts for the fact that the first two isomers undergo this reaction much more readily than the third isomer.

The somewhat acrimonious history of the reaction products from the condensation of acetoacetic ester and benzaldehyde began in 1885 when Hantzsch[1] isolated a product, mp 149–150°, from the reaction the structure of which he considered to be **1**. Some time later Knoevenagel[2] also proposed **1** as the structure of the product. In those days of difficult structure proof, Schiff[3] first considered structure **2** for the same material.



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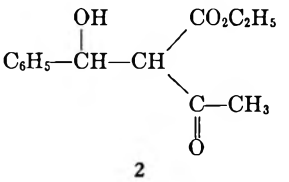

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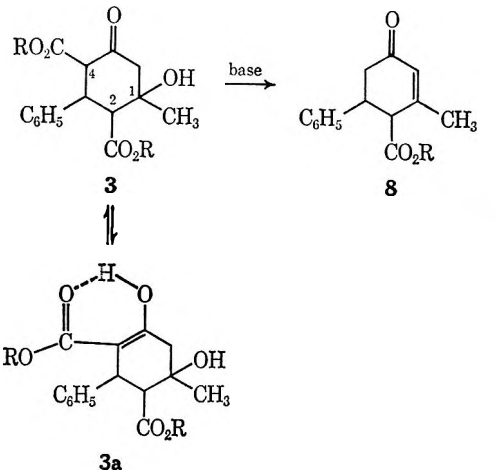
Later Schiff isolated three isomeric products from the condensation, mp 150, 134, and 120°, which he then considered to be the three isomers of **1**.

Rabe[4–9] began an extensive series of investigations of the condensation, in which he criticized Schiff on the basis that some of Schiff's materials were actually mixtures. Rabe gave 150, 154, and 107–108° as the melting points of the three isomers of **1** which he termed β_1, β_2, and β_3. Later Rabe realized that these compounds were cyclic and proposed structure **3**, which would demand the existence of eight diastereomers.[5,6] The cyclic nature of the products is generally accepted[10–12] and is consistent with the nmr data reported herein.

It was the purpose of this study to elucidate the configurations of the three known isomers and to study the very interesting reaction shown in eq 1.[8,9] Rabe and



(1)

coworkers were also able to separate the enols **3a** of the three isomeric ketones. These enols were shown to revert to their respective original ketones without additional isomerization. The reason for the specificity of the enolization–ketonization process was not investigated by Rabe, but becomes apparent upon proof of the configurations of **3**, as explained below.

Results and Discussion

The ethyl esters were rather inconvenient for nmr analysis, and therefore the methyl esters were prepared by reaction of methyl acetoacetate and benzaldehyde catalyzed by piperidine. The main product **4** (usually about 65% of theoretical), mp 189.5–190.5°, was shown to be analogous to β_1 by nmr and infrared spectra. The second product **5** (usually 5–10%), mp 175.5–176.1°, was similar to β_2. A third product, **8** (R = CH_3), mp

(1) R. Hantzsch, *Chem. Ber.*, **18**, 2579 (1835).
(2) E. Knoevenagel, *ibid.*, **31**, 738 (1898).
(3) R. Schiff, *ibid.*, **31**, 105 (1898); **32**, 332 (1899).
(4) P. Rabe, *Justus Liebigs Ann. Chem.*, **313**, 129 (1900).
(5) P. Rabe and F. Elze, *ibid.*, **323**, 83 (1902).
(6) (a) P. Rabe, *ibid.*, **332**, 1 (1904). (b) P. Rabe and F. Rahm, *ibid.*, **332**, 10 (1904).
(7) P. Rabe and F. Billmann, *ibid.*, **332**, 22 (1904).
(8) (a) R. Rabe and D. Spence, *ibid.*, **342**, 327 (1906). (b) P. Rabe and F. Rahm, *Chem. Ber.*, **38**, 970 (1905).
(9) W. Dieckmann, *Chem. Ber.*, **44**, 975 (1911); **45**, 2609 (1912).
(10) (a) B. D. Wilson, *J. Org. Chem.*, **28**, 314 (1963). (b) D. F. Martin, M. Shamma, and W. C. Fernelius, *J. Amer. Chem. Soc.*, **80**, 5851 (1958).
(11) (a) J. K. O'Loane, C. M. Combs, and R. L. Griffith, *J. Org. Chem.*, **29**, 1730 (1963). (b) I. L. Finar, *J. Chem. Soc.*, 674 (1961).
(12) A. Dunlop and F. Peters, "The Furans," Reinhold, New York, N. Y., 1963, p 613.

TABLE I

NMR PARAMETERS[a] FOR 4–9

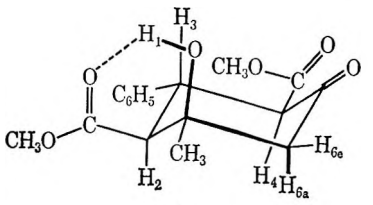
Compd	Chemical shifts, ppm							Coupling constants,[b] Hz				
	H_1	H_2	H_3	H_4	H_{6a}	H_{5e}	CH_3	$J_{1,6a}$	$J_{2,3}$	$J_{3,4}$	$J_{2,6e}$	$J_{6a,6e}$
4	3.56	3.05	4.00	3.70	2.51	2.69	1.32	2.4	12.2	12.4		14.2
5	...[c]	3.04	4.22	4.60	3.32	2.47	1.32		4.9	13.1	1.6	14.6
6[d]	2.01	3.53	2.71	4.87	*Ca.* 2.97[c]	2.38	1.09		5.2	13.2	1.4	13.2
7	3.95	3.36	3.91	3.78	2.47	2.65	1.20	2.2	11.0	12.0		14.2

	Chemical shifts, ppm						Coupling constants,[b] Hz						
	H_2	H_4	H_5	H_{6a}	H_{6e}	CH_3	$J_{6a,6e}$	J_{2,CH_3}	$J_{2,4}$	J_{4,CH_3}	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$
8[d]	5.93	3.23	3.46	2.31	2.34	1.55	16.4	1.2	0.4	1.2	9.1	12.4	3.7
9[d]	5.86	3.28	4.08	3.56		1.51		1.2	1.3	1.3	11.2	13.4	

[a] All 100 MHz; the parameters were varied until the California Computer Products plot of the computer calculated (LAOCOON program) spectrum was superimposible on the original spectrum. [b] The sign of the coupling constant is not implied. [c] Obscured by other peaks. [d] Solvent C_6D_6. All others, $CDCl_3$.

85.0–85.7° (about 5–10% in most runs), was the olefinic structure carefully elucidated by Dieckmann[9] and Rabe.[8] The third isomer **6**, mp 141–142°, proved to be very difficult to isolate, and eventually was obtained in minute yield as described in the Experimental Section.

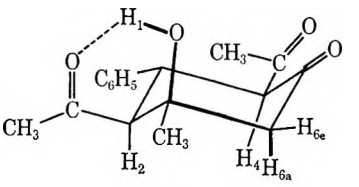
The 100-MHz spectral parameters of **4**–**6**, and **8** (R = CH_3) as duplicated by computer simulation, are recorded in Table I. Considering first of all the major product, **4**, the large coupling constants J_{23} and J_{31} (*ca.* 12 Hz) are clearly indicative of *trans* diaxial protons.[13–17] The large substituents at neighboring carbon then must occupy the preferred equatorial positions. *The hydroxyl proton was observed to be a doublet,* J = 2.4 Hz, coupled to the axial proton H_{6a}, the resonance of which appeared as a doublet of doublets. This is one of the few instances known of long-range coupling to hydroxyl.[18–20] As Figure 1 shows, one member of the hydroxyl doublet was obscured by the methoxyl absorption, but computer simulation proved it had to be present. Addition of deuterium oxide caused the disappearance of the hydroxyl doublet and concurrent simplification of the H_{6a} pattern.



4

The magnitude of the long-range coupling to the hydroxyl proton is substantially larger than other literature examples.[18–20] It is suggested that strong hydrogen bonding of the hydroxyl proton with the neighboring carbomethoxy function holds the hydroxyl proton in a conformation favorable for long-range coupling, namely the well-known W arrangement.[19,21] Thus, the observation of long-range coupling is strong evidence for an axial hydroxyl function. An equatorial hydroxyl group could not meet the geometric requirements considered necessary for a four-bond coupling of this magnitude.[18]

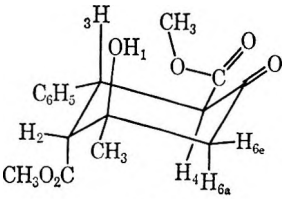
The predominant condensation product[22] of acetylacetone and benzaldehyde, **7**, clearly is very similar to



7

4. The resonance of the hydroxyl proton is again a doublet, coupled to H_{6a}. Again the hydroxyl doublet is eliminated on deuterium oxide addition and H_{6a} is simplified. In this case the hydroxyl absorption is not obscured by other absorptions, as Figure 2 shows.

Nmr evidence (Table I) indicates the second (ester) isomer, analogous to Rabe's β_2, to have structure **5**, in



5

which the C-2 carbomethoxy group is now axial. The magnitude of J_{34} = 13.1 Hz is indicative of *trans* diaxial protons. The smaller J_{23} = 4.9 Hz shows that these protons are *gauche*; H_2 is therefore equatorial. In moving from **4** to **5** the *ca.* 0.9-ppm downfield shift of the resonances ascribed to H_{6a} and H_4 is also consistent with the axial C-2 carbomethoxy group. The hydroxyl proton cannot hydrogen bond to the C-2 carbomethoxy group. Its resonance is markedly concentration sensitive. Since the hydroxyl proton is no longer conforma-

(13) N. C. Franklin, *Angew. Chem., Int. Ed. Engl.*, **4**, 774 (1965).

(14) A. A. Bothner-By, *Advan Magn. Resonance*, **1**, p 195; A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962).

(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 77–82.

(16) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964).

(17) See also R. A. B. Bannard, *Can. J. Chem.*, **44**, 775 (1966), and references cited therein.

(18) (a) J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. Driesen, *Tetrahedron Lett.*, 4363 (1967). (b) J. C. Jochims, W. Otting, A. Seeliger, and G. Taigel, *Chem. Ber.*, **102**, 255 (1969). (c) J. C. Jochims and G. Taigel, *Tetrahedron Lett.*, 5483 (1968).

(19) (a) C. W. Schoppee, F. P. Johnson, R. Lack, J. Shannon, and S. Sternhell, *Tetrahedron, Suppl.*, **8**, Part II, 421 (1966). (b) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, **87**, 302 (1965).

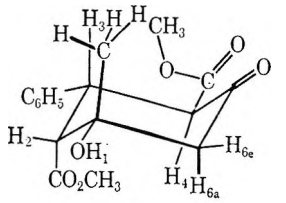
(20) See also (a) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964). (b) R. R. Fraser, M. Kaufman, P. Morand, and G. Gavil, *Can. J. Chem.*, **47**, 403 (1969). (c) C. P. Rader, *J. Amer. Chem. Soc.*, **91**, 3248 (1969). (d) E. F. Kiefer, W. Geriche, and S. Amimoto, *ibid.*, **90**, 6246 (1968).

(21) C. W. Jefford, J. Gunsher, and K. C. Ramey, *ibid.*, **87**, 4384 (1965).

(22) (a) R. Schiff, *Justus Liebigs Ann. Chem.*, **309**, 206 (1899). (b) E. Knoevenagel, *Chem. Ber.*, **36**, 2118 (1903).

tionally rigid, its resonance appears as a singlet. Weak π bonding to the ketone function is possible, however.[23]

The isomer isolated in smallest yield, **6**, has spectral parameters rather similar to **5**. We have no information whether **6** is similar to Rabe's β_3, since the latter was not available, but it seems likely the two are analogous. The magnitudes of the coupling constants again indicate *trans* diaxial protons H_3 and H_4 and *gauche* protons H_2 and H_3. Long-range coupling (J = 0.9 Hz) is observed between the methyl group at C-1 and the axial proton 6a. The W orientation is possible between H_{6a} and one of the three conformationally mobile protons of the axial methyl function. The assignment of the C-1 methyl as axial has several analogies to axial steroid angular methyl groups, in which long-range coupling is also observed.[19]



6

The chemical shift of the methyl group (δ 1.45 in $CDCl_3$) was also different from the corresponding group in **4** and **5** (both δ 1.32), which is consistent with their different configurations.[19] Unfortunately, too little of **6** was available to pursue hydrogen bonding studies; however, no long-range coupling involving hydroxyl was evident.

A nuclear Overhauser effect (NOE) experiment[24] was attempted in which the C-1 methyl group was irradiated and attempts were made to observe an increase in intensity of H_3, which is very close to the C-1 methyl in space. Based on peak heights, a 17% increase in intensity was observed for H_3. Integration showed only an 8% increase. Molecular models show that one *ortho* proton of the phenyl is also very close in space to H_3. Efficient relaxation of H_3 by this *ortho* proton prevents the expected >30% intensity increase on irradiation of methyl.

Thus, the yields of these three isomers parallels their stabilities. The major product, **4**, has all major groups equatorial save hydroxyl. The minor product, **5**, has an axial C-2 carbomethoxy function. The minute yield product, **6**, has axial C-1 methyl and C-2 carbomethoxy groups.[25]

As pointed out earlier, Rabe and coworkers were able to convert the ketones, β_1, β_2, and β_3, into their respective enols, which were termed α_1, α_2, and α_3. These enols stereospecifically ketonized to form the original ketone. In our hands, the base catalyzed enolization of **4** and **5** was also accompanied by formation of **8**, but generally speaking the observations of Rabe and coworkers are confirmed for these two compounds. In **4**–**6**, the C-4 carbomethoxy group is in the equatorial

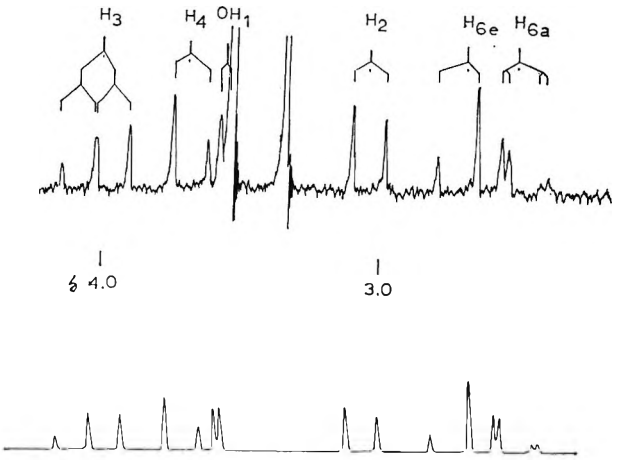


Figure 1.—Partial 100-MHz spectrum of condensation product, **4** and computer simulation of the spectrum.

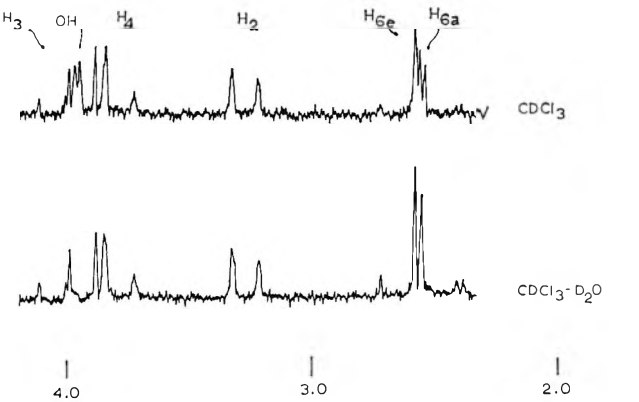
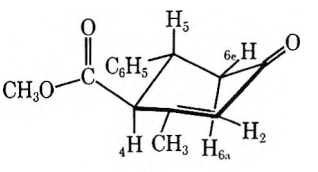


Figure 2.—Partial 100-MHz spectrum of the condensation product, **7**, of benzaldehyde and acetylacetone, showing the hydroxyl doublet and the collapse of long range coupling to H_6 on addition of D_2O.

position. Axial approach of a proton to the C-4 position of the enol then simply permits the C-4 carbomethoxy group to return to the favored equatorial orientation. Considerable precedent for this type of ketonization now exists.[26]

Base-Catalyzed Dehydration–Decarbomethoxylation.—In this unusual reaction the C-4 carbomethoxy group and the C-1 hydroxy group are lost, producing an α,β unsaturated ketone, **8**, as shown in eq 1.[8,9] Extensive long range coupling is observed in the nmr spectrum of **8** (Table I). However, it is clear that its structure is analogous to **4** with major groups equatorial or pseudoequatorial. In particular the large J_{45} = 9.1 and the pattern J_{56a} = 12.4, J_{56e} = 3.7 are consistent with *trans* diaxial protons 4 and 5, and therefore equatorial carbomethoxy and phenyl groups.[27]



8

In the **4** →→ **8** conversion, we feel that it is more than a coincidence that the C-1 carbomethoxy and the C-4

(23) L. Joris and P. Schleyer, *J. Amer. Chem. Soc.*, **90**, 4599 (1968).

(24) (a) F. A. L. Anet and A. J. R. Baum, *ibid.*, **87**, 3250 (1965). (b) J. G. Colson, P. T. Lansbury, and F. D. Saeva, *ibid.*, **89**, 7163 (1967).

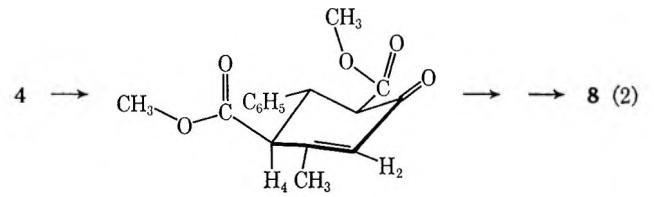
(25) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, pp 208, 236. Data in a cyclohexanone system is preferable, but not complete; N. L. Allinger, H. Blatter, L. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966), report a conformational free-energy preference of 1.4 kcal for the 3-methyl case.

(26) (a) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956). (b) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **81**, 4305 (1959), and earlier papers.

(27) H. L. Jakobsen, *Tetrahedron Lett.*, 1991 (1967).

hydroxyl functions are both eliminated. Observation of the course of reaction by nmr (in deuteriochloroform with *t*-butyl amine) and also by thin layer chromatography (sodium methoxide catalyst in methanol) revealed that **8** was formed virtually concurrent with the loss of **4**. Only a hint of an intermediate was discernible.

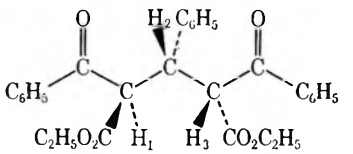
The pathway shown in eq 2 can be eliminated from consideration. The olefin **9** was prepared by acid-



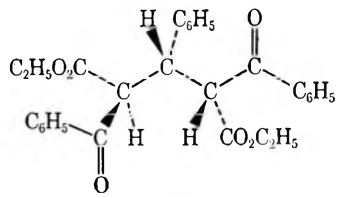
9

catalyzed dehydration[8] of **4**, and was shown by nmr (Table I) to have the same configuration at relevant centers as **4** and **8**. In parallel experiments, **9** did not form **8** during the same period in which **4** was smoothly converted to **8**.

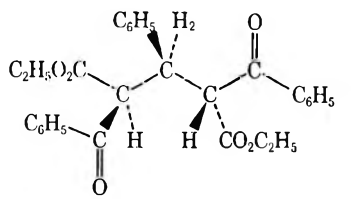
A number of other possible pathways should be considered. The cyclic structure, **4** could open and various types of decarboxylation and dehydration steps are possible, with subsequent recyclization occurring. Monitoring the course of the reaction by nmr revealed that no open-chain material was observable in the dehydration–decarbomethoxylation of **4**. A model compound, **10a**, was prepared, in which cyclization is not possible. In **10a** separate resonances were noted for



10a



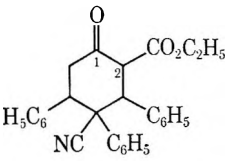
10b



10c

protons 1 and 3 and the two ethyl groups (J_{12} = 8.6 Hz, J_{23} = 9.3 Hz or *vice versa*). Thus **10a** is the *dl* isomer. Under conditions in which **4** smoothly formed **8**, **10a** apparently isomerized but did not decarboxylate. The 100 MHz spectrum of the equilibrated mixture, **10a**–**10c**, clearly showed the separate resonances of the *dl* and two *meso* isomers. The *dl* isomer **10a** was predominant (58 ± 5%), and the two *meso* isomers occurred in lesser amounts (27 and 15%). Although further assignments are extremely difficult, Stuart-Briegleb molecular models suggest that the C-2 phenylbenzoyl interactions would destabilize **10c**, and this *meso* isomer would probably be the minor product.

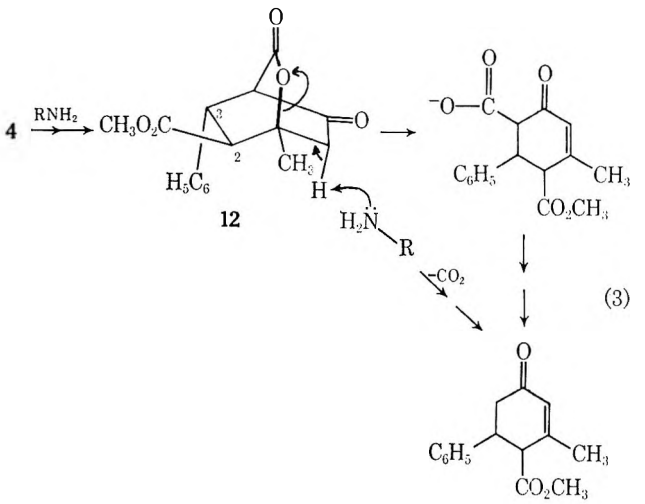
A second model compound, **11**, was prepared which



11

differed from **4**–**6** in the lack of the hydroxyl function. Again this model compound does not readily lose the carboethoxy function under conditions in which **4** reacts smoothly. Indeed the severe conditions necessary to condense phenylacetonitrile with ethyl cinnamate to form **11** (ethoxide catalyst at 140°) obviously do not involve the loss of the C-2 carboethoxy group. The literature reveals no examples of a decarboalkoxylation under the conditions in which **4** reacts.[28]

An attractive mechanism for the **4** → **8** conversion is shown in eq 3.

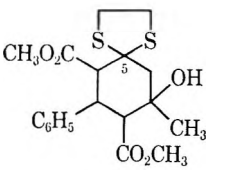


12

8

Formation of the bicyclic intermediate **12** has precedent from the work of Newman and coworkers.[29] A number of stable bicyclic lactones are known from the work of Perkin,[30] but the present intermediate, **12**, must be short lived, since no sizable resonance which could be assigned to **12** was visible in the nmr spectrum.

In an attempt to isolate a bicyclic lactone similar to **12**, **13** was subjected to the reaction conditions used for



13

(28) (a) F. Elsinger, *Org. Syn.*, **45**, 7 (1964). (b) P. Bavin, *Can. J. Chem.*, **38**, 882 (1960). (c) F. Bohlmann, *Chem. Ber.*, **89**, 792 (1956). (d) K. Campbell, J. Corrigan, and B. Campbell, *J. Org. Chem.*, **16**, 1712 (1951).

(29) (a) M. S. Newman and S. Mladenoric, *J. Amer. Chem. Soc.*, **88**, 4523 (1966), and many related papers. (b) See also D. S. Noyce and H. J. Weingarten, *ibid.*, **79**, 3093 (1957).

(30) W. Perkin, Jr., *J. Chem. Soc.*, **85**, 654 (1904).

the **4** → **8** conversion. Only starting material was recovered. The increased steric bulk at C-5 may prevent closure to the bicyclic lactone.

The second cyclohexanone isomer, **5**, also undergoes the dehydration–decarbomethoxylation reaction, although more slowly than **4**. The formation of a bicyclic lactone would be hindered by the eclipsing of the C-2 carbomethoxy and the C-3 phenyl groups. Under mild conditions, the olefin **8** is again the predominant product. The stereochemistry at C-2 in **8** (pseudoequatorial) is the opposite of that in **5** (axial); thus an isomerization must have occurred. Under the reaction conditions (*t*-butylamine catalyst in deuteriochloroform at 57°) **5** did not isomerize to **4**. Monitoring the course of the reaction by thin layer chromatography showed that the precursors of **8** were other probable olefins of similar general structure.

The minor product, **6**, did not undergo the dehydration–decarboxylation reaction under conditions in which **4** reacted smoothly. The *trans* C-1 hydroxyl and C-4 carbomethoxy groups are incapable of reacting to form a bicyclic lactone.

Experimental Section

Preparation of β_1 and β_2.—These materials were prepared by the method of Rabe. The product mixture was separated by crystallization and by chromatography on silica gel (Baker). The intramolecularly hydrogen bonded isomer, β_1, was eluted first with a few per cent ether in benzene solution. The isomer, β_1, was recrystallized twice from ethanol–methylene chloride yielding needles: mp 156.0–156.5°, lit.[8] 149–150°; ir (CH_2Cl_2) 3580 (weak) and 3480 (OH), 1745, 1720, 1455, 1375, 1345, 1205, 1185, 1160, 1035, 1025, 990, and 910 cm^{-1}. The hydroxyl absorptions changed very slightly on dilution. The nmr spectrum was very similar to that of **4** (Figure 1). The second isomer, β_2, was eluted immediately after β_1, and was recrystallized twice from ethanol: mp 154.3–156.8°, lit.[8] 150°; ir (CH_2Cl_2) 3580 and 3470 (OH), 1740, 1720, 1450, 1370, 1345, 1330, 1185, 1160, 1140, 1035, 925, and 910 cm^{-1}. The second hydroxyl absorption diminished in intensity upon dilution. The nmr spectrum was very similar to that of **5** (Table I). In several runs, although Rabe's procedure was followed as closely as possible, β_3 could not be separated.

Preparation of 4, 5, and 6.—These materials were prepared similarly to β_1 and β_2. To 137 g of methyl acetoacetate (1.18 mol) plus 58 g of benzaldehyde (0.55 mol), 1.0 ml of piperidine was added and the solution allowed to stand overnight. The resulting dense solid was broken up and triturated with two 200-ml portions of ether, and filtered. The solid was triturated again with two 200-ml portions of warm ethanol and filtered. A portion of the remaining solid, **4**, 216 g, mp 186–189°, was recrystallized twice from chloroform–ethanol: mp 189.5–190.5° lit.[9] 183°; ir (CH_2Cl_2) 3600 (w) and 3515 (OH), 1755, 1725, 1435, 1370, 1355, 1210, 1160, 1075, 1030, 990, and 950 cm^{-1}. A slight change occurred in relative intensity of the hydroxyl absorptions upon dilution. The ethanol filtrate yielded additional **4** upon evaporation. The ether filtrate produced **5** on evaporation, mp 172–173°. This material was recrystallized twice from ethanol: mp 175.5–176.1°; 7.8 g; ir (CH_2Cl_2) 3600 (OH), 1745, 1720, 1430, 1350, 1335, 1190, 1155, 1135, 1055, 1025, 990, and 970. The hydroxyl absorption was unchanged upon dilution.

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.70; H, 6.25. Found: C, 63.75; H, 6.27.

Upon further evaporation, **8** was deposited: mp 85.0–85.7°, lit.[9] 87°; 7.0 g.

All remaining solutions were recombined and chromatographed on a 2 × 30 cm silica gel column. The hexane eluents were unreacted starting materials and methyl benzalacetoacetate (**14**). With increasing quantities of benzene in hexane, other oils were eluted, probably the mixed isomers of **1** (methyl esters), which could not be separated. Small amounts of additional **8** were then eluted. In this particular run, *ca.* 0.1 g of an unknown material, mp 124.0–124.7°, was eluted (5% ether in benzene) originally thought to be **6**. However, this material was analyzed for $C_{15}H_{16}O_4$ and showed a mass spectrometric molecular ion at *m/e* 260.

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.30; H, 6.19. Found: C, 69.24; H, 6.29.

The nmr of this compound showed a vinyl multiplet at δ 6.07, coupled to a methyl doublet at δ 1.91. An ABX pattern was observed with J_{AB} = 15.5 Hz and chemical shifts of *ca.* δ 3.63, δ 3.32, and δ 2.62. The latter was also coupled to the vinyl proton with J = *ca.* 1.2 Hz. The preparation of this material could not be repeated.

The elusive material **6** was finally prepared by condensing carefully purified benzaldehyde and methyl acetoacetate with a trace of piperidine. In this case the condensation was only partially complete after a period of 10 days. The solid material was filtered off and triturated with slightly acidic ethanol as before. The combined filtrates were allowed to stand and several other crops of high melting products (**4** and **5**) were filtered off and checked by nmr (no **6**). After no more solid could be obtained, the ethanol was evaporated, the solution (about 30 ml) was dried ($MgSO_4$) and chromatographed on a 36 × 2 in. column of Florisil. The petroleum ether eluent contained starting materials and the olefins, **14**. With increasing quantities of benzene in petroleum ether, materials, very likely the open-chain isomers, **1** (methyl esters) were eluted, as well as **8**. Finally several oily fractions were obtained, whose nmr spectra, however, indicated bad mixtures of materials of the general structure as shown in eq 1. From these combined oils, only **4** could be crystallized, probably from conversion of the enol **4a** to **4** itself. The remaining oils were rechromatographed on 1 × 18 in. column of silica gel. The fractions generally were similar to the previous attempts, however, the fractions eluted immediately prior to **4** (70% benzene in petroleum ether to 100% benzene) again showed methyls in the nmr spectrum at δ *ca.* 1, possibly indicative of **6** plus at least three other components. On long standing (1–2 weeks) crystals of **6** were deposited: mp 133–135°, mp 141.4–142.4° recrystallized from ether–hexane; 0.08 g; ir (0.5%, CH_2Cl_2) 3590, 1745, 1715, 1405, 1225, 1150, 1095, 1030, and 990 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.70; H, 6.25. Found: C, 63.71; H, 6.31.

Preparation of 7.—This material was prepared by the method of Schiff,[23] mp 170.2–170.7° (lit. 168°). No attempt was made to isolate additional isomers. This material also readily enolized on addition of pyridine.

Preparation of 8 (R = CH_3).—Treatment of **4** or **5** with any of a number of bases (*e.g.*, piperidine, *t*-butylamine, or sodium methoxide) smoothly produced **8**, which was separated from starting materials by chromatography on silica gel (**8** was eluted with about 60% benzene in petroleum ether), mp 85.0–85.7°, lit.[13] mp 87°. This material was also formed in the condensation to form **4** or **5**, or by treatment of β_1 or β_2 with sodium methoxide. The latter reaction involved a transesterification.

Preparation of 9.—To a solution of 10 g of **4** in 100 ml of benzene was added 1 g of toluenesulfonic acid and the mixture refluxed overnight. Solvent was removed by rotary evaporation and the solution was chromatographed on silica gel. The benzene in hexane fractions were a mixture of **8** and **9**, which were separated by crystallization, **9**, mp 134.5–135.2°, 0.4 g.

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.55; H, 5.99. Found: C, 67.54; H, 6.00.

Base-Catalyzed Reactions of 4, 5, 6, and 9.—In parallel experiments about 100 mg of **4** and **5** were placed in 1 ml of methanol and 20 drops of 1.6 *N* solution of sodium methoxide was added. On standing markedly yellow solutions were formed owing to enolization of the above. The progress of the reaction at room temperature was followed by thin layer chromatography; **4** rapidly produced **8** with only a hint of an intermediate being observed. The substrate **5** also formed **8**, though somewhat more slowly, and other olefinic materials of generally the same constitution as **8** were observed. On a preparative scale, these olefins were separated from **8**, but their nmr spectrum was not indicative of a pure compound. The spectrum did exhibit a large vinyl multiplet δ *ca.* 6, coupled to a doublet methyl, δ *ca.* 2, similar to but slightly different from that of **8**.

In other experiments **4** and **5** were treated with about 25 mol % *t*-butylamine in deuteriochloroform at *ca.* 55° over a period of 1 week. The reaction was followed by nmr. The absorptions of **4** were cleanly replaced by those of **8**. With **5**, a second material of almost identical resonances as **8** was evident.

On the other hand, **6** did not form any **8** when treated under

identical conditions. The enol of **6** appeared to form, similar to the reaction of **4**, but not of **5**; no other products were observed.

The substrate **9**, in the same period of time, isomerized to other materials of a larger R_f, but no **8** was evident by tlc. The product mixture was worked up by extraction into ether, and dried ($MgSO_4$). The nmr spectrum did not show the characteristic absorptions of **8**.

Preparation and Reaction of 10.—This material was prepared by the procedure of Ruheman:[31] mp 129–130°, lit. 131°; nmr (100 MHz, pyridine) δ *ca.* 7.5 (m, 15, aromatic protons), 5.86 (d, 1, J = 8.6 Hz, H_1 or H_3), 5.67 (d, 1, J = 9.3 Hz, H_3 or H_1), δ 5.30 (doublet of doublets, 1, H_2), *ca.* 3.9 (interspersed quartets, 4, O—CH_2—CH_3), *ca.* 0.9 (superposed triplets, 6, O-CH_2-CH_3). Treatment with *t*-butylamine in deuteriochloroform this material rapidly changes in part to two other materials with nmr absorptions in the same general regions as starting material. However no change in integration was evident during the period which **4** readily formed **8**. Upon work-up by adding to ether, extracting three times with H_2O, drying ($MgSO_4$), and evaporating, the same materials were evident, in the same proportions. Thus ethanol was not formed and no decarboxylation had occurred.

In pyridine at 100 MHz, the resonances of the three isomers were well separated: nmr of the major *meso* isomer, δ 5.72 (superposed d, 2, J = 7.8 Hz, H_1 and H_3), δ 5.18 (d of d, 1, H_2); minor *meso* isomer, δ 5.88 (superposed d, 2, J = 9.2 Hz, H_1 and H_3), 5.17 (d of d, 1, H_2).

Preparation of 11.—This material was prepared by the method of Erlenmeyer:[32] mp 205–206°, lit. 206°; nmr (60 MHz, $CDCl_3$) δ 7.09 (m, 15, aromatic protons), 4.57 (d, 1, J = 12.5 Hz, H_1), 4.08 (d, 1, J = 13.5 Hz, H_2), 4.02 (9, 2, J = 7.0 Hz, OCH_2-CH_3), *ca.* 3.87 (m, 1, H_{4e}), 3.53 (d of d, 1, $J_{4e,4a}$ = 14 Hz, H_{3a}), 3.92 (d of d, 1, $J_{3,4e}$ = 1.5 Hz, $J_{3,4a}$ = 12.5 Hz, H_3), 0.98 (t, 3, J = 7 Hz, O-CH_3-CH_3). Upon treatment of 0.25 g of **11** with 0.1 g of *t*-butylamine in chloroform at 69° for 3 weeks, followed by evaporation to dryness and very slow crystallization, 0.203 g of starting material was recovered. The remainder was a tar.

Preparation of 13.—A solution of 5.0 g of **4** and 1.4 g of ethanedithiol in 50 ml of methylene chloride was treated with 0.5 ml of 47% boron trifluoride–ether complex. An immediate precipitate was observed, but the mixture was allowed to stand for 2 wks. The solvent was evaporated and the mixture was mixed with water and methylene chloride. The organic extract was washed with dilute base twice, dilute HCl, and water and dried ($MgSO_4$). Upon evaporation needles of **13** were deposited, mp 180°. These were recrystallized from methylene chloride and from ethanol: mp 202–203°, mmp 180–190° with **4**; 2.89 g; nmr (60 MHz, $CDCl_3$) δ 7.18 (s, 5, aromatic protons), 3.87, (d, 1, J = 1.9 Hz, hydroxyl), 3.77 (*t*, 1, J = 11.7, H_3), 3.28 (s, 6, methoxyl), 3.17 (broad s, 4, ethylene bisthioketal protons), 3.16 (d, 1, J = 11.7, H_4), 2.66 (d, 1, J = 11.7, H_2), 2.62 (d, 1, J = −14.3, H_{6e}), 2.35 (d of d, 1, J = −14.3, J = 1.9, H_{6a}).

Anal. Calcd for $C_{19}H_{24}O_3S_2$: C, 57.55; H, 6.10. Found: C, 57.51; H, 5.98.

Registry No.—**4**, 24904-00-5; **5**, 24904-01-6; **6**, 24961-35-1; **7**, 24904-02-7; **8** (R = CH_3), 24904-03-8; **9**, 24904-04-9; **13**, 24904-05-0.

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Proximity Effects. Reactions of Lead Tetraacetate with 4- and 5-Phenylcyclooctanol[1]

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The reactions of lead tetraacetate with the *cis* and *trans* isomers of 4- and 5-phenylcyclooctanol were examined in order to establish the magnitude of the directive effect of the phenyl substituent on the direction of transannular cyclization leading to bicyclic ethers. As compared with 5-phenylpentanol previously reported, there is observed a marked enhancement in the amount of cyclization at the benzylic position with the *trans* isomers. Thus *trans*-5-phenylcyclooctanol yields 1-phenyl-9-oxabicyclo[3.3.1]nonane in 72% yield. Although cyclization at the benzylic position in the *cis* isomers is not possible, the products obtained with *cis*-4-phenylcyclooctanol suggest that the phenyl group is exerting a directive effect here also. The structures of the new compounds isolated in this study were established by synthesis.

A large amount of data is available on features of the lead tetraacetate oxidation of alcohols such as the effect of solvent and structural variations in the alcohol. One process which has been particularly well examined with acyclic and steroidal substrates involves the formation of cyclic ethers from alcohols containing methyl or methylene groups at the δ and ϵ positions relative to the hydroxyl group. Indeed this particular reaction has contributed greatly to the solution of certain problems in steroid synthesis such as the introduction of functionality into angular methyl groups.[3] The products are usually five-membered rather than six-membered cyclic ethers, although in some cases mixtures of the two have been isolated. The important step in the cyclization process is the transfer of a hydrogen atom from a nonactivated methylene or methyl group to the oxygen atom within an alkoxy radical intermediate *via* a six- or seven-membered transition state. There are some indications that the subsequent steps may involve the oxidation of the resulting carbon radical to a carbonium ion *via* a one-electron transfer to lead followed by a cyclization of the hydroxy group onto the carbonium ion to give the cyclic ethers (Scheme I).[3-5] A competing fragmentation reaction, formulated as proceeding from the same precursor as in the cyclization reaction, gives rise to carbonyl compounds, olefins, and acetates.

The reactions of some medium-ring alcohols with lead tetraacetate have been examined since it was of interest to determine what effect the proximity of the δ and ϵ methylene groups to the hydroxyl group would

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(2) (a) Deceased June 4, 1966. (b) To whom inquiries should be addressed at the Department of Chemistry, Queen's University, Belfast, Northern Ireland. (c) NIH Fellow, 1964–1968. (d) NIH Fellow, 1960–1964.

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SCHEME I

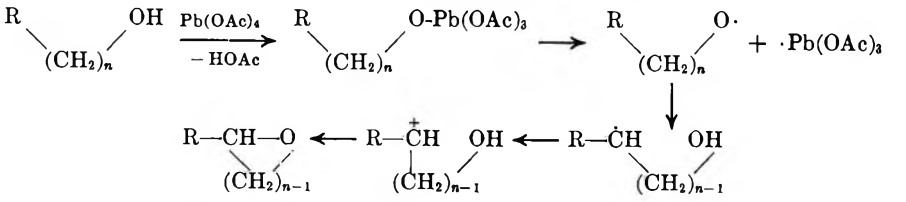
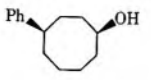
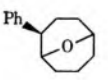
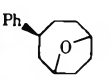
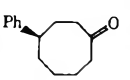
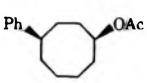
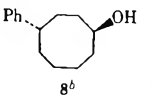
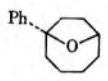
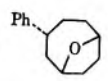
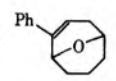
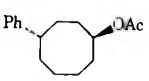
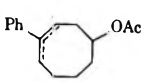
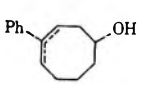
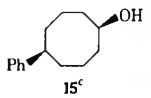
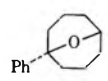
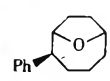
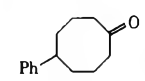
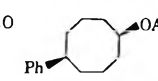
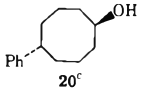
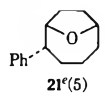
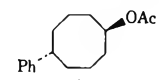


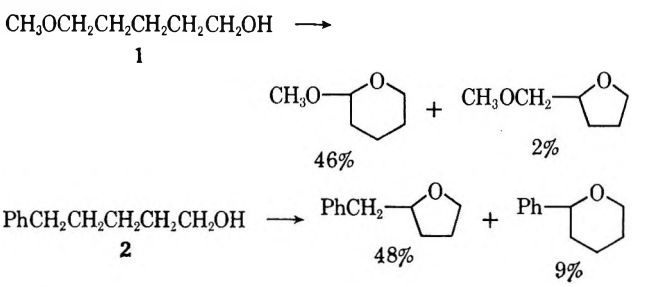
TABLE I

Alcohol	Products[a] (yield %)										
 3	 4(13)	 5(20)	 6(44)	 7(5)	3 (15)						
 8[b]	 9(18)	 10(8.5)	 11(6)	 12(5)	 13(3.5)	 14(15)	6 (10)	8 (28)			
 15[c]	 16(~1)	 17(54)	 18(~15)[d]	 19(7)	15 (3)						
 20[c]	16 (72)	 21[e](5)	 22(0.2)	18 (15)	20 (5)						

[a] Product distributions by vpc analysis. [b] Two unidentified compounds (3% each) were also formed in this reaction. [c] A compound with the infrared characteristics of an α-acetoxy ketone was also formed in this reaction. [d] This component was contaminated with a product having the same vpc retention time as 5-phenylcyclooctene oxide. [e] Identification based only on comparison of the vpc retention time with that of an authentic sample.

have on the direction and extent of the cyclization reaction. Cyclooctanol gave the 1,4-bridged ether, 9-oxabicyclo[4.2.1]nonane, in up to 36% yield together with a trace (0.8%) of the 1,5 isomer, 9-oxabicyclo-[3.3.1]nonane.[6,7] On the other hand, 1-methylcyclooctanol, under similar reaction conditions, gave a mixture of bicyclic ethers (23%) containing a preponderance of 1-methyl-9-oxabicyclo[3.3.1]nonane.[6a] Thus, introduction of the 1-methyl substituent may alter the conformation of the cyclooctane ring so as to favor the formation of a seven-membered transition state for hydrogen abstraction. Cyclodecanol is reported to give several bicyclic ethers (27.5%) although only one of these, *trans*-1,2-epoxycyclodecane, has been identified.[7] Irrespective of the direction of cyclization in this limited series, the yields are comparable with those obtained in the cyclization of simple acyclic alcohols with lead tetraacetate, suggesting that the proximity effects which play such a dominant role in transannular reactions are not important in the cyclization of medium-ring alcohols with lead tetraacetate.

Another feature of the reaction which is pertinent to the results presented in this paper emerges from an investigation of the influence of remote substituents on the direction of cyclization of acyclic alcohols. Placement of an ether grouping in the alcohol (as in 1) greatly enhances the amount of cyclization at the methylene group adjacent to the ether oxygen atom.[8] However, a phenyl substituent, similarly placed, appears to have little influence on the direction of cyclization as shown by the product distribution in the reaction of 5-phenyl-1-pentanol (2) with lead tetraacetate.[9,10]



In order to examine the directive effects of a phenyl group on the transannular cyclization of a medium-ring alcohol, we have studied the reactions of 4- and 5-phenylcyclooctanol with lead tetraacetate in benzene. The *cis* and *trans* isomers of each alcohol were prepared by the published methods[11,12] and the results are summarized in Table I. It is immediately clear that the phenyl substituent has a pronounced effect on both the direction and extent of transannular cyclization. For the case of *trans*-5-phenylcyclooctanol (**20**), abstraction of the ϵ (benzylic) hydrogen atom occurs much more readily than does abstraction of the δ hydrogen atom, in spite of the 2:1 statistical advantage of the latter and the requirement of a seven-membered transition state. In addition, the total yield of cyclized product (77%) is more than twice the highest yield

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(7) M. Lj. Mihailovic, Z. Cekovic, V. Andrejevic, R. Matic, and D. Jeremic, *Tetrahedron*, **24**, 4947 (1968).

(8) M. Lj. Mihailovic and M. Miloradovic, *ibid.*, **22**, 723 (1966).

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(10) M. Lj. Mihailovic, L. Zivkovic, Z. Maksimovic, D. Jeremic, Z. Cekovic, and R. Matic, *Tetrahedron*, **23**, 3095 (1967).

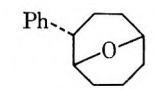
(11) A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **89**, 2932 (1967).

(12) A. C. Cope and R. B. Kinnel, *ibid.*, **88**, 752 (1966).

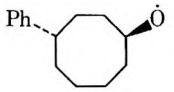
recorded for cyclooctanol. The yield of the bicyclic ether **17** obtained from *cis*-5-phenylcyclooctanol (**15**) is also good and the product results from abstraction of the δ hydrogen atom only; the ε hydrogen atom is inaccessible since it is *trans* to the oxygen atom in the alkoxy radical (the 1% of cyclization at the ε position is probably due to a trace of **20** present in **15** as an isomeric impurity). Both alcohols also give substantial amounts of the simple oxidation product, 5-phenylcyclooctanone (**18**).

The possibilities for cyclization with *cis*- and *trans*-4-phenylcyclooctanol are greater owing to their unsymmetrical structures; the *trans* isomer **8** possesses two types of δ hydrogen atoms, one of which is also benzylic. The ratio of the products **9** and **10** again demonstrates that the benzylic position is favored by a factor of 2:1 although the preference is much less than that shown with the *trans*-5 isomer. Although *endo*-2-phenyl-9-oxabicyclo[3.3.1]nonane (**23**), the product anticipated from cyclization at the ε position, had the same vpc retention time as **10**, it was judged to be present in not more than 0.85% yield on the basis of infrared and mass spectral evidence. The infrared spectrum of an authentic sample of **23** (*vide infra*) has a very strong absorption band at 1040 cm^{-1} which was not present in the spectrum of a sample of **10** collected from the crude reaction mixture. The mass spectrum of **23** had a peak at *m/e* 85 of intensity (55%) equal to that of a peak at *m/e* 91; the mass spectrum of **10**, on the other hand, contained a peak (100%) at *m/e* 91 and only a 10% peak at *m/e* 85. The interpretative difficulties with these reactions are well illustrated by the behavior of the *cis*-4 isomer **3**; in this case, the 1,5-bridged ether **4** constitutes 39% of the total amount of cyclized product. 4-Phenylcyclooctanone (**6**) is also formed in 44% yield.

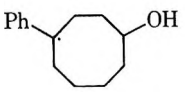
Three other products obtained from alcohol **8** can be rationalized in terms of transannular rearrangement of the alkoxy radical **24** to the carbon radical **25**. Oxidation of this latter species to the carbonium ion **26** fol-



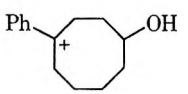
23



24



25

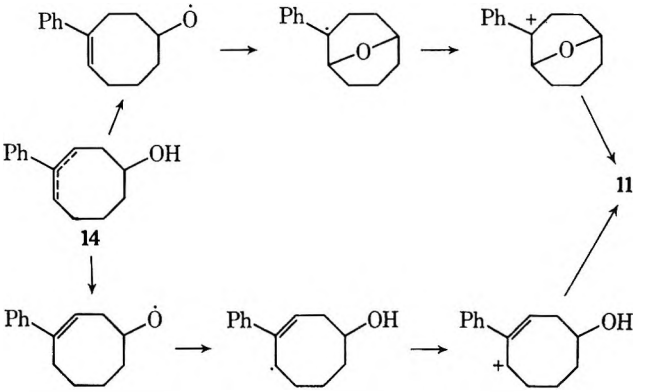


26

lowed by proton elimination could give the hydroxy–olefin mixture **14**. Further reaction of **14** with lead tetraacetate could then give the corresponding acetate mixture **13**. When a sample of **14** was subjected to the reaction conditions the product isolated was a mixture of **13**, two unidentified compounds, and the unsaturated bicyclic ether **11**; two possible mechanisms for the conversion of **14** into **11** are shown in Scheme II.[13] These secondary reactions consume lead tetraacetate and, therefore, the relatively large amount (28%) of the starting material in the product mixture is understandable.

(13) These mechanisms are derived from our earlier observation that transannular oxygen bridging occurs with great ease with various cyclooctenols; see ref 11 and literature cited therein. Yet another possibility, suggested by a referee, is that the unsaturated ether **11** is produced by reaction of **23** with lead tetraacetate. This possibility was not investigated.

SCHEME II

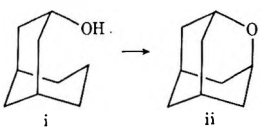


While it is not yet possible to interpret these results in conformational terms in the manner suggested for steroidal alcohols by Heusler and Kalvoda,[3,14] certain facts do emerge. The first of these is the demonstration that a phenyl substituent has a marked effect, at least with cyclooctanol, on the type of ether formed. This is most clearly seen by comparing the behavior of cyclooctanol, which gives only a trace of the 1,5-bridged ether, with *cis*-4-phenylcyclooctanol where the 1,5-bridged product constitutes 39% of the total amount of cyclization. Secondly, these results give the qualitative impression that the effects of the phenyl group depend on its position relative to the hydroxyl group. For example, nearly half of the total product from alcohol **8** are olefins, whereas no olefinic products are formed from the other three alcohols. It appears also that cyclization at the benzylic position is a much more facile process with alcohol **20** than with alcohol **8** in spite of the requirement of a seven-membered transition state in the former case. Proximity effects may play an important role here emphasizing the differences in behavior of medium-ring and acyclic alcohols.[15]

Identification of Products.—Compounds **6, 9, 16, 18, 19,** and **22** were identified by vpc and spectral comparisons with authentic samples; *cis*- and *trans*-4-

(14) These authors have compiled a considerable amount of data concerning the conformational requirements for intramolecular hydrogen abstraction by alkoxy radicals. They concluded that a six-membered chair form is the most favorable transition state. From studies involving steroidal alcohols, in which rigid conformations hold the internuclear distances nearly constant, certain trends could be discerned. These distances, as measured on Dreiding models, show that the optimum separation between the oxygen atom and the carbon bearing the hydrogen atom undergoing abstraction (called the C–O distance) in the alkoxy radical consistently lies between 2.5 and 2.7 Å. Within this range the rate of intramolecular abstraction far exceeds the rate of fragmentation or intermolecular reaction. As the C–O distance approaches 2.8 Å these trends tend to be reversed.

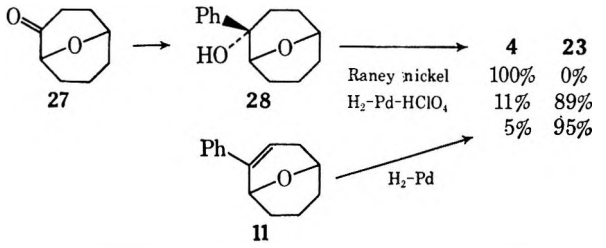
(15) (a) In certain favorable cases proximity effects may be responsible for the exclusive formation of 1,5-bridged ethers. For example, oxidation of *endo*-bicyclo[3.3.1]nonan-3-ol (i) with lead tetraacetate gives oxaadamantane (ii) in almost quantitative yield: M. Fisch, S. Smallcombe, J. C. Gramain, M. A. McKervy, and J. E. Anderson, *J. Org Chem.*, **35**, 1886 (1970). See also W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1965).



i ii

(b) The photochemically induced decomposition of 1-methylcyclooctyl hypochlorite proceeds *via* transannular radical rearrangements involving both the δ position (35%) and the ε position (24%). The hydrogen atoms at the single ε position are therefore about 1.4 times as reactive as those at the two δ positions in spite of the requirement of a seven-membered transition state for hydrogen abstraction from C–ε. A. C. Cope, R. S. Bly, M. M. Martin, and R. C. Petterson, *J. Amer. Chem. Soc.*, **87**, 3111 (1967). For similar effects in the transannular rearrangement of the 1-phenylcyclooctyloxy radical, see ref 11.

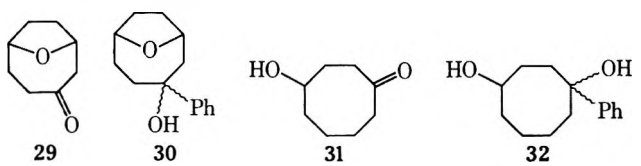
phenylcyclooctyl acetate (**7**) and (**12**) were prepared from the corresponding alcohols. The synthesis of *exo*- and *endo*-2-phenyl-9-oxabicyclo[3.3.1]nonane (**4**) and (**23**) was accomplished by the sequence outlined below. Treatment of 9-oxabicyclo[3.3.1]nonan-2-one



27 28 11

(**27**)[16] with phenyllithium in ether gave the crystalline tertiary alcohol **28**, mp 86–87.5°, which appeared to be homogeneous on vpc analysis. The phenyl group in **28** is assigned the *exo* configuration since addition of the organometallic reagent should occur from the less hindered side of the carbonyl group; the bridging oxygen atom may also play a part in controlling the direction of addition. Hydrogenolysis of **28** with Raney nickel in hot ethanol afforded a single product which was identical (vpc retention time and infrared spectrum) with the bicyclic ether **4** produced in 13% yield in the reaction of alcohol **3** with lead tetraacetate. This result is consistent with the known stereochemical tendencies of Raney nickel[17] in hydrogenolysis of benzyl alcohols and confirms the assignment of structure **28** to the tertiary alcohol. Compound **4** was also produced using palladium on carbon in ethyl acetate containing a trace of perchloric acid as the catalyst for hydrogenolysis of **28**. It was, however, the minor product. The major product was the epimeric bicyclic ether **23**. Dehydration of **28** with iodine in hot benzene gave a product which proved to be identical with the unsaturated bicyclic ether **11** isolated from the oxidation of alcohol **8**. Hydrogenation of **11** over palladium on carbon also gave the bicyclic ethers **4** and **23**.

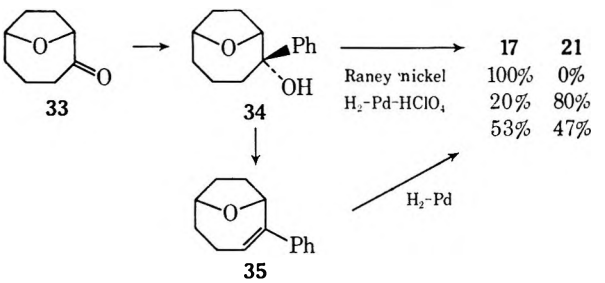
A similar scheme was used in the identification of *exo*- and *endo*-3-phenyl-9-oxabicyclo[4.2.1]nonane (**5**) and (**10**). Treatment of 9-oxabicyclo[4.2.1]nonan-3-one (**29**)[16,18] with phenyllithium in ether gave what



29 30 31 32

appeared to be a mixture of the epimeric alcohols **30**. These compounds were unstable to vpc analysis (dehydration occurred on an SE-30 column). Hydrogenolysis of the crude mixture employing Raney nickel in ethanol gave a monodeoxygenated product in excellent yield. Assuming that this reaction proceeded with retention of configuration (cf the hydrogenolysis of **28**), the product was expected to be a mixture of the *exo* and *endo* isomers. Efforts to achieve a separation by vpc analysis were unsuccessful although infrared analysis of the mixture did show the presence of both bicyclic ethers **5** and **10** which had been isolated from the lead tetraacetate oxidations of alcohols **3** and **8**, respectively. On the other hand, hydrogenolysis of **30** using palladium on carbon and perchloric acid gave a product which had an infrared spectrum identical with that of **5**. The remaining products from the reaction of *trans*-4-phenylcyclooctanol with lead tetraacetate were prepared from 4-hydroxycyclooctanone (**31**).[19] Treatment of this ketone with a large excess of phenylmagnesium bromide gave the diol mixture **32** which was subsequently dehydrated in benzene in the presence of iodine, yielding a mixture containing 90% **14** and 10% **9**. The unsaturated alcohol mixture **14** was identical (infrared and vpc analysis) with that obtained from alcohol **8**. Acteylation of **14** employing acetic anhydride in pyridine gave the acetate mixture **13**. Unlike the alcohols, these acetates could be resolved by vpc analysis (isomer ratio, 23:77).

The final synthetic sequence used in this work commenced with the preparation of the crystalline alcohol **34**, mp 93–93.5°, from 9-oxabicyclo[4.2.1]nonan-2-one (**33**)[16] and phenyllithium. Like alcohol **28**, the phenyl substituent in **34** is assigned the *exo* configuration and support for this was obtained from its behavior on Raney nickel hydrogenolysis. The product, which was



33 34 35

homogeneous on vpc analysis, had an infrared spectrum identical with that of the bicyclic ether **17** isolated in 54% yield from the lead tetraacetate reaction of alcohol **15**. Hydrogenolysis of **34** employing palladium on carbon and perchloric acid gave a mixture of bicyclic ethers containing **17** (20%) and **21** (80%) and these two compounds were also formed in about equal amounts when the unsaturated bicyclic ether **35**, obtained from **34** by dehydration, was hydrogenated on palladium.

Experimental Section

Melting points, determined using a Thomas–Hoover melting point apparatus, are uncorrected. Infrared data were obtained with a Perkin-Elmer Model 237 spectrophotometer. Vapor phase chromatography was performed using an F & M Model 720 instrument fitted with $^1/_4$-in. o.d. copper or stainless steel columns. The mass spectra were recorded using an Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. Microanalyses were performed by Dr. S. M. Nagy and associates at Massachusetts Institute of Technology.

exo-2-**Phenyl-9-oxabicyclo[3.3.1]nonan-2-ol** (**28**).—A solution of ketone **27** (525 mg) in ether (2 ml) was added to a stirred solution of phenyllithium prepared from bromobenzene (740 mg) and lithium (50 mg) in dry ether (10 ml) under nitrogen and the mixture was heated under reflux for 30 min. The cooled mixture was treated with saturated ammonium chloride solution and filtered. The ether solution was dried ($MgSO_4$) and concentrated, giving 470 mg of an oil. Vpc analysis (2 ft × 20% SE-30 at 195°) showed that the product was 95% pure. An analytical

(16) A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *J. Org. Chem.*, **34**, 2229 (1969).

(17) For a discussion of the sterochemistry of hydrogenolysis of some benzyl-type alcohols, see S. Mitsui, Y. Kudo, and M. Kobayashi, *Tetrahedron*, 1921 (1969), and references contained therein.

(18) A. C. Cope and B. C. Anderson, *J. Amer. Chem. Soc.*, **79**, 3892 (1957).

(19) We thank Badische Anilin und Soda Fabrik, Ludwigshafen, Germany, for a gernous gift of this material.

sample, obtained by preparative vpc, had mp 86–87.5° after crystallization from pentane; infrared (neat melt) 3375, 1035, 960, 900, 860, 760, and 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.47; H, 8.52.

2-Phenyl-9-oxabicyclo[3.3.1]non-2-ene (11).—A sample of the crude alcohol **28** (189 mg) in benzene (2.5 ml) containing a small crystal of iodine was heated under reflux for 6 hr. The cooled solution was washed with 10% sodium thiosulfate solution and dried ($MgSO_4$). Removal of the solvent gave 136 mg of **11** as an oil, *ca.* 90% pure by vpc analysis (2 ft × 20% SE-30 at 200°). An analytical sample was obtained by preparative vpc (8 ft × 10% Carbowax 20M at 245°): infrared (film) 1590, 1105, 1075, 1030, 1000, 915, 870, 865, 855, 750, and 690 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 200 (100, parent ion), 157 (36), 156 (38), 139 (30), 138 (38), 110 (31), 91 (27).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.91; H, 8.18.

endo-**2-Phenyl-9-oxabicyclo[3.3.1]nonane** (23).—To a solution of **11** (21.5 mg) in ethyl acetate (0.5 ml), 10% palladium on carbon (5 mg) was added. The solution was hydrogenated at atmospheric pressure for 1 hr. The catalyst was removed by filtration and the solution was analysed by vpc (5 ft × 5% XF-1150 at 175°). Two components, in the ratio 5:95, were present. A sample of the major component, assigned structure **23**, was obtained by preparative vpc: infrared (film) 1040, 990, 905, 870, and 690 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 104 (100), 91 (56), 85 (55), 39 (37).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 83.58; H, 8.79.

Hydrogenolysis of *exo*-2-Phenyl-9-oxabicyclo[3.3.1]nonan-2-ol (28). (a) **On Palladium.**—To a solution of **28** (10.6 mg) in ethyl acetate (250 μl) was added a few mg of 10% palladium on carbon. The solution was hydrogenated at atmospheric pressure for 2.5 hr. Vpc analysis indicated that little or no reaction had taken place. One drop of 70% perchloric acid was added to the solution and the hydrogenation was repeated. After 30 min the reaction was complete and vpc analysis (8 ft × 20% LAC-728 at 210°) of the solution showed the presence of the *endo* isomer **23** and the *exo* isomer **4** in the ratio of 89:11.

(b) **Raney Nickel.**—The alcohol (13 mg) was dissolved in absolute ethanol (0.5 ml) and commercial Raney nickel (100 mg) was added. The mixture was heated under reflux for 2 hr after which time vpc analysis (2 ft × 20% SE-30 at 195°) showed that reaction was complete. The cooled mixture was decanted into cold water and extracted with pentane. The pentane solution was washed with water, dried ($MgSO_4$), and concentrated, yielding an oil which contained a single component by vpc analysis (8 ft × 20% LAC-728 at 210°). A sample collected by preparative vpc was identical (infrared, retention time) with compound **4** obtained from the lead tetraacetate oxidation of *cis*-4-phenylcyclooctanol (**3**): infrared (film) 1500, 1470, 1080, 1030, 900, 865, 750, and 700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 202 (15, parent ion), 120 (12), 105 (38), 104 (100), 91 (18), 85 (15), 78 (10), 77 (31), 51 (16), 44 (44), 43 (10), 41 (14), 38 (11).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 82.87; H, 9.02.

exo- **and** *endo*-**3-Phenyl-9-oxabicyclo[4.2.1]nonane** (5) **and** (10).—9-Oxabicyclo[4.2.1]nonan-3-one (**29**) (51.8 mg) in ether (3 ml) was added to a stirred solution of phenyllithium prepared from lithium (15 mg) and bromobenzene (300 mg) in ether (3 ml). After 30 min the reaction mixture was processed in the usual way, yielding the tertiary alcohol **30** (76.7 mg) as a viscous oil. Trituration of a portion of the product with pentane at −78° gave a solid which, after recrystallization from hexane, had mp 105–108°. The product was not stable to vpc analysis and the crude material was used in the following hydrogenolysis experiments:

(a) **Raney Nickel.**—The crude alcohol **30** (25.5 mg) was dissolved in absolute ethanol (0.5 ml) and Raney nickel (~500 mg) was added. The mixture was heated under reflux for 1 hr. The cooled mixture was filtered and the ethanol solution was concentrated, yielding an oil (22 mg). Comparison of the infrared spectrum (film) of an analytical sample, obtained by preparative vpc (2 ft × 20% SE-30 at 190°), with the spectra of the two compounds **5** and **10** showed the product of hydrogenolysis with Raney nickel was a mixture of these two isomers. Their vpc retention times were identical on all available columns.

Anal. Calcd for $C_{14}H_{20}O$: C, 83.01; H, 8.97. Found: C, 83.42; H, 8.81.

A sample of isomer **10**, isolated from the lead tetraacetate oxidation of alcohol **8**, had principal infrared (film) bands at 1490, 1450, 1100, 1065, 1045, 1025, 750, 700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 202 (47), 174 (13), 158 (13), 156 (28), 145 (10), 144 (21), 143 (28), 131 (12), 130 (27), 129 (38), 128 (16), 119 (16), 118 (68), 117 (56), 116 (56), 115 (45), 105 (30), 104 (90), 103 (31), 91 (100), 85 (10), 78 (31), 77 (35), 65 (19), 63 (13), 55 (19), 54 (10), 51 (13), 44 (11), 43 (10), 41 (37), 39 (37).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 83.42; H, 8.81.

(b) **Palladium on Carbon.**—The crude alcohol **30** (19.6 mg) was dissolved in ethylacetate (0.5 ml) containing 70% perchloric acid (15 ml) and 10% palladium on carbon (25 mg) was added. The mixture was hydrogenated until hydrogen uptake had ceased. Work-up in the usual way gave an oil (17.4 mg). A sample of the product was purified by preparative vpc. The infrared spectrum which was identical with that of isomer **5** isolated from the lead tetraacetate oxidation of alcohol **3**, had principal bands at 1500, 1465, 1110, 1075, 1045, 1035, 1010, 750, and 700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 203 (10), 202 (60), 158 (19), 145 (12), 143 (38), 131 (31), 105 (29), 128 (12), 118 (50), 117 (48), 116 (13), 115 (31), 105 (29), 104 (100), 103 (19), 98 (10), 92 (10), 91 (66), 83 (10), 80 (17), 79 (10), 78 (18), 77 (24), 71 (10), 65 (12), 55 (14), 51 (19), 44 (29), 42 (29).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 83.27; H, 8.98.

1-Phenyl-1,4-cyclooctanediol (32).—A solution of 4-hydroxycyclooctanone (5.0 g) in tetrahydrofuran (25 ml) was added dropwise with stirring to a solution of phenylmagnesium bromide (prepared from 2.4 g of magnesium and 15.7 g of bromobenzene) in tetrahydrofuran (75 ml). The mixture was stirred for a further 30 min and then was treated with saturated ammonium chloride solution. The solids were removed by filtration and the filtrate was concentrated, yielding a viscous liquid. This material was dissolved in ether, dried ($MgSO_4$), and concentrated to a semicrystalline solid. Crystallization from chloroform gave 3.1 g (40%) of **32**, mp 116–118°. An analytical sample, mp 122–124°, was obtained by recrystallization from ethyl acetate.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.37; H, 9.05.

Dehydration of Diol 32.—A crystal of iodine was added to a solution of **32** (2.5 g) in benzene (20 ml) and the mixture was heated under reflux for 24 hr with continuous removal of water in a Dean–Stark apparatus. The cooled solution was washed with aqueous sodium thiosulfate solution, dried ($MgSO_4$), and concentrated, yielding 1.9 g of an oil. Vpc analysis (8 ft × 10% Carbowax 20M at 245°) indicated the presence of the hydroxy–olefin mixture **14** (82.5%) and 1-phenyl-9-oxabicyclo[4.2.1]-nonane (**9**) (17.5%). The hydroxy–olefin mixture was purified by preparative vpc using the same column; the individual isomers were not separated under these conditions. An analytical sample had principal infrared bands at 3350, 2910, 2840, 1590, 1035, 1025, 760, and 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 83.14; H, 8.53.

Acetoxy–Olefin Mixture 13.—A portion of the crude alcohol mixture **14** was treated with acetic anhydride in pyridine. Vpc analysis (8 ft × 10% Carbowax 20M at 245°) of the product showed the presence of the two isomers in the ratio of 23:77. A sample of the mixture, purified by preparative vpc, had infrared (film) absorptions at 2920, 1735, 1235, 1020, 950, 850, 760, 690 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.26; H, 8.52.

Reaction of Hydroxy–Olefin Mixture 14 with Lead Tetraacetate—A sample of crude **14** (179 mg) containing 17.5% 1-phenyl-9-oxabicyclo[4.2.1]nonane (**9**) was dissolved in dry benzene (5 ml) and lead tetraacetate (350 mg) was added. The mixture was heated under reflux for 1 hr, cooled, washed with aqueous sodium thiosulfate, and dried ($MgSO_4$). Removal of the solvent yielded an oil (186 mg). Vpc analysis (8 ft × 10% Carbowax 20M at 245°) showed the presence of six components; relative retention times (rrt) 0.85, 1.00, 1.23, 1.59, 2.59, 3.28. The component with rrt 1.00 (20%) was identified as the 1-phenyl-9-oxabicyclo[4.2.1]nonane present in the starting material. Excluding this compound, the other products were (1) rrt 0.85 (9%), an unidentified compound which was also detected in the product mixture from the reaction of *trans*-4-phenylcyclo-

octanol with lead tetraacetate; (2) rrt 1.23 (9%), unidentified product also present in the product mixture from **8**; (3) rrt 1.59 (24.8%), 2-phenyl-9-oxabicyclo[3.3.1]non-2-ene (**11**); (4) rrt 2.59 (4.0%), the acetates **13** of the starting alcohols; (5) rrt 3.28 (53.2%), unreacted starting material **14**. These components were identified by their infrared spectra and vpc retention times.

trans-**4-Phenylcyclooctyl Acetate** (**12**).—*trans*-4-Phenylcyclooctanol (**8**) (100 mg) was dissolved in pyridine (1 ml) and acetic anhydride (5 drops) was added. The solution was allowed to stand at room temperature for several days and was then poured into cold water. Extraction with ether in the usual way gave ~100 mg of an oil. An analytical sample was obtained by preparative vpc (2 ft × 20% SE-30 at 210°): infrared spectrum (film) 1725, 1235, 1020, 750, and 690 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.33; H, 9.07.

cis-**4-Phenylcyclooctyl Acetate** (**7**).—A sample of *cis*-4-phenylcyclooctanol (**3**) was treated with acetic anhydride as described above for the *trans* isomer. A pure sample of the product had principal infrared absorptions at 1735, 1250, 1035, 755, and 690 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.19; H, 8.98.

exo-**2-Phenyl-9-oxabicyclo[4.2.1]nonan-2-ol** (**34**).—To a solution of phenyllithium (prepared from 0.17 g lithium and 1.7 g bromobenzene) in dry ether was added 9-oxabicyclo[4.2.1]-nonan-2-one (1.3 g) in ether (10 ml). The mixture was stirred for 30 min and then was treated with saturated ammonium chloride solution. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent gave 1.6 g (80%) of **34** as a white solid. Recrystallization of a sample from hexane–ethanol gave material of mp 92.5–94°.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.91; H, 8.22.

Dehydration of 34.—A sample of 34 (1.3 g) was dissolved in benzene (30 ml) containing a crystal of iodine. The solution was heated under reflux for 24 hr with continuous removal of water. The cooled solution was washed with sodium thiosulfate solution, water, and dried ($MgSO_4$). Removal of the solvent gave *ca.* 1.3 g of an oil which was distilled, yielding 0.9 g (75%) of **35**: bp 111–113° (0.5 mm); infrared (film) 1590, 1500, 1474, 1450, 1190, 1110, 1070, 1020, 1000, 965, 925, 915, 855, 845, 755, and 695 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.91; H, 8.18.

Hydrogenolysis of 34. (a) **Raney Nickel**.—To a solution of **34** (30 mg) in ethanol (5 ml) was added Raney nickel (*ca.* 100 mg). The mixture was heated under reflux for 1 hr and the catalyst was then removed from the cooled mixture by filtration. The ethanol solution was diluted with water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and concentrated, yielding an oil. Vpc analysis (5 ft × 5 ft XF-1150 at 180°) under conditions which cleanly separated isomers **17** and **21** showed that the product contained a single component with the same retention time and infrared spectrum as the compound **17** isolated from the lead tetraacetate oxidation of *cis*-5-phenylcyclooctanol. The infrared spectrum of a sample of **17** collected by preparative vpc had principal absorptions at 1600, 1100, 1085, 1070, 980, 935, 925, 753, and 700 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 83.26; H, 9.05.

(b) **Palladium on Carbon**.—A sample of **34** (20 mg) was dissolved in ethyl acetate (5 ml) containing 10% palladium on carbon (10 mg) and perchloric acid (1 ml), and the mixture was hydrogenated at atmospheric pressure until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was concentrated. Vpc analysis (5 ft × 5% XF 1150 at 180°) indicated the presence of two components in the ratio of 20:80. The minor component was identified as the bicyclic ether **17** and the major component **21**.

Hydrogenation of 2-Phenyl-9-oxabicyclo[4.2.1]non-2-ene (**35**).—A sample of **35** (300 mg) in ethanol (30 ml) containing 10% palladium on carbon (100 mg) was hydrogenated at atmospheric pressure. After 1 hr, the theoretical amount of hydrogen had been taken up. The catalyst was removed by filtration and the ethanol solution was concentrated, yielding ~300 mg of an oil. Vpc analysis (5 ft × 5% XF-1150 at 180°) showed the presence of two components in the ratio 53:47. Pure samples of both components were obtained by preparative vpc. The major component was identical in retention time and infrared spectrum with the bicyclic ether **17**, and the minor component **21** had the same retention time as the compound formed in 5% yield in the reaction of *trans*-5-phenylcyclooctanol with lead tetraacetate. The infrared spectrum of **21** had principal absorptions at 1600, 1065, 980, 925, 750, and 700 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.01; H, 8.97. Found: C, 82.83; H, 9.00.

Lead Tetraacetate Reactions. (a) *cis*-**5-Phenylcyclooctanol** (**15**).—Commercial lead tetraacetate was dried at 0.3 mm and room temperature immediately before use. To a solution of *cis*-5-phenylcyclooctanol (1.5 g) in dry benzene (65 ml) was added lead tetraacetate (4.5 g) and the mixture was heated under reflux for 42 hr with stirring. The cooled solution was treated with ethylene glycol (8 ml) and stirring was continued for 10 min. The layers were then separated and the ethylene glycol layer was diluted with water and extracted three times with ether. The ether extracts and the main benzene solution were combined, washed successively with water, 10% sodium thiosulfate, and saturated sodium chloride solution, and dried ($MgSO_4$). Removal of the solvent gave 1.7 g of an oil which was distilled, yielding a fraction (1.5 g), bp 113–145° (0.6 mm). Partial separation of the products was achieved by chromatography on Merck acid washed alumina (70 g). Elution with pentane followed by pentane–methylene chloride mixtures (from 10% methylene chloride up to 50%) gave partial separation. Ten fractions, containing a total of 1.49 g of material, were collected. Each fraction was examined by vpc (5 ft × 5% XF-1150 at 180°) and the individual components were isolated by preparative vpc using the same column. Final purification was achieved in some cases by recollection from a 2 ft × 20% SE-30 column.

(b) *trans*-**5-Phenylcyclooctanol** (**20**).—This reaction was carried out using 100 mg of the alcohol and the products were isolated as described above except that the distillation of the crude product was omitted.

(c) *cis*- and *trans*-**4-Phenylcyclooctanols** (**3**) and (**8**).—These reactions were conducted on a 1.5-g scale. In each case, the products were isolated by a combination of distillation, column chromatography, and vapor phase chromatography.

In all cases, the identifications are based on comparison of retention times and infrared spectra with those of authentic samples. Compounds **6**, **9**, **16**, **18**, **19**, and **22** were available from earlier studies.[11,12]

Registry No.—Lead tetraacetate, 546-67-8; **3**, 14573-36-5; **5**, 25090-54-4; **7**, 25090-55-5; **8**, 14573-37-6; **10**, 25090-57-7; **11**, 25090-58-8; **12**, 25090-59-9; **13a**, 25090-60-2; **13b**, 25090-37-3; **14a**, 25090-61-3; **14b**, 25090-38-4; **15**, 7286-96-6; **17**, 25096-34-8; **20**, 7286-64-8; **21**, 25096-36-0; **23**, 25096-37-1; **28**, 25096-38-2; **32**, 25096-39-3; **34**, 25096-40-6; **35**, 25096-41-7.

Benzene-Ring-Substituted 2-Acetyl-1,3-indandiones

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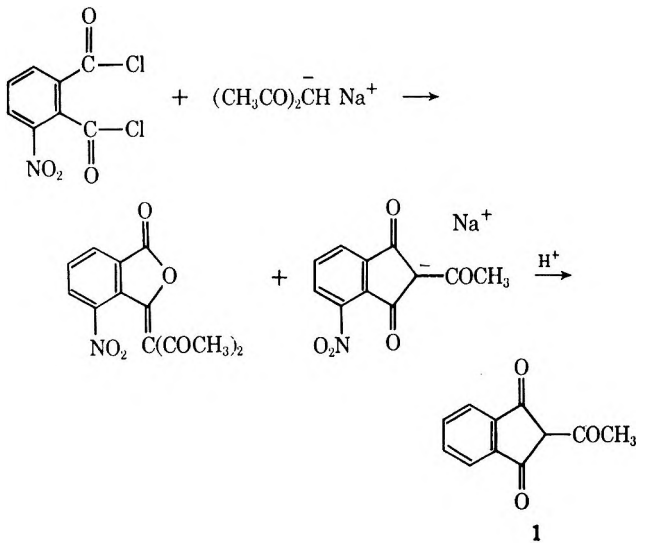
2-Acetyl-4-nitro- and 2-acetyl-5-nitro-1,3-indandione (1 and 2) were synthesized by the reaction of 2,4-pentanedione with 3-nitro- and 4-nitrophthalic anhydride, respectively. A possible mechanism for the formation of 1 is presented. 3-(4-Nitrophthalidylidene)-2,4-pentanedione and the following compounds made from 1 and 2 are described: 4- and 5-amino-, 4- and 5-acetamido-, 4-hydroxyamino-, 4-hydroxy-, 4-methoxy-, and 4-acetoxy-2-acetyl-1,3-indandione.

Because direct nitrations of 1,3-indandione[1] and of 2-alkyl-1,3-indandiones[2,3] have failed to effect substitution onto the benzene ring, two indirect methods were investigated to synthesize 2-acetyl-4-nitro-1,3-indandione (1). By following a method developed by Bülow and Deseniss[4] for the preparation of 2-acetyl-1,3-indandione, we found that, when 3-nitrophthaloyl chloride reacted with the sodium salt of 2,4-pentanedione, a mixture of 3-(4-nitrophthalidylidene)-2,4-pentanedione and the sodium salt of 2-acetyl-4-nitro-1,3-indandione was formed (Scheme I).

SCHEME I



A more practical method for the synthesis of 1, in 76% yield, was found in the reaction of 3-nitrophthalic anhydride with 2,4-pentanedione in the presence of pyridine and a small amount of piperidine at 35–40° (Scheme II).

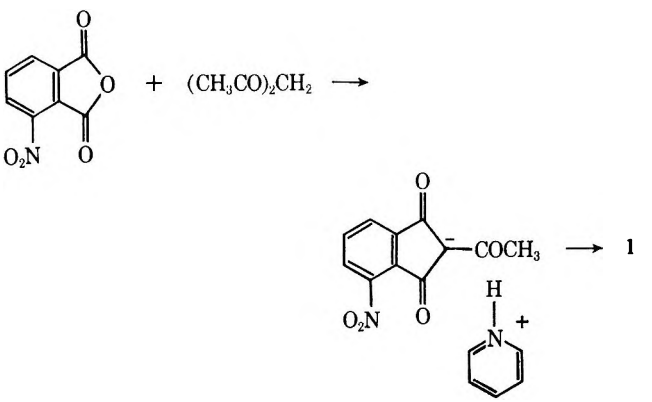
This reaction is a modification of that developed by Vanag and Oshkaia[5] for 4-nitro-1,3-indandione. It differs principally in the substitution of 2,4-pentanedione for malonic acid.

A possible mechanism for the formation of 1 is illustrated in Scheme III.

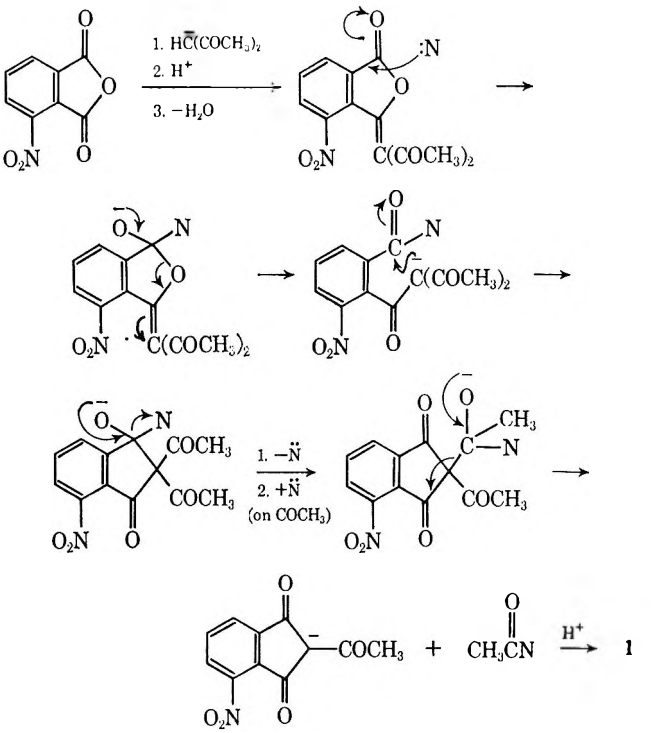
The 3-(4-nitrophthalidylidene)-2,4-pentanedione, a proposed intermediate in this reaction, was not isolated. However, its formation seems likely if one considers the numerous examples in the literature of phthalide preparation by the condensation of a phthalic anhydride with an active methylene compound.[6,7]

The rearrangement portion of the suggested mechanism is similar to one proposed by Shapiro, Geiger, and Freedman[8] for the base-catalyzed rearrangement of 3-benzylidenephthalide to 2-phenyl-1,3-indandione. The

SCHEME II



SCHEME III



(1) G. Vanag, *Chem. Ber.*, **69**, 1069 (1936).

(2) L. Zalukajevs, *Latv. PSR Zinat. Akad. Vestis*, **1** (54), 147 (1952); *Chem. Abstr.*, **48**, 3942 (1954).

(3) T. A. Michelfeld, M. S. Thesis, University of Delaware, 1960.

(4) C. Bülow and M. Deseniss, *Chem. Ber.*, **37**, 4381 (1904).

(5) G. Vanag and V. Oshkaia, *J. Gen. Chem., USSR*, **28**, 1570 (1958).

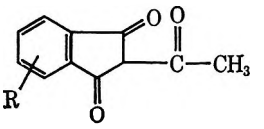
(6) S. Gabriel and A. Michael, *Chem. Ber.*, **11**, 1679 (1878).

(7) E. Leupold, *ibid.*, **34**, 2836 (1901).

(8) S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960).

TABLE I

BENZENE-RING-SUBSTITUTED 2-ACETYL-1,3-INDANDIONES



Compd	R	Mp, °C	Recrystn solvent	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	4-NO_2	148–150	*t*-BuOH	$C_{11}H_7NO_5$	56.65	3.00	6.01	56.94	2.80	5.97
2	5-NO_2	210.5–211.5	MeOH	$C_{11}H_7NO_5$	56.65	3.00	6.01	56.71	2.89	5.83
3	4-NH_2	127.5–129	EtOH	$C_{11}H_9NO_3$	65.02	4.43	6.90	64.88	4.46	6.90
4	5-NH_2	187–190 dec	Aqueous MeOH	$C_{11}H_9NO_3$						
5	4-$NHCOCH_3$	179–180	MeOH	$C_{13}H_{11}NO_4$	63.67	4.49	5.71	63.34	4.38	5.85
6	5-$NHCOCH_3$	241–241.5	Aqueous MeOH	$C_{13}H_{11}NO_4$	63.67	4.49	5.71	63.49	4.64	5.83
7	4-NHOH	163–165	MeOH	$C_{11}H_9NO_4$	60.27	4.11	6.39	60.54	4.02	6.83
8	4-OH	128.5–129.5	EtOH	$C_{11}H_8O_4$	64.71	3.92		64.90	3.84	
9	4-OCH_3	129–130	MeOH	$C_{12}H_{10}O_4$	66.06	4.59		65.66	4.82	
10	4-$OCOCH_3$	133–134.5	EtOH	$C_{13}H_{10}O_5$	63.41	4.07		63.16	3.83	

cleavage step is similar to that proposed by Soeder[9] to explain the formation of 2-methyl-1,3-indandione from the methoxide ion catalyzed condensation of dimethyl phthalate with diethyl ketone.

The ease with which nitrophthalic anhydride reacted with 2,4-pentanedione under these mild conditions is probably due to the strong inductive effect exerted by the nitro group. The ease with which the subsequent rearrangement occurred is, in all likelihood, due to the combined presence of the nitro and acetyl groups. That a strongly electron-withdrawing group in the benzene ring facilitates this reaction is indicated by the fact that 3-acetamidophthalic anhydride did not react with 2,4-pentanedione under otherwise identical experimental conditions.

When 4-nitrophthalic anhydride was used in place of 3-nitrophthalic anhydride in the reaction with 2,4-pentanedione, 2-acetyl-5-nitro-1,3-indandione (**2**) was obtained in 11% yield.

Evidence for the structures of the nitro compounds **1** and **2** is provided by elemental analyses, absorption spectral data, the preparation of the derivatives listed in Table I and the formation of the substituted indeno-[1,2-*c*]pyrazol-4(1H)-ones, which will be described in a subsequent paper.[10]

Nitro compounds **1** and **2**, when treated with sodium dithionite in alkaline solution, or reduced catalytically, gave the corresponding amines **3** and **4**. These amines are very weak bases. Their hydrochlorides hydrolyzed easily by exposure to air. With acetic anhydride they formed acetyl derivatives (**5** and **6**). The 2-acetyl-4-hydroxy-1,3-indandione **8**, obtained by diazotization of the amine **3**, followed by treatment of the diazonium salt with dilute sulfuric acid, gave the typical alkylation and acylation reactions.

Experimental Section[11]

2-Acetyl-4-nitro-1,3-indandione (1). A. From 3-Nitrophthaloyl Chloride.—A suspension in ether of the sodium salt of 2,4-pentanedione was prepared by adding dropwise a solution of freshly distilled 2,4-pentanedione (5 g, 0.05 mol) in anhydrous ether (10 ml) to a stirred suspension of sodium sand[12] (1 g, 0.045 mol) in anhydrous ether (40 ml) and stirring for an additional 24 hr. To this suspension was added a solution of 3-nitrophthaloyl chloride[13] (5 g, 0.02 mol) in a mixture of ether (20 ml) and dioxane (2 ml). The suspension was stirred at room temperature for an additional 36 hr; then the solid product was collected by filtration, dried, and extracted for 16 hr in a Soxhlet extractor with ether. Removal of the solvent from ether extract gave 0.5 g (9%) of 3-(4-nitrophthalidylidene)-2,4-pentanedione, as pale yellow needles, mp 175–177° (ethanol). The ir spectrum shows a carbonyl peak at 1810 cm^{-1}.

Anal. Calcd for $C_{13}H_9NO_6$: C, 56.75; H, 3.27; N, 5.09. Found: C, 56.72; H, 3.50; N, 5.59.

The yellow powder left in the Soxhlet extractor was extracted for 2 hr with methanol and then treated dropwise with 6 *N* hydrochloric acid until it dissolved momentarily. Compound **1** immediately precipitated as a pale yellow solid. This crude product, 1.2 g (26%), was recrystallized from *t*-butyl alcohol to give **1** as fine yellow needles: ir 1730, 1665, 1615, 1595, and 1550 cm^{-1}.

B. From 3-Nitrophthalic Anhydride.—A mixture of 3-nitrophthalic anhydride (25 g, 0.13 mol), pyridine (25 ml), piperidine (0.2 ml), and 2,4-pentanedione (12.5 g, 0.125 mol) was stirred at 35–40°.

A dark solution was formed in a short time and a bright yellow precipitate began to form. After 6 hr the reaction mass was cooled and the very thick crystalline product was collected by filtration, washed with ether and dried to give 33.2 g (82.2%) of the crude pyridinium salt of **1**. This salt, treated with 6 *N* hydrochloric acid (100 ml), gave a yellow crystalline precipitate, which, collected by filtration, washed with water, and dried, yielded 19.0 g (76% overall yield) of **1** as fine yellow needles. A mixed melting point taken with compound **1**, obtained from 3-nitrophthaloyl chloride as described under A, showed no depression.

2-Acetyl-5-nitro-1,3-indandione (2).—A mixture of 4-nitrophthalic anhydride[14] (5 g, 0.025 mol), 2,4-pentanedione (2.5 g, 0.025 mol), anhydrous pyridine (5 ml), and piperidine (3 drops) was stirred at 35–40° for 7 hr and then filtered. The solid was washed with ether and dried to give 4 g (30%) of the pyridinium salt of **2**, which, treated with hydrochloric acid, as in the above procedure for compound **1**, yielded 2.5 g (11%) of **2** as pale yellow crystals: ir 1730, 1660, 1610, 1595, and 1545 cm^{-1}.

2-Acetyl-4-amino-1,3-indandione (3). A. $Na_2S_2O_4$ Reduction.—To a stirred solution of concentrated ammonium hydroxide (50 ml) in water (300 ml) were added nitro compound **1** (3.8 g, 0.016 mol) and then a solution of sodium dithionite (10 g, 0.043 mol) in water (50 ml). The solution immediately turned deep orange and slightly warm. After 1 hr concentrated hydrochloric acid was added at room temperature to make the reac-

(9) R. W. Soeder (University of Delaware, Newark), University Microfilms (Ann Arbor, Mich.), Order No. 62-5873; *Diss. Abstr.*, **23**, 2326 (1963).

(10) W. A. Mosher and W. E. Meier, *J. Org. Chem.*, in press.

(11) Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken as nujol mulls on a Perkin-Elmer Infracord Model 137, using sodium chloride plates. Elemental analyses were performed by Dr. A. Bernhardt Microanalytisches Laboratorium in Max-Planck Institut für Kohlenforschung, Mülheim (Ruhr), Germany.

(12) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., p 125.

(13) V. J. Chambers, *J. Amer. Chem. Soc.*, **25**, 607 (1903).

(14) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **95**, 208 (1909).

tion mixture strongly acidic. The precipitate was collected by filtration, washed with water, and dried to give 1.8 g (54%) of **3** as yellow crystals: ir 3520, 3400, 3250, 1710, 1660, 1630, 1610, and 1590 cm^{-1}.

B. Catalytic Reduction.—A suspension of **1** (10 g, 0.043 mol) and 10% Pd–C (1 g) in absolute ethanol (250 ml) was hydrogenated at 50 psi (Paar shaker) at room temperature until the calculated amount of hydrogen was absorbed. The reduction was somewhat exothermic. Then the catalyst was removed immediately by filtration. The filtrate on cooling gave 5.6 g (64%) of **3** identical with the amine obtained under A, by mixture melting point and by comparison of the infrared spectra.

The **hydrochloride** of **3**, which hydrolyzed quickly to the free base on contact with air, was formed as white crystals, by bubbling dry hydrogen chloride into an ether solution of **3**.

Treatment of a solution of **3** (2.5 g, 0.012 mol) in anhydrous methanol (25 ml) with methyl iodide (4 ml, 0.064 mol) and sodium bicarbonate (2.5 g, 0.030 mol) at reflux for 16 hr gave **(2-acetyl-1,3-dioxo-4-indanyl)trimethylammonium iodide** as yellow crystals, which decomposed at 238–240°.

Upon treating a concentrated aqueous solution of the above iodide with a few drops of 70% perchloric acid, the **perchlorate** was obtained as pale yellow crystals which decomposed at 282–285°.

Anal. Calcd for $C_{14}H_{16}ClNO_7$: C, 48.70; H, 4.64. Found: C, 48.63; H, 4.72.

2-Acetyl-5-amino-1,3-indandione (**4**), was obtained by treating the nitro compound **2** (6 g, 0.026 mol) with sodium dithionite (23 g, 0.13 mol) and ammonium hydroxide (200 ml), as described in procedure A for the isomer **3**. In this case the reaction mass was heated to 50° on a steam bath and then allowed to return to room temperature. A 36% yield of **4**, as bright yellow crystals was obtained. These crystals darkened quickly upon exposure to air. Recrystallization from aqueous methanol gave brown crystals: ir 3550, 3425, 3300, 1710, 1650, 1620, 1600, 1580 cm^{-1}.

4-Acetamido-2-acetyl-1,3-indandione (**5**).—A mixture of amine **3** (0.5 g, 0.003 mol) and acetic anhydride (1 ml, 0.01 mol) refluxed for 3 min gave, after cooling to 0°, a yellow precipitate, which was purified by sublimation under a high vacuum at 120°. A 58% yield of **5** as pale yellow powder was obtained: ir 3400, 1725, 1700, 1650, 1620, and 1600 cm^{-1}.

5-Acetamido-2-acetyl-1,3-indandione (**6**) was obtained in 54% yield by treating amine **4** with acetic anhydride as described above for the isomer **5**. Sublimation at 210° (1.5 mm) and recrystallization from aqueous methanol gave pale yellow crystals: ir 3400, 1725, 1700, 1655, 1625, 1605, and 1540 cm^{-1}.

2-Acetyl-4-hydroxyamino-1,3-indandione (**7**).—A suspension of **1** (13 g, 0.056 mol) and 10% Pd–C (1g) in absolute ethanol (250 ml) was hydrogenated at 12 psi (Paar shaker) at room temperature until the calculated amount of hydrogen was absorbed. Then the catalyst was removed by filtration and the filtrate was diluted to 500 ml with water, and cooled in a Dry Ice–acetone mixture to give 9 g of crude **7** contaminated with amine **3**. The amine was removed by washing the crude with ether. Recrystallization of the residue, 7 g (57%), from methanol gave **7** as yellow orange crystals: ir 3370, 1715, 1695, 1650, 1610, and 1585 cm^{-1}.

2-Acetyl-4-hydroxy-1,3-indandione (**8**).—A solution of **3** (5 g, 0.025 mol) in a mixture of acetic acid (50 ml) and concentrated sulfuric acid (20 ml) was added dropwise to a stirred and cooled (below 10°) solution of nitrosylsulfuric acid, prepared from sodium nitrite (5 g, 0.07 mol) and concentrated sulfuric acid (25 ml) following the standard procedure. After stirring for an additional 0.5 hr at 10° the reaction mass was added slowly to a stirred and warm (80°) solution of concentrated sulfuric acid (30 ml) in water (90 ml). The precipitate was collected and purified by sublimation at 100° under a high vacuum to give 2.5 g (49%) of **8** as pale yellow crystals: ir 3450, 1705, 1655, and 1610 cm^{-1}.

The **methoxy** derivative **9** was obtained in 93% yield by adding dimethyl sulfate (0.7 ml, 0.07 mol) to a stirred mixture of **8** (1 g, 0.005 mol), sodium hydroxide (0.4 g, 0.01 mol), and water (30 ml), heating to 35° for 15 min, cooling to room temperature, and stirring for 2 days. The infrared spectrum of the collected pale yellow precipitate showed peaks at 1720, 1660, 1630, 1595, and 1280 cm^{-1}.

The **acetoxy** derivative **10** was formed by adding **8** (0.5 g, 0.003 mol) to 97% acetic anhydride (3 ml, 0.03 mol). The mixture was refluxed for 15 min, the excess of acetic anhydride and acetic acid evaporated under vacuum, and the residue triturated with petroleum ether (bp 60–70°) to give, after several crystallizations from ethanol, 0.46 g (75%) of **10**, as silky colorless crystals: ir 1770, 1730, 1670, 1635, and 1610 cm^{-1}.

Attempted Preparation of 4-Acetamido-2-acetyl-1,3-indandione from 3-Acetamidophthalic Anhydride.—2,4-Pentanedione (2.5 g) and 2 drops of piperidine were added to a stirred mixture of 3-acetamidophthalic anhydride (5 g) and anhydrous pyridine (5 ml). The mixture was maintained at 40° for 24 hr. Only starting materials were recovered.

Registry No.—**1**, 25125-04-6; **2**, 25125-05-7; **3**, 25125-06-8; **4**, 25125-07-9; **5**, 25125-08-0; **6**, 25125-09-1; **7**, 25125-10-4; **8**, 25125-11-5; **9**, 25125-12-6; **10**, 25125-13-7; 3-(4-nitrophthalidylidene)-2,4-pentanedione, 25125-14-8; (2-acetyl-1,3-dioxo-4-indanyl) trimethylammonium iodide, 25125-15-9; (2-acetyl-1,3-dioxo-4-indanyl)trimethylammonium perchlorate, 25125-16-0.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.

Synthesis of 2-Nitroindanones by Dieckmann Cyclization of 2-(2-Nitroethyl)benzoates[1]

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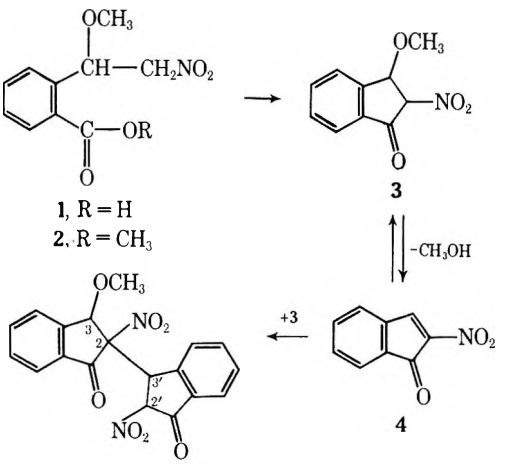
Received December 19, 1969

Methyl 2-(1-methoxy-2-nitroethyl)benzoate (2) was prepared from its acid (1) with diazomethane and was found to undergo a Dieckmann-type cyclization by the action of sodium methoxide. The reaction is followed by an elimination–addition process that leads to 3-methoxy-2-nitro-2-(2-nitroindanon-3-yl)indanone (5). Methyl and phenyl 2-(2-nitroethyl)benzoate (6 and 8) are cyclized to 2-nitroindanone (7), and methyl 2-(1,3-dinitro-2-propyl)benzoate (9) gives 3-nitromethyl-2-nitroindanone (10). Trifluoroperoxyacetic acid oxidation of 2-oximino-1-indanone (11) provided an alternative route to 7.

Subsequent to the synthesis[2] of 2-(1-methoxy-2-nitroethyl)benzoic acid (1), it was observed that storage of a methanolic solution of 1 (1 day at 25°) followed by addition of sodium methoxide produces a strong ultraviolet peak at 370 nm. This absorption did not correspond to a β-nitrostyrene system (310–320 nm)[2,3] but was reminiscent of the absorptions reported for ω-nitroacetophenone (352 nm)[4] and 2-nitrotetralone (370 nm).[5] It seemed possible that part of 1 had become esterified to its methyl ester (2) which was then cyclized by the base, in a Dieckmann-type reaction, to give a nitro ketone (Scheme I). This prompted us to

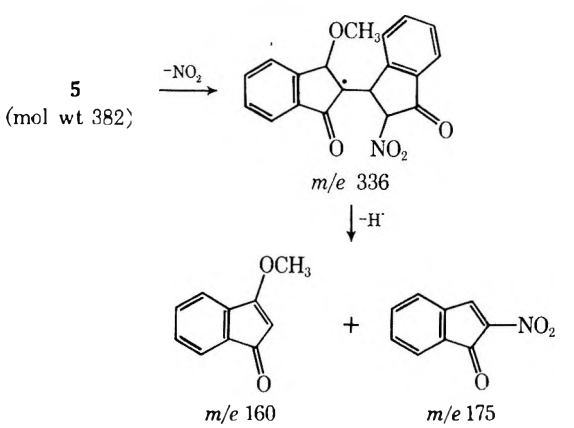
SCHEME I



examine whether such a reaction might provide a preparative avenue to the 2-nitroindanone system. When crystalline methyl 2-(1-methoxy-2-nitroethyl)benzoate (2), prepared from 1 and diazomethane, was treated with methanolic sodium methoxide it was indeed converted, within a few minutes, into a product possessing λ_{max} 370 nm. The isolated product, however, proved to be 3-methoxy-2-nitro-(2-nitroindanone-3-yl)indanone (5) rather than 3-methoxy-2-nitroindanone (3). This is explained by a (reversible) β elimination of methanol from part of the cyclization product 3 to give the intermediate nitroalkene 4 which is then removed from the equilibrium by Michael addition of surviving 3 (Scheme I). A closely related precedent for such a Michael addition is the base-catalyzed formation of 1-methoxy-2,4-dinitro-1,3-diphenylbutane from β-nitrostyrene and methanol.[6]

The structure of 5 was established by analytical and spectral data. Although the mass spectrum did not exhibit a molecular ion peak at *m/e* 382, it showed a strong peak at *m/e* 336 resulting from loss of NO_2 and two further, intense peaks (*m/e* 175 and 160) that may have arisen by fragmentation with loss of a hydrogen atom as depicted in Scheme II. The nmr spectrum in

SCHEME II



$CDCl_3$ showed an intensity ratio of 8:3 in the signals attributable to the aromatic protons (multiplet at τ 2.28) and the methoxyl protons (singlet at τ 6.69). A one-proton singlet (τ 4.52) was assigned to H-3; H-2′ and H-3′ fortuitously had identical chemical shifts (τ 4.43) and gave a two-proton singlet.

Cyclization of methyl 2-(2-nitroethyl)benzoate (6) and of the corresponding phenyl ester (8) gave 2-nitroindanone (7), and methyl 2-(1,3-dinitro-2-propyl)-benzoate (9) afforded 3-nitromethyl-2-nitroindanone (10) (Scheme III). The yields in these reactions were 43–62%. Proof of structure was provided for 7 and 10 by spectral data and, for 7, by an independent synthesis recorded in a later paragraph. The mass spectra of 7 and 10 exhibited molecular ion peaks at *m/e* 177 and 236, respectively. The nmr spectrum of 7 (in $CDCl_3$) showed a 4:2 intensity ratio for the aromatic protons (multiplet at τ 2.32) and benzylic protons (two overlapping quartets near τ 6.20). A quartet attributable to H-2 (τ 4.49) had an intensity 25% less than that calculated for one proton, and this may be explained by

(1) Taken from the Ph.D. Thesis of S. R. Naik, University of Ottawa, 1967.

(2) H. H. Baer and F. Kienzle, *Can. J. Chem.*, **43**, 190 (1965).

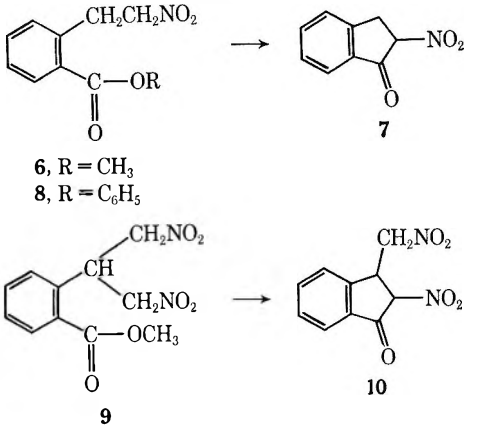
(3) E. A. Braude, E. R. H. Jones, and G. G. Rose, *J. Chem. Soc.*, 1105 (1947); R. Stuart and L. G. Walker, *Can. J. Chem.*, **35**, 1561 (1957).

(4) R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

(5) H. Feuer and P. M. Pivawer, *ibid.*, **31**, 3152 (1966).

(6) J. Meisenheimer and F. Heim, *Ber.*, **38**, 467 (1905); *Justus Liebigs Ann. Chem.*, **355**, 260 (1907).

SCHEME III

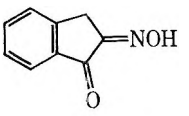


partial enolization as has been previously observed[5] in other cyclic α-nitro ketones. In agreement herewith, the signal disappeared upon deuterium exchange with D_2O. In the spectrum of **10** (in DMSO-d_6) the corresponding H-2 signal was a doublet (τ 3.9, J = 4 Hz) that showed a similarly reduced intensity. An intensity ratio of 4:3 was seen for the aryl protons (multiplet at τ 2.19) and a group of poorly resolved resonances (τ 4.3–5.3) assignable to the benzylic and nitromethyl protons.

In attempts to prepare 2-nitropentanone by cyclization of methyl 5-nitropentanoate[7] an absorption maximum at 345 nm was generated. This may be taken as evidence[5] for the formation of the desired ketone nitronate. However, on deionization and work-up, no product other than the starting ester was detected. Feuer and coworkers[5,8] in their studies on the alkyl nitrate nitration of ketones also were unable to isolate 2-nitrocyclopentanone, and they as well as other workers commented upon the fact that certain α-nitro ketones are extremely prone to cleavage under basic[5,9] and acidic[10] conditions.

As far as we are aware, ester condensations utilizing a reactive nitromethylene group as the nucleophilic reaction partner are not common in the literature. One analogous reaction is the condensation of nitroalkanes with the ethoxymethylene derivatives of various β-dicarbonyl compounds;[11] the latter were viewed as vinylogous esters; and the similarity of the reaction to the Claisen ester condensation was pointed out. Another reaction, more closely akin to ours, involved condensation of ethyl acetonedicarboxylate with 1-dimethylamino-2-nitroethylene, which led to an aromatic product by way of cyclization of an intermediate ω-nitro ester.[12]

In order to confirm the structure of the cyclization product obtained from **6** or **8**, the then unknown 2-nitroindanone (**7**)[13] was synthesized by an independent route. It was obtained in 18% yield by oxidation of 2-oximino-1-indanone (**11**) with trifluoroperacetic acid[14]



11

in acetonitrile solution at room temperature.[15] We were unable to prepare **7** from 2-bromoindanone and sodium nitrite, or by nitration of indanone with acetyl nitrate[16] or alkyl nitrates.[5,17]

Experimental Section[18]

Methyl 2-(1-Methoxy-2-nitroethyl)benzoate (2).—To a solution of 2-(1-methoxy-2-nitroethyl)benzoic acid[2] (1) (0.80 g) in ether (75 ml) was added a distilled, ethereal solution of diazomethane in slight excess. The solution was kept at 4° for 1 hr and then evaporated to give **2** which crystallized from methanol as colorless plates (0.60 g, 71%): mp 98°; ν_{max} 1720 (C=O) and 1560 cm^{-1} (NO_2); nmr spectrum ($CDCl_3$) τ 2.22 (4 H, aromatic), 4.26 (q, H-1′), 5.30 and 5.42 (two quartets due to the magnetically nonequivalent nitromethyl protons), 6.67 and 6.72 (s, OCH_3).

Anal. Calcd for $C_{11}H_{13}NO_5$ (239.2): C, 55.24; H, 5.48; N, 5.85. Found: C, 55.31; H, 5.46; N, 5.98.

3-Methoxy-2-nitro-2-(2-nitroindanon-3-yl)indanone (5).—A solution of sodium methoxide (444 mg) in methanol (10 ml) was added (over a period of 30 min) to a solution of the ester **2** (1.195 g) in methanol (100 ml). After standing at room temperature for 8 hr the solution was deionized with cation-exchange resin, Rexyn-50 (H^+), and evaporated to give a solid which, on recrystallization from methanol, afforded **5** as colorless prisms (475 mg): mp 164°; ν_{max} 1750 (C=O) and 1550 cm^{-1} (NO_2); λ_{max} 372 nm (ϵ 8300, in methanol). For nmr data see the discussion.

Anal. Calcd for $C_{19}H_{14}N_2O_7$ (382.3): C, 59.69; H, 3.66; N, 7.35; OCH_3, 8.15. Found: C, 59.56; H, 3.97; N, 7.50; OCH_3, 9.20; mol wt, 380 (by osmometry in acetone solution).

2-Nitroindanone (7). A. By Cyclization of the Methyl Ester 6.—A solution of sodium methoxide (13 mg) in methanol (1 ml) was added to a solution of methyl 2-(2-nitroethyl)benzoate[19] (**6**) (50 mg) in methanol (5 ml). A yellow precipitate was formed after a few minutes. The mixture was stirred at room temperature for 6 hr and then cooled to 0°, neutralized with cold 1 *N* hydrochloric acid, and evaporated to dryness. The residue was extracted with boiling petroleum ether (bp 60–80°), and evaporation of the extract gave a white solid that was recrystallized from petroleum ether to yield **7** (26 mg) as colorless plates: mp 80–81°; ν_{max} 1730 (C=O) and 1550 cm^{-1} (NO_2); λ_{max} in methanol 256 nm (ϵ 11,000) and 372 (8600). For nmr data see the discussion. Kametani, *et al.*, described **7** as "pale yellowish brown scales, mp 80–81.5°."

Anal. Calcd for $C_9H_7NO_3$ (177.1): C, 61.01; H, 3.95; N, 7.91. Found: C, 61.15; H, 3.99; N, 7.81.

B. By Cyclization of the Phenyl Ester 8.—The phenyl ester[19] (**8**) (about 45 mg) was cyclized as described for **6**, except for a

(7) This nitro ester was prepared from the corresponding bromo ester by displacement with sodium nitrite according to N. Kornblum, *Org. React.*, **12**, 101 (1962), but was obtained in an impure state only.

(8) H. Feuer, A. M. Hall, S. Golden, and R. L. Reitz, *J. Org. Chem.*, **33**, 3622 (1968).

(9) A. S. Matlack and D. S. Breslow, *ibid.*, **32**, 1995 (1967), and references cited therein.

(10) H. Feuer and P. M. Pivawer, *ibid.*, **34**, 2917 (1969), and references cited therein.

(11) A. Dornow and S. Lüpfert, *Justus Liebigs Ann. Chem.*, **606**, 56 (1957).

(12) T. Severin, B. Brueck, and P. Adhikary, *Ber.*, **99**, 3097 (1966).

(13) A compound previously described as **7** [J. Thiele and E. Weitz, *Justus Liebigs Ann. Chem.*, **377**, 1 (1910)], had been shown to be, in fact, 1-hydroxy-2-nitroindene: see F. W. Lichtenthaler, *Tetrahedron Lett.*, 775 (1963), and H. H. Baer and B. Achmatowicz, *J. Org. Chem.*, **29**, 3180 (1964). A synthesis of **7** departing from indene nitrosite has since been reported by T. Kametani, H. Sugahara, and S. Asagi, *Chem. Pharm. Bull.*, **14**, 1408 (1966).

(14) W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, **77**, 4557 (1955).

(15) An earlier attempt[4] to perform the same reaction at reflux temperature had been unsuccessful.

(16) F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 2323, 3049 (1962); **28**, 1765 (1963). A. A. Griswold and P. S. Starcher, *ibid.*, **31**, 357 (1966).

(17) W. Wislicenus and M. Waldmueller, *Ber.*, **41**, 3334 (1908); H. Feuer, J. W. Shepherd, and C. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956).

(18) Melting points were taken in capillaries in an electric aluminum block apparatus. Evaporations were performed *in vacuo* at a bath temperature of 35–40°. Infrared spectra were taken from Nujol mulls on a Perkin-Elmer infracord instrument. Ultraviolet spectra were recorded with a Perkin-Elmer spectrometer, Model 202. Nmr spectra (60 MHz) were obtained from a Varian HA-60 instrument using tetramethylsilane as internal standard.

(19) H. H. Baer and S. R. Naik, *J. Org. Chem.*, **35**, 3161 (1970).

reaction time of 1 hr. The product (13 mg) was identical in all respects with **7** as prepared from **6**.

C. By Oxidation of the Oxime 11.—Trifluoroacetic anhydride (504 mg) was added with stirring to an ice-cooled solution of 98% hydrogen peroxide (68 mg) in acetonitrile (5 ml). The solution was allowed to reach room temperature and was then added dropwise (over a period of 1 hr) to a stirred solution of 2-oximino-1-indanone[20] (**11**) (161 mg) and urea (150 mg) in acetonitrile (15 ml). After 8 hr the reaction mixture was poured onto crushed ice. The product was extracted by ether which was dried (Na_2SO_4) and evaporated to leave a brown residue. This residue was extracted with boiling petroleum ether (bp 60–80°). Evaporation of the extract gave a pale yellow solid (71 mg) that was recrystallized from petroleum ether to furnish **7** (32 mg) as colorless plates, mp 81°. The product was identical with **7** from the cyclization (see A and B), according to ir and uv spectra.

3-Nitromethyl-2-nitroindanone (10).—To an ice-cooled solution of methyl 2-(1,3-dinitro-2-propyl)benzoate[18] (**9**) (380 mg) in methanol (35 ml) was added a solution of sodium methoxide (160 mg) in methanol (3 ml) over a period of 15 min. The mixture was stirred at 0° for 1 hr and was then neutralized with cold 1 *N* hydrochloric acid and evaporated to dryness. The residue was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), concentrated to a small volume, and cooled in a refrigerator. Yellow crystals (135 mg) melting at 116–117° were deposited: recrystallization from chloroform raised the melting point to 118–119°; for nmr data see the discussion: ν_{max} 1725 (C=O) and 1550 cm^{-1} (NO_2); λ_{max} 370 nm (ϵ 8400, in methanol).

Anal. Calcd for $C_{10}H_8N_2O_5$ (236.2): C, 50.84; H, 3.41; N, 11.85. Found: C, 50.90; H, 3.60; N, 11.98.

Attempted Preparation of 2-Nitrocyclopentanone.—Commercial methyl 5-bromopentanoate (4.2 g), sodium nitrite (2.8 g), and phloroglucinol (1.75 g) were stirred in a mixture of methyl sulfoxide (28 ml) and N,N-dimethylformamide (7 ml) for 5 hr at room temperature. The mixture was then poured into a large volume of ice water which was extracted with ether. The extract was washed twice with water and dried (Na_2SO_4), and the ether was evaporated leaving a brown liquid which was distilled *in vacuo*. The distillate (1.5 g) collected at 100–102° (0.8 Torr) was colorless and exhibited infrared bands at 1730 (C=O) and 1550 cm^{-1} (NO_2). It was presumed to contain methyl 5-nitropentanoate although the elemental analysis was unsatisfactory (Calcd: C, 44.75; H, 7.32; N, 8.68. Found: C, 47.77; H, 7.59; N, 7.92). The high carbon and low nitrogen content possibly indicated contamination by methyl 4-pentenoate that may have arisen by partial dehydrobromination of the starting ester. Attempts at purification were unsuccessful. A part (0.1 g) of the product was mixed with methanol (2.5 ml) containing sodium methoxide (35 mg). A uv maximum at 345 nm developed. After standing at room temperature for 8 hr the solution was deionized with Rexyn-101 (H^+), the solvent was removed under reduced pressure, and a liquid remained which showed no absorption in the 300–390-nm region and gave an infrared spectrum completely identical with that obtained prior to the methoxide treatment.

Registry No.—**2**, 25116-44-3; **5**, 25116-45-4; **7**, 13943-70-9; **10**, 25116-47-6.

Acknowledgment.—The authors thank the National Research Council of Canada for support of this work.

(20) H. O. House, W. F. Gannon, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1463 (1960).

The Acid-Catalyzed Disproportionation of Indan

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The hydrogen fluoride–boron trifluoride catalyzed disproportionation of indan was investigated over a range of temperatures, contact times, and boron trifluoride concentrations. At 30° phenylpropylindans were the major products while at 70° *as*-hydrindacene was the principal tricyclic product formed. The isomerization of *s*-hydrindacene and *as*-hydrindacene was also investigated at 30, 50, and 70°. An explanation is offered for the formation of *as*-hydrindacene.

The acid-catalyzed disproportionation of alkyl aromatic compounds has been given considerable attention in the literature.[1-4] By comparison, little has been published on the acid-catalyzed disproportionation of alicyclic systems. Schroeter,[5] some time ago, investigated the action of aluminum chloride on 1,2,3,4-tetrahydronaphthalene (tetralin). Several products were obtained, the major ones being benzene, 1,2,3,4,5,6,7,8-octahydroanthracene, 1,2,3,4,5,6,7,8-octahydrophenanthrene, and 6-(4-phenylbutyl)-1,2,3,4-tetrahydronaphthalene. All were produced in very low yield. More recently we reexamined this reaction[6] and found hydrogen fluoride–boron trifluoride to be superior to any other catalyst for the formation of 1,2,3,4,5,6,7,8-octahydroanthracene and 1,2,3,4,5,6,7,8-octahydrophenanthrene or 6-(4-phenylbutyl)-1,2,3,4-tetrahydronaphthalene. The type of products that was obtained was very much dependent upon the reaction conditions employed.

The disproportionation of other alicyclic systems such as indan has likewise received little attention. A report by Turova-Pollak and Podolskaya[7] described the use of aluminum chloride at 170–230° for 10 hr to give a mixture of "hexamethylene hydrocarbons, pentamethylene hydrocarbons, and some saturated aliphatic hydrocarbons."

We wish to report our results for the hydrogen fluoride–boron trifluoride catalyzed disproportionation of indan. The effect of changes of reaction parameters on the products formed will be presented and discussed, and certain comparisons will be made with the results of our previous work on tetralin disproportionation.[6]

Experimental Section

Materials.—The anhydrous hydrogen fluoride and boron trifluoride were commercial grade of 99.9 and 99.0% purity, respectively, obtained from the Matheson Company. They were used without further purification. The indan was purchased

(1) A. P. Lien and D. A. McCaulay, *J. Amer. Chem. Soc.*, **75**, 2407 (1953).

(2) D. A. McCaulay in "Friedel-Crafts and Related Reactions," G. A. Olah, Ed., Part II, Vol. 2, Wiley-Interscience, New York, N. Y., 1964, Chapter XXIV, and references therein.

(3) H. C. Brown and C. R. Smoot, *J. Amer. Chem. Soc.*, **78**, 2176 (1956).

(4) D. V. Nightingale, *Chem. Rev.*, **25**, 329 (1939).

(5) G. Schroeter, *Chem. Ber.*, **57**, 1990 (1924).

(6) R. D. Bushick, *Ind. Eng. Chem., Prod. Res. Develop.*, **6**, 172 (1967).

(7) M. B. Turova-Pollak and F. I. Podolskaya, *Zh. Obshch. Khim.*, **7**, 1738 (1937); *Chem. Abstr.*, **32**, 538 (1938).

from Aldrich Chemical Company and after distillation showed a purity (vpc) of 99%. It was stored over 5A molecular sieves.

Disproportionation with Hydrogen Fluoride–Boron Trifluoride.—The disproportionation experiments were carried out in 75-ml stainless steel Hoke pressure vessels equipped with a Hoke valve on each end. All runs were based on an indan charge of 0.1 mol. A measured quantity of hydrogen fluoride was transferred by nitrogen pressure from a storage cylinder through a stainless steel manifold, a calibrated Jerguson sight gauge (shielded with Kel-F), and then into an evacuated Hoke vessel containing the indan. The pressure vessel was immersed in a constant temperature bath and allowed to equilibrate while being shaken by means of a wrist-action shaker before the boron trifluoride was added. Reaction begins immediately after addition of the boron trifluoride. The work-up of the product has already been described.[5]

Disproportionation with Aluminum Chloride.—Into a 50-ml three-necked, round-bottomed flask equipped with a thermometer, water condenser, and stirrer was added 11.8 g (0.100 mol) of indan and 0.65 g (0.00486 mol) or 5.5 wt % aluminum chloride. After 2 hr at a given temperature (30, 50, and 90°), the entire reaction mixture was quenched over an ice–water mixture, neutralized, extracted with pentane and petroleum ether (30–60°), and dried over anhydrous calcium sulfate. The extract was concentrated and analyzed by vpc.

Isomerization Studies.—All isomerization studies involving *s*-hydrindacene[8] and *as*-hydrindacene were carried out in 75-ml Hoke pressure vessels using the apparatus mentioned previously. A 0.500-g (0.00318 mol) sample of the hydrocarbon and 10 ml of dry heptane (99% pure) was added to the reaction vessel. The vessel and contents were immersed in Dry Ice–acetone. A measured quantity of anhydrous hydrogen fluoride was transferred into the evacuated reaction vessel, after which the entire system was equilibrated at a predetermined reaction temperature. The boron trifluoride was metered in and the reaction commenced. The product was treated in the manner described previously.[6] The isomer distribution of the product was determined by infrared spectroscopy.

Analyses.—The products resulting from the indan disproportionation reaction were analyzed by gas chromatography (vpc) and, whenever possible, this was supplemented by infrared and ultraviolet spectroscopy, nuclear magnetic resonance, and mass spectrometry. Comparisons with literature values were made whenever possible. An F & M Model 720 gas chromatograph was used for the separation of products. Each column was 6 ft × 0.25 in. and packed with SE-54 (15%) on Chromosorb W, 60–80 mesh. The temperature was programmed at 7.5°/min from 90 to 325° and a helium flow rate of 75 ml/min was used. Peak areas were determined by integration with either a Disc chart integrator or a planimeter. The weight per cent of each component present in the product was then determined by comparing the area of the component in question with total area, based on all components present.

A calibration curve (area *vs.* weight per cent) was constructed using *as*-hydrindacene as an external standard and was used to check some of our vpc results. The agreement was reasonably good as indicated by the examples shown in Table I.

TABLE I
COMPARISON OF VPC CALIBRATION CHART DATA

Run no.	*as*-Hydrindacene (wt %)	
	Vpc chart	Calibration chart
2	31	34
4	44	43

In another example, run 12 (Table II), the hydrindacene content of the entire product mixture, which contained an internal standard, compared to within *ca.* 4% with the original vpc value. This difference (with and without an internal standard) also reflects the error involved in sampling and in using a planimeter to determine areas. By using internal standards we have shown that, within experimental error, the entire sample that is injected into the vpc can be accounted for.

Table III below lists some pertinent information regarding the major reaction products.

(8) The author wishes to thank Professor Wayland E. Noland, University of Minnesota, for supplying an authentic sample of *s*-hydrindacene, originally synthesized in the laboratory of Professor R. T. Arnold.

TABLE II
INTERNAL STANDARD DATA

Run no.	Internal standard	
	Wt % added to sample	% calcd from vpc scan
2	10.00	12
4	12.13	15
12	9.79	10

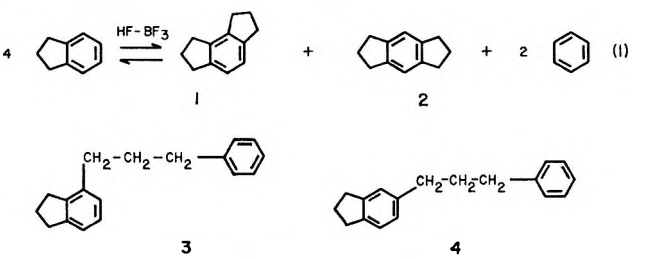
TABLE III
RETENTION TIME AND SOME PHYSICAL PROPERTIES OF MAJOR PRODUCTS

Compd	Retention, time, min	Mp, °C	Bp, °C (mm)	Ref
s-Hydrindacene	12.3	52–54	116–120 (9)	*a*
as-Hydrindacene	12.7	39–40	124–128 (9)	*b*
1,3-Diphenylpropane	15.9	6	109–111 (0.5)	*c*
Phenylpropylindanes	21.4	?	150–155 (0.7)	*b*
4-(3-Phenylpropyl)-*as*-hydrindacene	25.7	?	>155 (0.7)	*b*

[a] Reference 11. [b] This work. [c] P. Sabatier and M. Murat, *Ann. Chim.*, **4**, 286 (1915); *C. R. Acad. Sci., Ser. C*, **155**, 385 (1912).

Results and Discussion

One would expect to find experimental conditions where the formation of *as*-hydrindacene (1) and *s*-hydrindacene (2) can be optimized if indan behaves as expected based upon similar reactions[6] in the presence of hydrogen fluoride and boron trifluoride. The overall reaction is represented by eq 1. One would also expect to be able to isolate and identify the precursors to the tricyclic compounds, 4-(3-phenylpropyl)indan (**3**) and 5-(3-phenylpropyl)indan (**4**), based on the results in the literature for an analogous reaction involving tetralin.



At 70° using a tenfold excess of anhydrous hydrogen fluoride and a boron trifluoride:indan mol ratio of 0.9:1, the only tricyclic product formed in a substantial amount was *as*-hydrindacene. The reaction time was 90 min and the yield was 66%. An increase in reaction temperature led to by-products, while a decrease in reaction temperature resulted in a very low conversion of indan, and gave phenylpropylidanes as the major products.

Effect of Boron Trifluoride.—As with some of our previous studies,[6,9] and as has been pointed out by McCauley and Lien,[1] the disproportionation reaction was found to be quite dependent upon the boron trifluoride concentration. Table IV shows the effect of boron trifluoride concentration on the course of the reaction at 70°.

The indan reaction must be carried out at 70° in order to realize a high yield of the corresponding tricyclic hydrocarbon. At this temperature, however,

(9) R. D. Bushick, *J. Org. Chem.*, **33**, 4085 (1968).

TABLE IV
EFFECT OF BORON TRIFLUORIDE CONCENTRATION ON PRODUCT DISTRIBUTION AT 70° [a]

Run no.	1	2	3	4
Boron trifluoride:indan ratio (mol:mol)	0.09	0.6	0.7	0.9
	Product distribution (wt %)			
Benzene[b]	4.1	15.2	15.8	21.2
Indan	25.0	6.5	8.5	5.0
Hydrindacenes[c]	8.4	31.0	32.0	44.1
1,3-Diphenylpropane	7.7	1.6	1.7	1.2
Phenylpropylindans[d]	23.6	14.7	10.2	12.0
By-products[e]	31.2	31.0	31.8	16.5

[a] All reactions were run for 90 min. The hydrogen fluoride:indan mol ratio was ~10:1. [b] Calculated value, based on the yield of hydrindacenes. [c] *as*-Hydrindacene is the major tricyclic product; *s*-hydrindacene may account for 6 wt % (average) of the total hydrindacene fraction. [d] The 4 and 5 isomers of (3-phenylpropyl)indan. [e] By-products consist of a number of unidentified components appearing beyond the phenylpropylindans.

side reactions were more extensive, as evidenced by the large amount of by-products formed (Table IV). The amount of phenylpropylidans in the product mixture decreased as the boron trifluoride concentration was increased from 0.09 to 0.9.

Effect of Temperature.—The maximum amount of the tricyclic product was not formed when the temperature was lowered to avoid extensive by-product formation. This observation was further supported by an examination of the effect of temperature on the product distribution, illustrated in Figure 1. At 0°, little conversion of indan to products occurred. At these same reaction conditions about 8–10% phenylpropylindans were formed. These were the major products. At 30°, phenylpropylindans were by far the major products and were formed to the extent of 80%. As the temperature was raised the phenylpropylindan concentration in the product mixture decreased sharply and was accompanied by a corresponding increase in the tricyclic products, benzene, and various by-products in the reaction mixture. There appeared to be no temperature where the formation of the tricyclic products could be maximized and the by-products minimized. This was in contrast to the experimental results reported for tetralin,[6] where this kind of optimization was achieved.

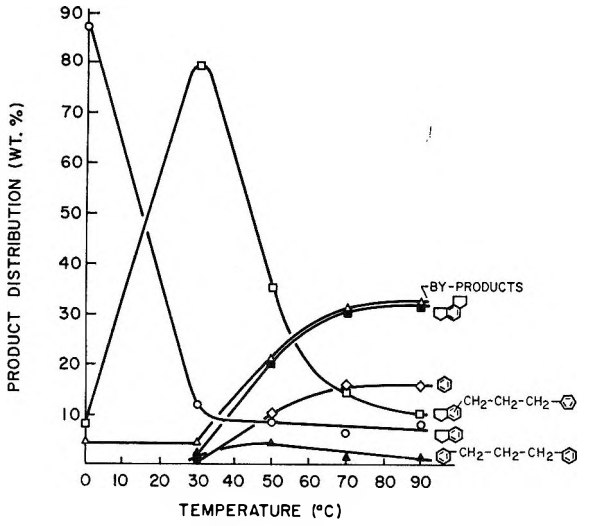
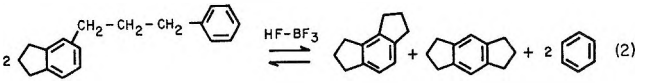


Figure 1.—Effect of temperature on product distribution. Hydrogen fluoride:indan mol ratio was ~10:1; boron trifluoride:indan mol ratio was ~0.6:1; reaction time was 90 min.

Formation of Phenylpropylindans.—Phenylpropylindans, mentioned above, are believed to be the precursors involved in the disproportionation of indan to the hydrindacenes, as illustrated below (eq 2). These



intermediates were the major products at 30° (Figure 1). Their behavior was examined in somewhat more detail over a range of boron trifluoride concentrations and the results are shown in Table V.

TABLE V
EFFECT OF BORON TRIFLUORIDE CONCENTRATION ON PHENYLPROPYLINDAN FORMATION AT 30° [a]

Run no.	5	6	7	8
Boron trifluoride:indan ratio (mol:mol)	0.1	0.6	0.9	1.2
	Product distribution (wt %)			
Benzene[b]		0.7	0.6	0.6
Indan	95.6	12.0	11.0	11.0
Hydrindacenes		1.4	1.3	1.3
Phenylpropylindans[c]	2.7	79.8	80.5	66.6
By-products[d]	1.7	6.1	6.6	20.5

[a] All reactions were run for 90 min. The hydrogen fluoride:indan mol ratio was ~10:1. [b] Calculated value based upon hydrindacene yield. [c] The 4 and 5 isomers of 3-phenylpropylindan. [d] By-products, most of which have not been identified. This includes up to 1.5% 1,3-diphenylpropane.

The maximum yield of the phenylpropylindans was found to occur at a boron trifluoride:indan ratio between 0.6 and 0.9:1. Beyond that point, an increase in boron trifluoride mole ratio became detrimental, as evidenced by the decrease in the amount of phenylpropylindans in the product mixture and also by the increase in the amount of by-products being formed. The ratio of 4-(3-phenylpropyl)- and 5-(3-phenylpropyl)indan was found to vary between 1:1 and 2:1 depending upon the experimental conditions.

To offer more support to the view that phenylpropylindans may be the precursors involved in going from indan to tricyclic products, a sample rich in these isomers was subjected to reaction conditions which closely approximated those used for the disproportionation of indan itself. The starting material consisted of 47.9% 4-(3-phenylpropyl)indan, 26.6% 5-(3-phenylpropyl)indan, 0.8% *as*-hydrindacene, 10% 1,3-diphenylpropane, and the remainder higher molecular weight condensation products. There was no indan present. The *major* products were 48.3% indan, 21.2% hydrindacenes (predominantly the asymmetric product), and 5.2% each of 4- and 5-(3-phenylpropyl)indan, indicating that an equilibrium between indan, the precursor, and the tricyclic compound does exist, and that to some extent one can direct the reaction toward a given product or products by varying the reaction conditions and catalyst concentration.

Effect of Reaction Time.—Examination of the effect of reaction time on the course of the disproportionation reaction at 70° with an excess of hydrogen fluoride and close to a 1:1 mol ratio of boron trifluoride:indan re-

vealed that within 5 min from the start of the reaction the major products formed were phenylpropylindans. As the reaction continued, the concentration of this particular species in the product mixture decreased and larger amounts of the hydrindacenes were formed. These data are shown in Table VI. Some 1,3-diphenylpropane was shown to be present in the reaction product.

TABLE VI
EFFECT OF REACTION TIME ON THE INDAN DISPROPORTIONATION REACTION AT 70° [a]

Run no.	9	10	11	12	13	b
Reaction time, min	5	10	15	30	60	90
	Product distribution (wt %)					
Benzene[c]	4.8	6.7	10.9	13.8	16.5	21.2
Indan	8.4	12.0	9.1	10.1	5.7	5.0
Hydrindacenes	9.7	12.8	22.1	28.0	33.6	44.1
Phenylpropylindans[d]	64.2	48.9	39.8	21.8	11.9	12.0
1,3-Diphenylpropane	1.3	2.0	2.6	2.3	2.1	1.2
By-products[e]	11.6	17.6	15.5	24.0	30.2	16.5

[a] The hydrogen fluoride:indan mol ratio was ≃10:1 and the boron trifluoride:indan mol ratio was 1:1. [b] This is run 4, Table IV, which had a boron trifluoride:indan mol ratio of 0.9:1, and is included here for the purpose of extending the range of reaction time being compared. [c] Calculated value based on yield of hydrindacenes. [d] The 4 and 5 isomers of 3-phenylpropylindan. [e] Thought to be condensation products involving indan and various reaction products. Includes 4 to 9% 4-(3-phenylpropyl)-*as*-hydrindacene.

Hydrindacene Products.—At no time during our indan disproportionation studies did we observe (*via* vpc) a second peak indicative of *s*-hydrindacene, although infrared spectra indicated that a small percentage of the *s*-hydrindacene was indeed present. Likewise, there was no nmr evidence for the presence of *s*-hydrindacene in several vpc-trapped samples of the hydrindacene peak. Disproportionation reactions with a similar hydrocarbon[5,9] resulted in an equilibrium mixture of tricyclic products. In an attempt to explain our present results; that is, why we did not observe a large amount of *s*-hydrindacene, we synthesized *s*-hydrindacene following the procedure of Arnold and Rondestvedt[10] and subjected this hydrocarbon to experimental conditions that duplicated those used for our disproportionation studies. Table VII contains the data obtained for the isomerizations conducted at various temperatures and reaction times.

TABLE VII
ISOMERIZATION OF *s*-HYDRINDACENE[a]

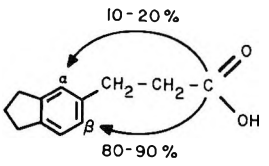
Run no.	Temp, °C	Time, min	*s*-Hydrindacene	*as*-Hydrindacene
A	30	60	91	9
B	50	60	38	62
C	70	60	27	73
D, E[b]	70	90	24	76
F[c]	70	90	19	81

[a] The hydrogen fluoride:charge mol ratio ranged from 10 to 40:1 and the boron trifluoride:charge mol ratio was between 1 and 2:1. All results were based on infrared spectra of the products and comparisons were made between the 11.4-and 12.4-μ bands, representative of 1,2,4,5 substitution and 1,2,3,4 substitution on benzene. [b] Duplicate runs which gave identical results. [c] Isomerization of *as*-hydrindacene.

(10) R. T. Arnold and E. Rondestvedt, *J. Amer. Chem. Soc.*, **67**, 1265 (1945).

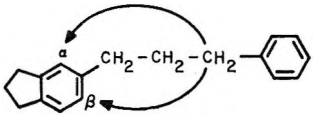
The isomerization of *s*-hydrindacene was halted after 60 min at 30, 50, and 70° and the product was examined to determine the extent of isomerization. A 90-min run was also carried out at 70° since much of our disproportionation work was done at this temperature. Note that there was little change in product composition after 60 and 90 min of reaction at 70°. Furthermore, if the equilibrium was approached from the opposite direction (using *as*-hydrindacene), the results (run F) are in fairly close agreement with what was obtained with *s*-hydrindacene. The fact that *s*-hydrindacene could be made to undergo isomerization was also of interest. Arnold and Barnes[11] attempted to isomerize *s*-hydrindacene with sulfuric acid at 70°, but only tar and starting material were recovered. With aluminum chloride, Arnold and Rondestvedt[10] likewise observed no isomerization to *as*-hydrindacene.

Another point which must be taken into consideration in order to help explain our results has to do with the work of Granger, Orzalesi, and Muratelle,[12] as well as that of Arnold and Rondestvedt,[10] who studied acid-catalyzed cyclizations of substituted indans. The cyclization of 3-(5-indanyl)propionic acid, for example, was shown to occur in the way illustrated below.



Arnold and Rondestvedt[10] obtained *s*-hydrindacene *via* the cyclization of either 5-(2-chloropropionyl)indan or the corresponding carboxylic acid. A similar type of cyclization involving 4-(5-indanyl)-*n*-butyric acid[13] was also shown to give the symmetrical tricyclic compound as the major product.

As already mentioned, the ratio of 4-(3-phenylpropyl)indan to 5-(3-phenylpropyl)indan can be as much as 2:1 (:6733%), depending upon reaction conditions. Ring closure of the 4 isomer will lead exclusively to *as*-hydrindacene while the 5 isomer may ring close to either the α position or β position as depicted below.



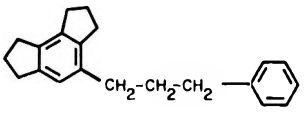
Since ring closure in substituted indans of this type is predominantly to the β position, approximately 26% (0.8 × 33%) to 30% (0.9 × 33%) of the symmetrical tricyclic compound might be expected to form. We have also noted that the *s*-hydrindacene–*as*-hydrindacene equilibrium is displaced toward the *as*-hydrindacene in a ratio of *ca.* 3:1 in the presence of hydrogen fluoride–boron trifluoride. The amount of *s*-hydrindacene at equilibrium is in good agreement with the estimated values shown above.

The products of several disproportionation runs were combined and the hydrindacene fraction was recovered by distillation. Our infrared spectra of the hydrindacene peak (trapped *via* vpc) for several of these distilla-

(11) R. T. Arnold and R. A. Barnes, *ibid.*, **66**, 960 (1944).
(12) R. Granger, H. Orzalesi, and A. Muratelle, *C. R. H. Acad. Sci.*, **252**, 1971 (1961).
(13) S. C. Sen-Gupta, *Curr. Sci.*, **5**, 133 (1936).

tion samples revealed a *s*-hydrindacene content as high as 6.0% of the total hydrindacene fraction. A hydrindacene content of 44% can be obtained from a typical run carried out at 70° and 90 min. This value, after adjustment for the *s*-hydrindacene content, together with 6.5% [which is an average value for the amount of alkylated *as*-hydrindacene appearing in the by-product mixture as 4-(3-phenylpropyl)-*as*-hydrindacene] accounts for all of the identified structures which contain the *as*-hydrindacene moiety (*ca.* 48%). If one assumes that the *s*-hydrindacene–*as*-hydrindacene equilibrium is rapid in relation to the formation of higher molecular weight by-products, then one can estimate that about one-fourth of the total of these combined values (*e.g.*, 0.25 × 48.0), or 12%, may be accounted for in terms of structures which should contain the symmetrical tricyclic compound. The difference between this 12% value and *ca.* 3%, which is the amount of *s*-hydrindacene present in the *total* product mixture, is a measure of the amount of *s*-hydrindacene not accounted for in terms of known products and which as a result of side reactions may be present in the by-product fraction.

The mass spectrometric results show that high molecular weight products are present, and we believe that these products may arise as a result of secondary reactions between indan and the initially formed tricyclic compounds. Of the many components that make up this particular by-product fraction, only one has been isolated in high enough yield to make identification possible. This compound was 4-(3-phenylpropyl)-*as*-hydrindacene (**5**), which could arise *via* the condensa-

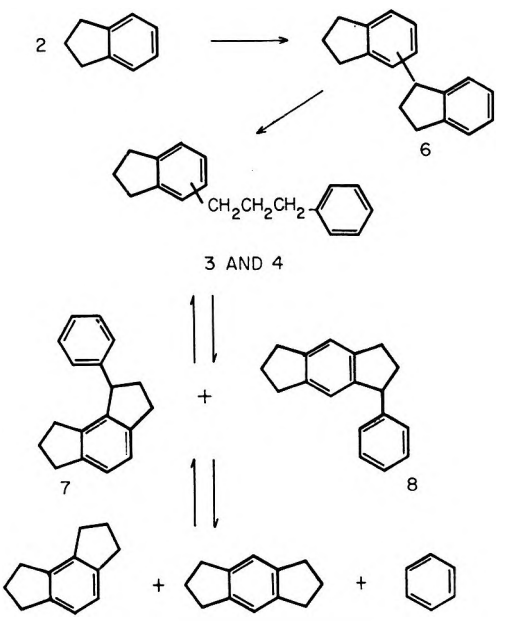


5

tion of *as*-hydrindacene and indan followed by ring opening of the initially formed condensation product. The typical yield of this product ranges between 4 and 9% at 70°. Identification was based upon infrared spectroscopy, mass spectrometry (*m/e* 277), and nuclear magnetic resonance. The infrared spectrum contains monosubstitution bands at 13.35 and 14.25 μ, a single hydrogen band at 11.50 μ, and pentasubstitution on benzene bands at 5.38 and 5.70 μ. The nmr spectrum contained a singlet at 7.17 ppm (5 aromatic hydrogens) and another at 6.75 ppm (1 aromatic hydrogen), a multiplet centered at 2.70 ppm (12, α hydrogens), and another multiplet centered at 1.83 ppm (6, β hydrogens). The ultraviolet spectrum, in isooctane, with absorption bands at 255 mμ (ϵ 1480), 262 (1500), 270 (1310), and 280 (1210) and shoulders at 260 mμ (ϵ 1490) and 265 (1350), was consistent with structure **5**.

The use of aluminum chloride (5 wt % based upon indan) in place of hydrogen fluoride–boron trifluoride resulted in poorer yields of hydrindacenes and phenylpropylindans. As an example, after 2 hr at 30° only 5.0% phenylpropylindans was formed. At 50° and the same reaction time, 11.6% phenylpropylindans was formed, and, if the temperature was raised to 90°, the yield of this compound was only 14.8%. Only a 3.3% yield of hydrindacenes was obtained at 90°.

Reaction Scheme.—The formation of the observed products is envisioned to occur by way of the following reaction scheme where all steps take place in the presence of the hydrogen fluoride–boron trifluoride catalyst.



It is suggested that a self-alkylation of indan occurs to form biindanyl (**6**). This compound has not been isolated and identified; however, it is reasonable to form a structure of this type which can undergo ring opening to give 4-(3-phenylpropyl)indan (**3**) and 5-(3-phenylpropyl)indan (**4**). The isolation and identification of these two compounds has been already discussed elsewhere in the paper. Compounds **3** and **4** may subsequently undergo cyclization to give the phenyl-substituted hydrindacenes shown in the reaction scheme. Upon further reaction in the presence of the strong acid catalyst the phenyl-substituted hydrindacenes, **7** and **8**, can undergo rearrangement leading to the observed tricyclic products, *as*-hydrindacene, **1**, and *s*-hydrindacene, **2**.

Registry No.—Indan, 496-11-7; hydrogen fluoride, 7664-39-3; boron trifluoride, 7637-07-2.

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Tetrasubstituted 2,5-Hydrofuranols and Their Anomerism[1]

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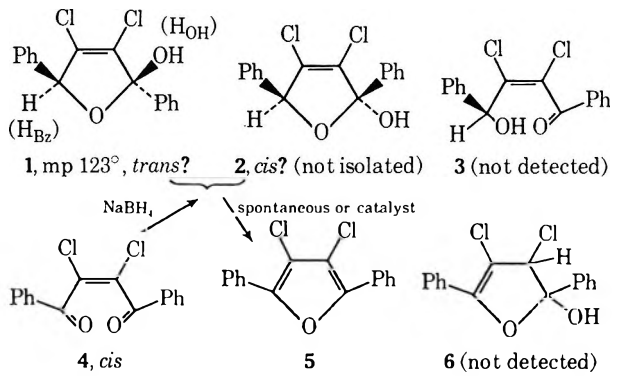
Four *cis*-2,3-disubstituted 1,4-diaryl-unsaturated 1,4 diketones were reduced by $NaBH_4$ to metastable 2,5-hydrofuranols. The solid 3,4-dichloro-2,5-diphenyl-2,5-hydrofuranol upon dissolving underwent equilibration within minutes between *cis* and *trans* forms. Detailed nmr study delineated solvent, concentration, and temperature effects. Reactions included facile dehydration to the furan and reduction by $NaBH_4$ to the *cis* unsaturated glycol. The stabilities of the hydrofuranols are related to the degrees of stabilization by substituents of the hydrofurylium ion intermediate to aromatization.

Many unsaturated 1,4-diketone reactions[4] such as the facile "*cis*-reductive–furanization"[4a] of dibenzoylstilbene by sodium borohydride and by phosphorus trichloride[4b] under conditions which are without effect upon the *trans* isomer, appear to be dependent upon *cis*-group interactions and participation involving cyclic transition states and intermediates such as the unstable 2,5-hydrofuranol **1**. Actual isolation of two metastable intermediates of this type have been reported, α-hydroxy-α,α'-diphenyldihydroisobenzofuran[5] and 2,5-di(*p*-bromophenyl)-3,4-diphenyl-2,5-hydrofuranol (**14**).[6]

Reduction of *cis*-dibenzoyldichloroethylene **4** by one-fourth molar equivalent of sodium borohydride followed by ice–water quench gave a single metastable crystalline compound which is one of the two possible anomers of 3,4-dichloro-2,5-diphenyl-2,5-hydrofuranol (**1**) (*trans*-dibenzoyldichloroethylene did not react under the same conditions). The second anomer **2** appears only in solution where equilibration occurs; it has not been isolated. These anomers are intramolecular hemiketals of the acyclic ketol **3** which may be involved or intermediate in the reduction of **4** and in the equilibration **1** $\rightleftharpoons$ **2** but which has not been isolated or detected in solution by spectral means.[7] The hydrofuranols **1** and **1** $\rightleftharpoons$ **2** underwent the expected slow spontaneous and rapid catalyzed elimination of water with aromatization to the furan **5**.



1, mp 123°, *trans*? **2**, *cis*? (not isolated) **3** (not detected)

4, *cis* **5** **6** (not detected)

That the product of borohydride reduction of **4** was indeed the hydrofuranol **1**–**2** was demonstrated by analysis and by ir, uv, and nmr spectra. The ir spectrum showed a moderately intense band at 1645 cm^{-1} attributable to a double bond bearing an electronegative substituent,[8] a hydroxyl band at 3450 cm^{-1}, and no carbonyl or enol ether group absorptions in the 1690- or 1640-cm^{-1} regions, respectively. That it was the 2,5- and not the conceivable 2,3-hydrofuranol **6** was established by its lack of uv absorption above 220 nm (**6** would have absorbed strongly at *ca.* 250 nm). The nmr spectrum observed immediately after solution (60 mg/0.4 ml of $CDCl_3$) showed a ten-proton aromatic multiplet at *ca.* δ 7.5, a benzyl proton singlet (H_{Bz}) at 5.75, and a hydroxylic proton singlet (H_{OH}) at 3.55, the latter shown to be hydroxylic by disappearance upon treatment with D_2O.

Equilibration of the *cis* and *trans* anomers 1 $\rightleftharpoons$ 2 was first noticed when nmr solutions of **1** in $CDCl_3$ (60 mg/0.4 ml) had been allowed to stand after spectral determination. Over 34 hr the benzylic proton-5 (H_{Bz}) singlet integrating for one proton (which was subsequently recognized as being composed of two overlapping singlets) slowly separated into and became two individual singlets very close together with total integration intensities of one proton. This separation of peaks was subsequently shown to be due to an unequal effect on the anomers of the change in solvent brought about by slow spontaneous generation of water accompanying furanization to **5**. This same separation of the one-proton H_{Bz} singlet into two singlets occurred *immediately* when a microdrop of water, D_2O, or DMSO-d_6[9] was added to a freshly prepared solution of **1** in pure $CDCl_3$.

That equilibration of the anomers **1** and **2** was indeed involved was shown as follows. The nmr spectrum of **1** in DMSO-d_6 at the low concentration of 10 mg/0.4 ml, observed *immediately* upon solution, showed a single benzylic proton peak at δ 5.96. A second peak then appeared upfield at δ 5.88 (for 2 H_{Bz}) which grew while the first peak diminished, until a constant peak integration ratio of *ca.* 1.5 for 1/2 was reached within 56 min. The first and stronger downfield peak must

(1) Supported by research grants from the National Science Foundation.

(2) W. M. Hankins, Ph.D. Dissertation, University of Virginia, 1969.

(3) E. L. Anderson, M. S. Thesis, University of Virginia, 1964.

(4) (a) R. E. Lutz, C. R. Bauer, R. G. Lutz, and J. S. Gillespie, *J. Org. Chem.*, **20**, 218 (1955); (b) R. E. Lutz and W. J. Welstead, Jr., *J. Amer. Chem. Soc.*, **85**, 755 (1963); (c) R. E. Lutz and J. S. Gillespie, *ibid.*, 344 (1950); (d) *ibid.*, 2002 (1950).

(5) A. Guyot and J. Catel, *Bull. Soc. Chim. Fr.*, **35**, 1124 (1906).

(6) H. H. Freedman and G. A. Doorakian, *Tetrahedron*, **20**, 2181 (1964).

(7) *Cf.* examples of this type of interconversions: B. G. Hudson and R. Barker, *J. Org. Chem.*, **32**, 2101 (1967); B. Casu, M. Geggiani, G. G. Gallo, and A. Vigevani, *Tetrahedron Lett.*, No. 27, 2253 (1965).

(8) G. Eglinton in "Physical Methods in Organic Chemistry," J. C. P. Schwartz, Ed., Oliver and Boyd, Edinburgh and London, 1964, p 76.

(9) (a) Because of its strong hydrogen-bonding effect DMSO has been used in carbohydrate chemistry to lower the anomerization rate and thereby to make possible the detection and analysis of the anomers: B. Casu, *et al.*, *Tetrahedron*, **22**, 3061 (1966). *Cf.* also (b) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **85**, 1256 (1964); (c) C. P. Rader, *ibid.*, **88**, 1713 (1966); (d) C. S. Springer and P. W. Meek, *J. Phys. Chem.*, **70**, 481 (1956); (e) R. J. Oulett, *J. Amer. Chem. Soc.*, **86**, 3089, 4378 (1964); (f) N. Bagett, *et al.*, *Chem. Ind. (London)*, 106 (1961); (g) Y. Aito, T. Matsuo, and C. Aso, *Bull. Chem. Soc. Jap.*, **40**, 130 (1967); (h) R. A. Newark and C. R. Cantor, *J. Amer. Chem. Soc.*, **90**, 510 (1968).

therefore represent the anomer of the solid state, **1**, and the smaller second and upfield peak therefore must represent the anomer **2** which has not been isolated. At the higher concentration of substrate of 60 mg in 0.4 ml of DMSO-d_6, a similar equilibrium ratio was reached but in the *much shorter time* of 15 min. This greater speed of equilibration in the more concentrated solution is presumably due in large part to increased catalysis by, or involving, the weakly acid substrate.

This same anomer equilibrium ratio of *ca.* 1.5 for **1**/**2** was attained in $CDCl_3$ more rapidly than in DMSO-d_6, but it was visible by nmr only at concentrations of substrate *less* than 60 mg in 0.4 ml of $CDCl_3$. At the concentration of 20 mg in 0.4 ml of $CDCl_3$, only the upfield and larger of the two anomer peaks of the mixture at equilibrium was seen immediately upon solution of the solid **1**; this peak integrated for one proton and necessarily corresponds to the isomer of the solid state **1**. The second peak (as was the second peak in $CDCl_3$) was the smaller of the two peaks at equilibrium and must represent **2**. In contrast to the case in DMSO-d_6, this second peak for **2** appeared *downfield* rather than upfield of the first, and within the very short time of 9 min it grew to about the same equilibrium ratio of *ca.* 1.5 for 1/2 with a total integrated intensity of one for the pair. Thus, the change in solvent from the polar DMSO-d_6 to $CDCl_3$ had reversed the relative positions of the two peaks, that of **1** from downfield to upfield of **2**.

The magnitude of the differences between the chemical shifts of the respective protons H_{Bz} and H_{OH} of the two anomers is of a very low order. Furthermore, the equilibrium ratios of **1** and **2** in the two aprotic solvents of widely different dielectric constants, DMSO and $CDCl_3$, are very similar. This indicates that the differences both in polarity and in thermodynamic stability of the anomers **1** and **2** are exceedingly small.[10]

Solvent effects on nmr chemical shifts are shown in Table I where the δ of H_{Bz} and H_{OH} were followed systematically in mixtures starting with pure $CDCl_3$ and ending with pure DMSO-d_6. Addition of the first microdrop of DMSO-d_6 to the $CDCl_3$ solution caused separation of the respective one-proton H_{Bz} and H_{OH} singlets into corresponding pairs of singlets. The larger peak of **1** was slightly upfield of the corresponding and smaller peaks of **2**, each pair integrating for one proton. With further dropwise addition of DMSO-d_6 to the $CDCl_3$ solution, the larger **1** H_{Bz} peak moved very slowly downfield, and, when the solvent ratio reached 0.67 for $CDCl_3$/DMSO-d_6, this larger **1** H_{Bz} peak crossed over the corresponding and smaller **2**-H_{Bz} peak which also had been moving downfield but more slowly. The total range of variations in the positions of the H_{Bz} signals was small, *ca.* δ 0.2.

When 4 drops of DMSO-d_6 had been added, the H_{Bz} and H_{OH} pairs of singlets merged into a two-proton multiplet as the faster moving H_{OH} pair of singlets crossed over the much slower moving H_{Bz} pair. At 5 drops of added DMSO-d_6, the **1** and **2** H_{OH} singlets merged in a crossover. And at 0.67 and lower for $CDCl_3$/DMSO-d_6, the **1** H_{OH} singlet appeared just downfield of the aromatic multiplet, whereas the **2** H_{OH} peak was under the aromatic multiplet. In going from pure $CDCl_3$ to pure DMSO-d_6, the H_{OH} δ of the anomers varied from *ca.* -0.1 to $+0.6$ and underwent drastic downfield shift of *ca.* δ 4.

Dropwise addition of DMF or acetone to the equilibrium mixture in $CDCl_3$ produced changes in the nmr spectrum similar with those above except that acetone caused a significantly lower rate of downfield shift of the H_{OH} signals, which is understandable in terms of the expected lesser strength of hydrogen bonding with the substrate.[11]

Concentration Effects on Nmr (10–60 mg/0.4 ml).—In DMSO-d_6 the δ values for both **1** and **2** pairs of H_{Bz} and H_{OH} protons did not change significantly, which is consistent with the observation[9c] that the chemical shift of a number of alcohol hydroxyl protons in this solvent is independent of concentration below 0.12 mol fraction of solute. This indicates that in dilute solutions the relative population of hydrogen bonded species OH–DMSO does not change significantly.

In $CDCl_3$ the **1** H_{Bz} peak did not move, while the **2** H_{Bz} peak moved upfield (δ 0.08). On the other hand, the **1**–**2** H_{OH} broad singlet moved *downfield* (δ 0.2); furthermore, there was a very large increase in the broad infrared hydroxyl absorption at *ca.* 3425 cm^{-1}. These effects suggest markedly increasing association by intramolecular hydrogen bonding at higher concentration.[9]

The effect of temperature (34 to $-20°$) on nmr ($CDCl_3$ with DMSO-d_6) was to shift the signals progressively downfield, slightly for H_{Bz} (δ 0.07) and considerably for H_{OH} (δ 1.0). The H_{OH} shift was approximately linear (like that with cyclohexanol in DMSO-d_6[9c]) and comparable to the effect of addition of DMSO-d_6 at room temperature. At 0°, all of the **1**–**2** H_{Bz} and H_{OH} peaks were in a multiplet close to the solvent crossover point for the H_{Bz} and H_{OH} pairs of signals. At

TABLE I

SOLVENT EFFECTS ON NMR OF 1 AND 2 (60 mg/0.4 ml) IN $CDCl_3$–DMSO-d_6 MIXTURES[a]

DMSO-d_6, drops[b]	δ H_{Bz} 1	δ H_{Bz} 2	δ H_{OH}[c] 1	δ H_{OH}[c] 2
0	5.76	5.76	3.67	3.67
1	5.80	5.86	4.27	4.37
3	5.79	5.88	5.46	5.55
4	5.8 (m, 2 H)[d]			
5	5.80	5.92	6.07 (s)[d]	
7	5.80	5.92	6.57	6.51
10	5.80	5.92	7.02	6.92
Vol %				
25	5.77	5.84	7.72	*e*
50	5.82	5.85	7.78	*e*
60	5.88 (s)[d]		7.83	*e*
75	5.91	5.87	7.84	*e*
100	5.96	5.88	7.90	*ca.* 7.3

[a] Assignments of δ values specifically to **1** or **2** are based on the near constancy of the equilibrium position (1/2 = 1.5), on the assumption that the progression of these values is smooth, and on the specific demonstration above, that immediately upon solution of the solid **1** in both $CDCl_3$ (40 mg/40 ml) and in DMSO-d_6, only the solid-state isomer was initially present. Solvent samples were drawn from common batches. [b] Added to 0.4 ml of $CDCl_3$; wt of microdrop, 6.2 ± 0.1 mg. [c] Deleted by D_2O. [d] Crossover point. [e] The **1** H_{OH} δ value falls under the aromatic multiplet at *ca.* δ 7.46 in $CDCl_3$ and 7.2 in DMSO-d_6.

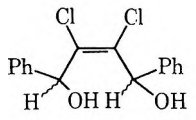
(10) *Cf.* The very dissimilar equilibrium constants of the *cis* and *trans* isomers of 2,3-dibenzoyl-1-benzylaziridine where K (*cis*/*trans*) varies greatly from 5.25 in DMSO to 0.32 in *t*-butyl alcohol: R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968).

(11) W. C. Drinkard and D. Kivelson, *J. Phys. Chem.*, **62**, 1494 (1958).

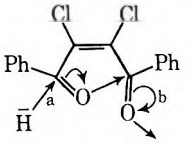
$-20°$, the H_{Bz} and H_{OH} signals were one-proton singlets. These results are consistent with supposition of exothermic hydrogen bonding.[9h]

Assignment of Configurations.—Consideration of Dreiding models, the very small effects of differences in polarity of the solvent, and the small but relatively constant equilibrium ratio K of *ca.* 1.5 for **1**/**2** suggest an overriding determinative importance of steric over polar factors. It seems reasonable, therefore, tentatively to assign the *trans* configuration to the more favored solid-state anomer **1**.

Reactions and Mechanisms.—Dehydration of **1**–**2** to furan **5** occurred slowly in chloroform, and rapidly in boiling glacial acetic acid and in moist ether containing iodine. Reduction by sodium borohydride gave only one of the diastereoisomeric *cis*-glycols **7** which was also obtainable in one step from the *cis* unsaturated diketone **4** by using an excess of borohydride. The structure of the glycol **7** was demonstrated by analysis and spectra; the broad ir bands (KBr) at 3600 and 3400 cm^{-1} indicated free and hydrogen-bonded OH groups; and the uv spectrum (EtOH) showed no absorption above 230 nm. The fact that one glycol only was obtained suggests involvement of a typical *cis* group proximity effect or participation which exerts a high degree of steric control over the configuration of the product, a very interesting subject for further study.



7 (*dl* or *meso*)



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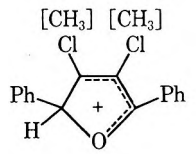
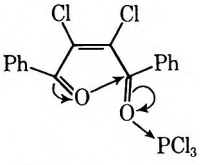


9 (**10**)



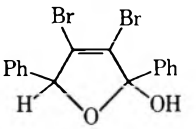
11 (→ $POCl_3$ + **5**)

Because the hydrofuranols **1**–**2** are the major products obtained upon borohydride reduction of the unsaturated diketone **4**, and because the reduction of **1** ⇌ **2** to the glycol requires an excess of borohydride, it can be said that there is a *cis*-group effect facilitating the first step in the reduction of **4** wherein the product is presumably stabilized to a very considerable extent in the intramolecular hemiketal forms **1** ⇌ **2**. The isolation of **1** as the chief product therefore supports the types of mechanism proposed earlier for borohydride "*cis*-reductive–furanizations" of unsaturated 1,4 diketones[4] the simplest of which is hydride attack at one carbonyl of **4** (**8**) with simultaneous or subsequent cyclization and protonation to the hydrofuranol.

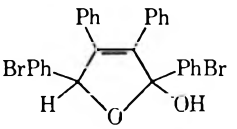
The furanizations of the hydrofuranols are presumed to require passage through hydrofurylium ions (**9**) where the inductive effects of the 3,4 halogens sufficiently destabilize this intermediate to lower the rate of dehydration and thereby to permit the isolation of the metastable intermediates. This principle should apply also in the reduction of the *cis*-2,3-dimethyl analog of **4** where several attempts have failed to yield the hydrofuranol and gave only the furan. In this case the intermediate 3,4-dimethyl cation **10** would be formed relatively easily from the 3,4-dimethyl analog of **1**–**2** because of stabilization of the positive charge by the electron-repelling methyl groups, and this would greatly facilitate the dehydration.

The reduction of the dichloro *cis* unsaturated diketone **4** to the furan **5** was accomplished in one step by refluxing phosphorus trichloride, conditions which were without effect on the *trans* isomer.[4b] This reduction is consistent with the assumption that facilitating *cis*-group interaction or participation is involved such as is depicted in **11**, which would not be possible with the *trans* isomer.[4b]

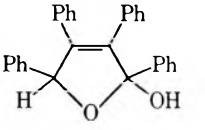
Other Hydrofuranols.—Several of these were made to show the generality of their formation and isolation where the structural setup is favorable, to test relative stabilities, and to determine whether the anomer equilibration in solution is generally involved. Like the dichlorohydrofuranol **1**, the 3,4-dibromo analog **12**[12] was easily made and isolated through borohydride reduction of the dibromo analog of *cis* unsaturated diketone **4**.[12] It was metastable as was **1**, and the anomer equilibration **12** ⇌ **13** in solution was demonstrated by nmr. The structure **12** is supported by analysis, spectral data, and reactions. Hot glacial acetic acid quickly converted it into the corresponding furan, and nmr tracking in $CDCl_3$ showed the spontaneous loss of water upon standing at a rate comparable with that of **1**–**2**. As with **1**–**2**, a series of nmr spectra in $CDCl_3$ with added increments of DMSO-d_6 showed separation of the H_{Bz} and H_{OH} one-proton singlets into two signals for each. In pure DMSO-d_6 the H_{Bz} signals for **12** and **13** were at δ 5.87 and 5.98, respectively, but for H_{OH} there was only a broad one-proton singlet at δ 7.8.



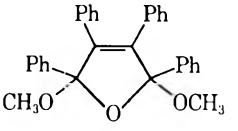
12, mp 129°, *trans*?
13, *cis* (not isolated)



14[6]



15, mp 161°, *trans*?
16, *cis* (not isolated)



17, **18**
cis, *trans*

3,4-Diphenyl-2,5-di-(*p*-bromophenyl)-2,5-hydrofuranol (**14**)[6] was remade by borohydride reduction of *cis*-di(*p*-bromobenzoyl)stilbene. Although moderately stable, it was somewhat less stable than **1** and **12** as shown by nmr tracking in $CDCl_3$. The ir spectrum of the hydrofuranol **14** displayed associated hydroxyl absorption at 3425 cm^{-1} but none for a carbonyl; its uv spectrum in ethanol was very similar to that of the cyclic diketal of the corresponding *cis* unsaturated diketone. The nmr spectrum in $CDCl_3$ contained six discrete lines: four peaks in the phenyl region (δ 7.1–7.5 integrating for 18 protons), and two singlets integrating for one proton each for H_{Bz} and H_{OH} at δ 6.35 and 3.45, respectively, the latter shown to be hydroxylic by disappearance upon addition of D_2O. Dropwise

(12) The work on **12** was carried out by L. Hayes.

addition of 10 drops of DMSO-d_6 did not change the H_{Bz} peak position but did shift the H_{OH} peak rapidly downfield to δ 6.74, crossing over the nearly stationary H_{Bz} peak at 5 drops of DMSO-d_6. Using both the HA-100 and R-20 instruments, addition of DMSO-d_6 dropwise to a $CDCl_3$ solution of **14** (60 mg/0.4 ml) failed to bring about separation of either the H_{Bz} or H_{OH} peaks into a pair of peaks, as happened in the cases of **1** and **12**. Only the one sharp singlet each was observed for H_{Bz} and for H_{OH} in both solvents and at several concentrations.

2,3,4,5-Tetraphenyl-2,5-hydrofuranol (**15**) (not isolated in earlier attempts)[3,6] was prepared by borohydride reduction of *cis*-dibenzoylstilbene in methanol. It proved to be unstable and attempts to purify it always entailed partial spontaneous dehydration to tetraphenylfuran.[6] From the reaction solution a small amount of a mixture of the *cis* and *trans* cyclic diketals **17** and **18** was obtained and separated on a Florisil column; evidently these had been formed by reaction with the solvent in competition with reduction.

The hydrofuranol **15** was characterized by analysis and spectral data. The ir (KBr) showed broad hydroxyl absorption at *ca.* 3400 cm^{-1} and no carbonyl absorption. Nmr (60 mg/0.4 ml) in $CDCl_3$ showed two singlets, H_{OH} (eliminated by D_2O) at δ 3.46, and H_{Bz} at δ 6.35, and a 20-proton aromatic multiplet centered at *ca.* δ 7.2. Upon seven dropwise additions of DMSO-d_6 the H_{Bz} singlet was unchanged while the H_{OH} singlet moved downfield to δ 6.53. Only in pure DMSO-d_6 did there appear an anomer peak (corresponding to **16**); the H_{Bz} peak consisted of two separate peaks close together at δ 6.33 and 6.48 with total integration for one proton.

The hydrofuranol **15** was easily converted to tetraphenylfuran, spontaneously in solution, and rapidly by hot glacial acetic acid. It is relatively unstable compared with the 3,4-dihalo analogs **2** and **12**, but was not far different in stability from **14**. These stability differences are consistent with electronic and steric effects expected in the presumed intermediate carbonium ions of type **9**.

All of the four hydrofuranols studied were metastable. Nmr data show that three of them, **1**, **12**, and **15**, underwent anomer equilibration in solution but did not reveal anomerism in the *p*-dibromohydrofuranol **14**. This uniqueness of **14** might be explained by the effect of the *para* bromines in significantly increasing the polarity in the *cis* configuration, thus making the *trans* isomer relatively the more stable and predominent at equilibrium. However, it is not excluded that the *para* bromines have increased stabilization of the anomer intermediate and made equilibration too rapid to observe by nmr, or have diminished the differences in chemical shifts for the anomer signals and made them indistinguishable under the conditions and instrumentation used. Further studies in this field would be interesting.

Experimental Section[13]

3,4-Dichloro-2,5-diphenyl-2,5-hydrofuranol (1). Reduction of *cis*-2,3-Dichloro-1,2-dibenzoylethylene (4).—A solution of 52 mg of $NaBH_4$ in 19 ml of absolute methanol was added slowly to a stirred solution of 1.5 g of **4**[14] in 20 ml of absolute methanol at room temperature. After continued stirring for 15 min, addition of 1 ml of acetone, pouring into ice water, extracting with ether, and evaporating under reduced pressure at 40°, the product was dissolved in the minimum amount of benzene and chromatographed on 50 g of Florisil, eluting with petroleum pentane containing increasing percentages of benzene. Hydrofuranol **1** was in the 40–50% benzene effluent and was recrystallized from *n*-hexane to give 0.9 g (60%): mp 120–121°; ir ($CHCl_3$) 3425, 1645 cm^{-1}, no absorption in the region of 1690 cm^{-1}; λ_{EtOH}, no absorption above 220 nm; nmr (in $CDCl_3$, Table I) ten-proton aromatic multiplet at δ 7.5.

Anal. Calcd for $C_{16}H_{12}O_2Cl_2$: C, 62.56; H, 3.94. Found: C, 62.65; H, 4.26.

Dehydration of 1. Nmr Tracking of Spontaneous Dehydration in $CDCl_3$ (60 mg/0.4 ml).— The spectrum of a freshly prepared solution showed singlets for both H_{Bz} and H_{OH}. Over 24 hr at room temperature there was progressive separation of the H_{Bz} peak into a pair of peaks with total integration for one proton, but the H_{OH} singlet progressively broadened greatly and began to diminish in integrated intensity to *ca.* 0.75. Then diminution of the H_{Bz} peaks began and that of H_{OH} continued, the latter more rapidly until after 131 hr the H_{Bz} peaks had separated further and almost disappeared, and the broadened H_{OH} peak had completely disappeared.[15] The spectrum also showed a growing broad aromatic multiplet centered at δ 7.6 which was assigned to the *ortho* protons of furan **4** on the basis of a comparison with the nmr spectrum of pure **5**. Furthermore there was a growing peak at δ 4.8 assignable to water.

Dehydration of **1** (15 mg) in 0.5 ml of refluxing glacial acetic acid (5 min) and pouring the mixture into ice gave 12 mg of **5**, mp 94–95°. In another experiment a solution of **1** in moist ether containing iodine, after shaking for 5 min and evaporating, gave **5**.

Attempted autoxidations[5] of **1–2** were unsuccessful, unchanged material being recovered in which no carbonyl group impurities were detected by ir. Conditions: dry air bubbled through solutions of **1** in (a) ethanol (1 hr), (b) ethanol containing triethylamine (overnight), and (c) $CHCl_3$ containing benzoylperoxide.

Reduction of *cis*-1,2-dichloro-1,2-dibenzoylethylene (4) by PCl_3 (0.5 g in 50 ml), refluxing for 32 hr followed by hydrolysis in ice, chromatographing over Al_2O_3, and elution with 10% benzene–petroleum pentane gave 0.24 g of **5** (mp 91–93°) and 0.19 g of starting material (mp 66–68°). The *trans* isomer of **5** was recovered unchanged (86%) under these conditions.

1,4-Diphenyl-2,3-dichloro-2-butene-1,4-diol (7). A. By Borohydride Reduction of 5.—A stirred solution of 1 g of **5** in 25 ml of methanol was treated with a large excess of $NaBH_4$ (250 mg) in two portions (30 min). Pouring into water, extraction with ether, washing with water, drying over Na_2SO_4, evaporation, and crystallization from $CHCl_3$ gave 0.87 g of **7**, mp 139.5–141.5°.

B. By Borohydride Reduction of 1.—Compound **1** (100 mg in 10 ml of methanol), with excess $NaBH_4$ (25 mg), was worked up as above, and, after crystallization from *n*-hexane, gave 90 mg of **7**: mp 139–141°; ir (KBr) 3600, 3400 (broad), 1630 cm^{-1}, no absorption in the 1690-cm^{-1} region; λ_{EtOH}, no absorption above 230 nm; nmr ($CDCl_3$) δ *ca.* 7.4 (m, 10, aromatic), 6.2 (s, 2, CH–OH), 3.1 (hydroxyl envelope, 2, disappearing on treatment with D_2O).

Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56. Found: C, 62.42; H, 4.63.

3,4-Dibromo-2,5-diphenyl-2,5-hydrofuranol (12). Borohydride reduction of *cis*-dibenzoyldibromoethylene (0.4 g in 5 ml of CH_3OH by 1.6 mg of $NaBH_4$ in 5 ml of CH_3OH, 15 min), quenching in ice water, and recrystallization from hexane gave 0.2 g (50%) of **12**: mp 128–129°; ir (KBr) 3400 cm^{-1} (b, OH), none in 1650–1700-cm^{-1} region; $\lambda_{max}^{CHCl_3 \text{ or } EtOH}$, none above 220 nm. For nmr [60 mg/0.4 ml $CDCl_3$ + drops of DMSO-d_6 (wt per drop, 6.2 ± 0.1 mg)], see Table II.

(13) Melting points were taken on a Thomas–Hoover apparatus (corrected), ir on a Perkin-Elmer 137 (KBr pellet), uv on a Perkin-Elmer 4000A Spectracord or Beckman DK-2, and nmr on a Varian A-60 and HA-100 and Hitachi Perkin-Elmer R-20, TMS. Identifications were by mixture melting point and/or ir.

(14) R. E. Lutz and F. N. Wilder, *J. Amer. Chem. Soc.*, **56**, 978, 2145 (1934).

(15) The observation that the loss of the H_{OH} resonance was faster than that of H_{Bz} during the spontaneous dehydration may be explained by proton exchange with DOH which is commonly present in $CDCl_3$. Trace amounts of DOH as impurity in $CDCl_3$ have been utilized to identify absorption bands from other OH groups which undergo slow reversible proton exchange with H_2O: J. Feeney and A. Henrich, *Chem. Commun.*, **10**, 295 (1966).

TABLE II

DMSO-d_6, +drops	δ HBr2 12	δ HBr2 13	δ HOH 12	δ HOH 13
0	5.85	5.85	3.53	3.53
1	5.84	5.87	4.51	4.61
2	5.83	5.90	5.49	5.58
3	5.82	5.90	6.28	6.28
4	5.82	5.90	6.75	6.68
Pure DMSO-d_6	5.98	5.87	7.8 (s, broad)	

Anal. Calcd for $C_{16}H_{12}Br_2O_2$: C, 48.48; H, 8.03. Found: C, 48.51; H, 3.19.

Dehydrations of **12**, and also **14** and **15**, to the corresponding furans were practically quantitative in warm glacial acetic acid (15 min).

2,3,4,5-Tetraphenyl-2,5-hydrofuranol (15). Borohydride reduction of *cis*-dibenzoylstilbene[3,6] (2.8 g in 200 ml of absolute methanol with 2 g of $NaBH_4$ warmed with stirring for 20 min), followed by ice–water quench, and crystallization from hexane gave 2.5 g of **15** (90%), mp 160–161°.

Anal. Calcd for $C_{28}H_{22}O_2$: C, 86.12; H, 5.69. Found: C, 86.01; H, 5.67.

Preparation of 2,5-di-(4-bromophenyl)-3,4-diphenyl-2,5-hydrofuranol (14) was done by $NaBH_4$ reduction of the *cis* unsaturated diketone[4b] (91%, recrystallized from hexane, mp 158–160°): ir (KBr) 3425 cm^{-1} (associated OH), none between 1650 and 1700 cm^{-1} (C=O).

Registry No.—**1**, 25244-40-0; **2**, 25244-41-1; **5**, 25244-42-2; **7**, 25244-43-3; **12**, 25244-44-4; **14**, 1888-40-0; **15**, 25244-46-6.

Acknowledgment.—The preparations of some intermediates and the synthesis of **12** were carried out by L. Hayes.

Aldol Condensations of Leucoquinizarin

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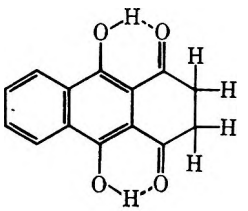
Hydrochloric acid was found to be an effective catalyst for condensation of leucoquinizarin with aromatic mono- and dialdehydes but ineffective with aliphatic aldehydes; monoaldehydes gave 2-alkylquinizarins; *o*-dialdehydes gave polycyclic compounds. Piperidinium acetate was found to be effective for both aliphatic and aromatic aldehydes. 2-Alkylleucoquinizarins likewise gave 2,3-dialkylquinizarins. They are presented in relationship to previously reported alkaline dithionite condensations. A mechanism is proposed in which the dehydration step is suggested to be rate determining.

Leucoquinizarin has been shown by proton magnetic resonance studies to exist, in solution, entirely as the diketo tautomer, 2,3-dihydro-9,10-dihydroxy-1,4-anthracenedione **1**.[1] This diphenolic diketone is known to undergo aldol condensations with aldehydes.



1

Earlier workers[2,3] investigated the condensation of leucoquinizarin with aldehydes in alkaline dithionite solution under nitrogen at 90–95° and then allowed the products to interact with air. Under these conditions formaldehyde gave 2,3-dimethylquinizarin; however, other aliphatic aldehydes up to C_8 and aromatic aldehydes gave condensation products involving only one molecule of aldehyde per molecule of leucoquinizarin. Aldehydes above C_8 failed to give condensation products.

Marschalk, *et al.*,[2] were able to reduce 2-ethylquinizarin with dithionite and then to react the reduced product with formaldehyde; 2-ethyl-3-methylquinizarin was obtained. As will be shown later the failure of most aldehydes (except formaldehyde) to give 2,3-disubstituted products in the alkaline dithionite procedure cannot be attributed to steric hindrance of the monocondensation product, *i.e.*, 2-alkylquiniazrin.

Alkaline Dithionite Condensations.—In the present investigation, we repeated the condensation of leucoquinizarin with a large excess of butyraldehyde in alkaline dithionite and then followed the fate of the aldehyde.

Vapor phase chromatography revealed the absence of butyraldehyde at the end of the reaction; the only product isolated had one molecule of aldehyde per mole of quinizarin as observed by the previous investigators. We conclude that the alkaline dithionite procedure is not a general method for introducing two molecules of aldehyde in quinizarin owing to the competing self-condensation of aldehydes having α hydrogens. The observation that aldehydes above C_8 fail to react at all may simply reflect lack of solubility of these aldehydes in the reaction medium.

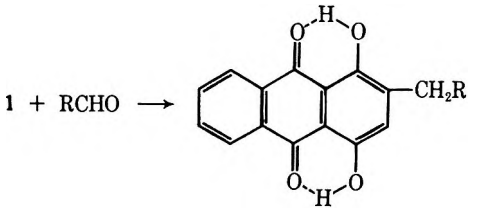
Aqueous Hydrochloric Acid Catalyzed Condensations.—We have studied the reactions of leucoquinizarin with a variety of aldehydes in 2-propanol using concentrated hydrochloric acid as catalyst with the following results. Aliphatic aldehydes[4] C_4 through C_{12} failed to give condensation products. This failure cannot be attributed to the destruction of the aldehyde prior to its condensation with leucoquinizarin, since, at least in the case of butyraldehyde, considerable excess of the aldehyde remained after a 20-hr reaction period. Aromatic monoaldehydes including those with electron-releasing and -withdrawing substituents gave condensation products **2**, **3**, **4**, **5**, involving one molecule of aldehyde per molecule of leucoquinizarin.

(1) S. M. Bloom and R. H. Hulton, *Tetrahedron Lett.*, No. 28, 1993 (1963).

(2) Ch. Marschalk, F. Koenig, and N. Ouroussoff, *Bull. Soc. Chim., Fr.*, 1545 (1936).

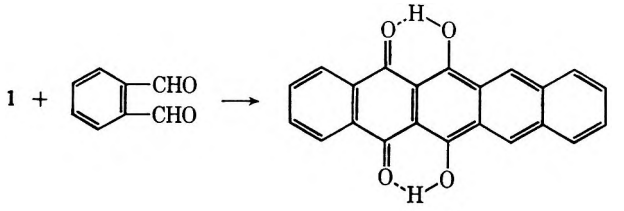
(3) A. T. Peters, Jr., and A. T. Peters, *J. Chem. Soc.*, 1125 (1960).

(4) In the present investigation we were concerned only with aldehydes C_4 through C_{12}.



2, R = C_6H_5
3, R = p-C_6H_4Cl
4, R = p-$C_6H_4OCH_3$
5, R = p-$C_6H_4NMe_2$

Aromatic o-dialdehydes, *i.e.*, o-phthaldehyde and naphthalene-2,3-dialdehyde, gave the corresponding pentacence **6** and hexacene **7** derivatives resulting from a two-stage condensation involving one molecule of dialdehyde and one molecule of leucoquinizarin.



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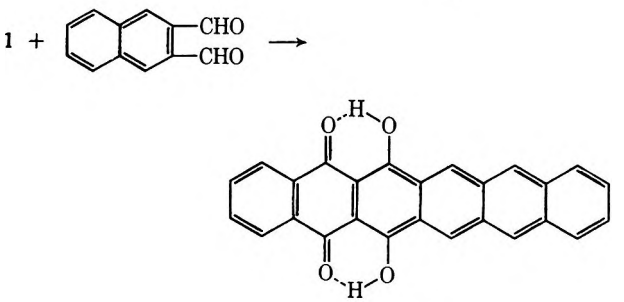


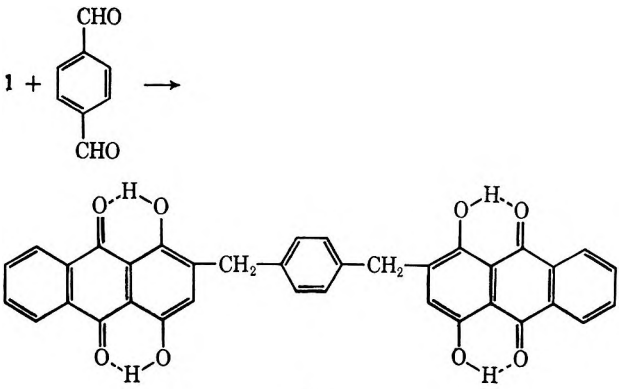
7

The ease with which o-dialdehydes condense indicates the high degree of reactivity of both the 2 and 3 positions of leucoquinizarin, thus providing a convenient route to polycyclic aromatics.

The pentacene derivative **6** has been described by Weizmann[5] who prepared it by the fusion of naphthalene-2,3-dialdehyde with 1,4-dihydroxynaphthalene in presence of boric acid. We repeated Weizmann's preparation and verified the identity of **6** made by the two methods by mixture melting points and ir and mass spectra. Ir and mass spectral data for the hexacene derivative **7** were also consistent with the assigned structure.

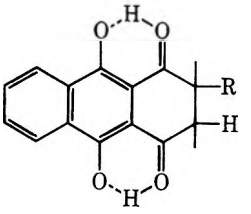
Terephthaldehyde gave a product resulting from the condensation of one molecule of aldehyde with two molecules of leucoquinizarin **8**.

Piperidinium Acetate Catalyzed Condensations.—Piperidinium acetate in 2-propanol was found to be an excellent catalyst for aliphatic aldehydes in the C_4–C_{12} range. Under these conditions 2-n-butyl-, 2-n-decyl-, and 2-n-dodecylquinizarin **9**, **10**, and **11** were readily prepared. Likewise, one molecule of an aromatic aldehyde and dialdehydes condensed with one molecule of leucoquinizarin to give compounds **2**, **6**, and **7**.



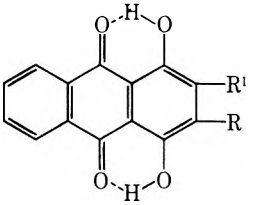
8

A useful extension of the scope of the piperidinium acetate catalyzed condensation consists in reducing the 2-substituted quinizarins to the corresponding leuco form with alkaline dithionite and then condensing these with a second molecule of an aliphatic or aromatic aldehyde. These leuco forms, **12** and **13**, are formulated as diphenolic diketo tautomers on the basis of their ir and nmr spectra. Both **12** and **13** underwent facile



12, R = C_4H_9n
13, R = $CH_2C_6H_5$

condensation with aliphatic and aromatic aldehydes to give 2,3-disubstituted quinizarins **14**, **15**, and **16**.



14, R = C_4H_9n; R' = C_4H_9n
15, R = C_4H_9n; R' = $CH_2C_6H_5$
16, R = $CH_2C_6H_5$; R' = $CH_2C_6H_5$

Benzaldehyde reacted much faster than butyraldehyde; it gave 73 and 67% yields, respectively, of the 2,3-disubstituted products **15** and **16** in a 4-hr reaction period, whereas butyraldehyde required 20 hr to produce a 42% yield when condensed with **12**, and gave a mixture of 2-benzylquinizarin **2** and **15** when condensed with **13**. This is seen as evidence that the failure of most aldehydes to give 2,3-disubstituted products in the alkaline dithionite procedure is due to the reactivity of the aldehyde rather than to steric hindrance.

Mechanism of the Acid-Catalyzed Aldol Condensation of Leucoquinizarin.—Noyce and Pyror[6] have studied the kinetics of the condensation of benzaldehyde with acetophenone in strong acid. They found the rate to be proportional to the concentration of benzaldehyde, the concentration of acetophenone, and to Hammett's

(5) C. H. Weizmann, L. Haskelberg, and (in part) T. Berlin, *J. Chem. Soc.*, 398 (1939).

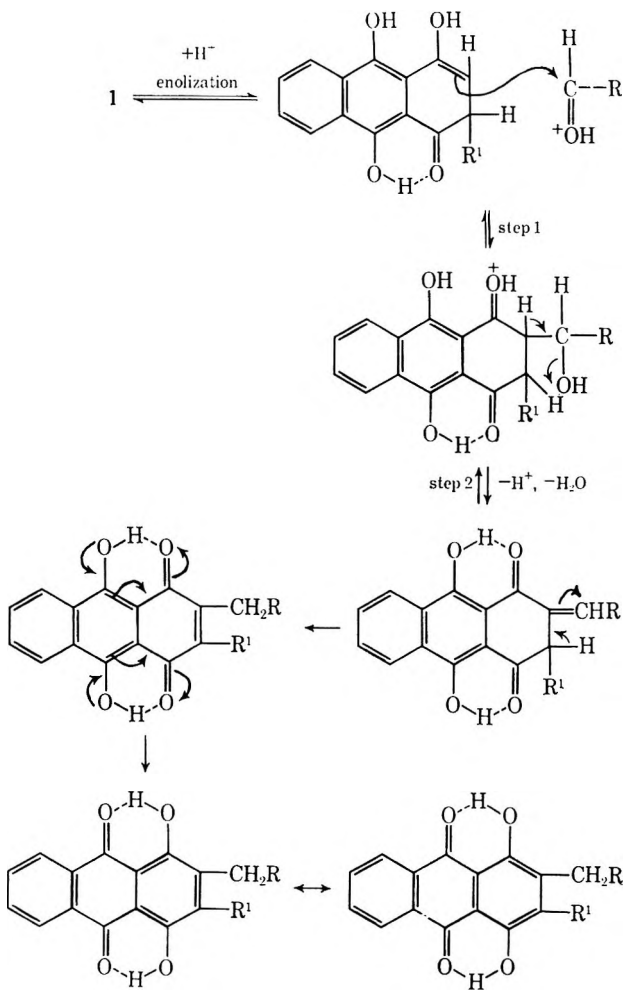
(6) S. D. Noyce and W. A. Pyror, *J. Amer. Chem. Soc.*, **77**, 1397 (1955).

acidity function, h_0. They suggested that the rate-determining step could be either (1) the condensation between the enol of acetophenone and a protonated benzaldehyde or (2) the dehydration of the β-hydroxy ketone intermediate.

Our results can be interpreted by suitable modification of this mechanistic scheme. The following facts must be accommodated: (1) aliphatic aldehydes failed to condense with leucoquinizarin when aqueous hydrochloric acid was the catalyst but did so when piperidinium acetate was used (in both cases 2-propanol was the solvent); (2) aromatic aldehydes condensed readily in the presence of either catalyst; (3) aromatic *o*-dialdehyde involved both aldehydes in the condensation, but only one molecule of monoaldehyde entered in the condensation.

A mechanism for the condensation of leucoquinizarin with monoaldehydes is suggested in Scheme I. Since aliphatic aldehydes, in general, are more reactive than

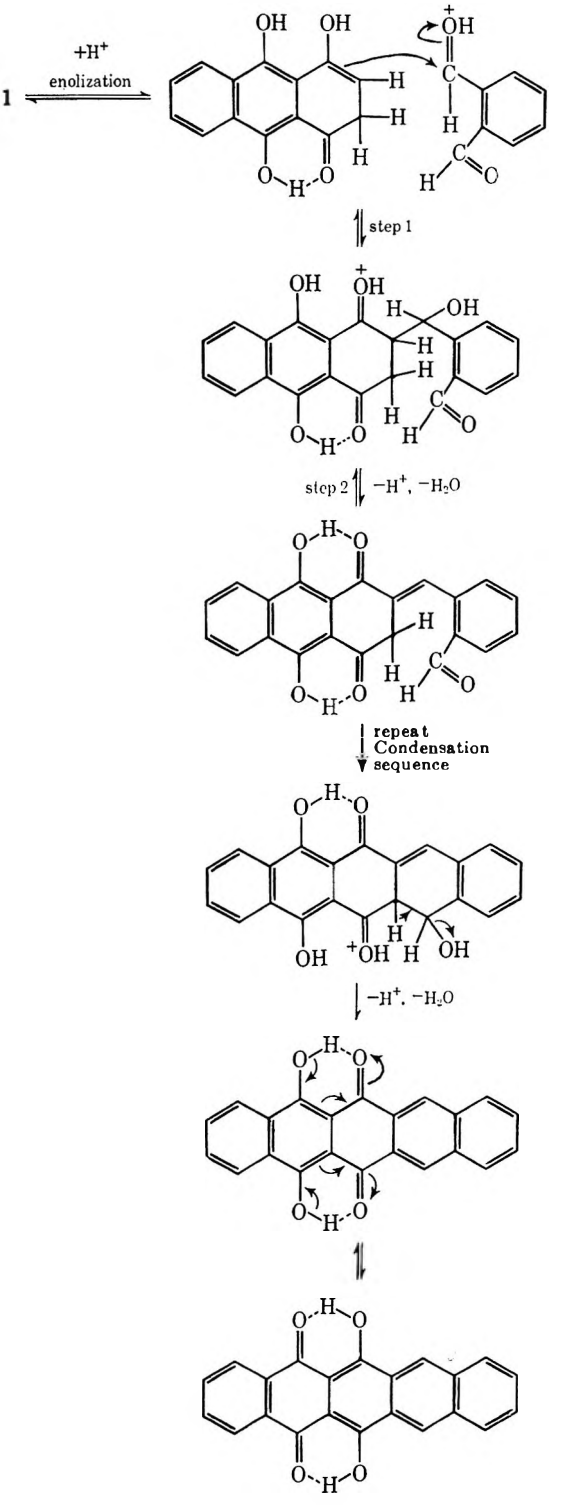
SCHEME I



R = alkyl or aryl
R′ = H, alkyl, or arylmethylene

aromatic aldehydes in aldol condensations, our observations suggest that the dehydration (step 2) may be rate determining in the case of leucoquinizarin. Aromatic aldehydes result in β-aryl, α,β-unsaturated ketones which are more stable and hence provide greater driving force for the dehydration than the corresponding

SCHEME II



β-alkyl unsaturated ketones. Note that the oxidation level of leucoquinizarin is raised to that of quinizarin in this mechanism.

The superior catalytic activity of piperidinium acetate as compared with hydrochloric acid in the condensation of aliphatic aldehydes may be explained in terms of Brønsted's extended theory of acid and basic catalysis.[7] The piperidinium ion (acid) promotes the dehydration step 2 augmented by the acetate ion (base) acting as the proton acceptor.[8]

(7) J. N. Brønsted, *Chem. Rev.*, **5**, 231 (1928).

TABLE I
PHYSICAL DATA

Compd	Aldehyde, mol	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
2	Benzaldehyde, 0.05	181–182[a]	$C_{21}H_{14}O_4$	76.36	4.24	76.03	4.13
3	*p*-Chlorobenzaldehyde, 0.02	181–182[b]	$C_{21}H_{13}O_4Cl$	69.23	3.57	69.40	3.47
4	*p*-Methoxybenzaldehyde, 0.05	144–145[b]	$C_{22}H_{16}O_5$	73.33	4.49	73.44	4.38
5	*p*-Dimethylaminobenzaldehyde, 0.01	208–209[b]	$C_{23}H_{19}NO_4$	73.99	5.09	73.88	4.88
6	*o*-Phthalaldehyde, 0.01	396–398[c]	$C_{22}H_{12}O_4$	77.64	3.53	77.56	3.44
7	Naphthalene-2,3-dialdehyde, 0.01	434–436[b]	$C_{26}H_{14}O_4$	80.00	3.59	79.93	3.48
8	Terephthaldehyde, 0.005	>400[d]	$C_{36}H_{22}O_8$	74.24	3.78	73.93	4.00

[a] Reference 2a. [b] Crystallized from Methyl Cellosolve. [c] Reference 5b. [d] Crystallized from *o*-dichlorobenzene.

TABLE II
PHYSICAL DATA

Compd	Aldehyde	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
9	Butyraldehyde	123–124[a]	$C_{18}H_{16}O_4$	72.97	5.40	72.90	5.32
10	*n*-Decylaldehyde	86–87[b]	$C_{24}H_{28}O_4$	75.79	7.37	75.57	7.41
11	*n*-Dodecylaldehyde	91–92[c]	$C_{26}H_{32}O_4$	76.47	7.84	76.56	7.74

[a] Reference 2a. [b] Crystallized from ethanol. [c] Crystallized from 1-butanol.

TABLE III
PHYSICAL DATA

Compd	Reactants: Leucoquinizarin	Reactants: Aldehyde	% yield: 4 hr	% yield: 20 hr	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
14[a]	2-*n*-Butyl	*n*-Butyraldehyde	0	42	136–137	$C_{22}H_{24}O_4$	75.00	6.82	75.05	6.77
15[b,c]	2-*n*-Butyl	Benzaldehyde	73		136–137	$C_{25}H_{22}O_4$	77.72	5.70	77.58	5.56
15[b,c]	2-Benzyl	*n*-Butyraldehyde	0	*d*	136–137					
16[a]	2-Benzyl	Benzaldehyde	67		198–199	$C_{28}H_{20}O_4$	80.00	4.65	80.17	5.01

[a] Crystallize from methylcyclohexane. [b] Crystallized from 2-propanol. [c] Mixture melting point of products made by these two routes showed no depression. [d] Mixture of 2-*n*-butyl- and 2-*n*-butyl-3-benzylquinizarin (identified by comparing tlc with tlc of authentic samples on silica gel plate, eluent ethyl acetate–chloroform).

This picture is consistent with the ready formation of the pentacene and hexacene from *o*-dialdehydes as shown in Scheme II. Note that the intermediate in the condensation would be sufficiently stabilized by the α,β-unsaturated ketone system (chalcone structure) to permit aromatization. Eventually a series of tautomerizations can lead to the stable form of the substituted quinizarin.

Experimental Section

Melting points were taken on a Mel-Temp electrically heated melting point unit and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 21 spectrophotometer; visible spectra were measured on a No. 2 Hardy General Electric spectrophotometer in ODCB; nmr spectra were obtained on a Varian A-60 spectrophotometer.

Hydrochloric Acid Catalyzed Condensation.—A mixture of 0.01 mol of leucoquinizarin,[9] the aldehyde (quality given in Table I), and 2 ml of concentrated hydrochloric acid in 50 ml of 2-porpanol was refluxed 4 hr. The reaction mixture was cooled to room temperature; the precipitate was removed by filtration, washed with methanol, and dried at 80°. The product was purified by recrystallization. Compounds prepared by this procedure are listed in Table I.

In one experiment where butyraldehyde was used, the reaction was refluxed for 20 hr. The only product isolated was leucoquinizarin, mp 155–156°. The filtrate was treated with dinitrophenylhydrazine; the product isolated had mp 123–124°; mixture melting point with the dinitrophenylhydrazone of butyraldehyde was not depressed.

(8) A. C. Cope, *J. Amer. Chem. Soc.*, **59**, 2327 (1937), reported piperidinium acetate to be more effective as catalyst for the condensation of ketones with cyanoacetic esters. He attributed the effectiveness of the salt to its ability to act as both acid and basic catalyst, according to Brønsted's definition.

(9) Commercial leucoquinizarin recrystallized from Methyl Cellosolve was used in this study.

Piperidinium Acetate Catalyzed Condensations. A. With Leucoquinizarin.—A mixture of 0.01 mol of leucoquinizarin, 0.03 mol of the aldehyde, and 0.5 g of piperidinium acetate in 50 ml of 2-propanol was refluxed 4 hr, cooled, filtered, washed with methanol, and dried at 80°. It was then purified by recrystallization. The compounds thus prepared, with physical data, are listed in Table II.

B. With 2-Substituted Leucoquinizarin.—The above procedure was followed. In each case reaction times of 4 and 20 hr were used. The physical data are given in Table III.

2-Butylleucoquinizarin (12).—To 280 cc of 6% sodium hydroxide solution in a flask continuously swept with nitrogen was added 8.0 g of 2-butylquinizarin, and the mixture was stirred at 45–50° until solution was complete. To this blue solution was added 20 g of sodium dithionite, and after the blue color was discharged stirring was continued 2 hr at 45–50°. Then 100 ml of 20% sulfuric acid solution was added dropwise making the reaction mixture acid to congo red indicator paper. Nitrogen was blown through to expel the excess sulfur dioxide. The precipitate was separated by filtration and washed acid free. The wet cake was crystallized twice from ethanol to give 7.4 g (93%) of purified material, mp 99–100°.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.48; H, 5.70. Found: C, 72.16; H, 5.55.

2-Benzylleucoquinizarin (13).—This compound was prepared by the above procedure in 92% yield, mp 153–155°.

Anal. Calcd for $C_{21}H_{16}O_4$: C, 57.90; H, 4.82. Found: C, 58.11; H, 5.00.

Alkaline Dithionite Condensation with Butyraldehyde.—To 500 cc of 1.4% sodium hydroxide solution was added 5 g (0.02 mol) of quinizarin (mp 194–195°); the mixture stirred under N_2 at 30° until it dissolved; 10 g of sodium dithionite was added and; stirring was continued 0.5 hr until the blue color was discharged. Then 7.5 g (0.1 mol) of butyraldehyde was added and the reaction mixture was heated 1.25 hr at 95°. It was cooled to room temperature and aerated until the product was oxidized. After acidification to congo red indicator paper with dilute sulfuric acid the reaction mixture was filtered. The precipitate (2-butylquinizarin 2) was washed with water and crystallized from Methyl Cellosolve to yield 4.0 g (67%), mp 123–124°.

The volume of filtrate was 550 cc. Analysis of the filtrate on a F & M Model 500 gas chromatograph using a Porapak Q column showed that only a trace of butyraldehyde was present.

Registry No.—**1**, 17648-03-2; **2**, 2106-03-5; **3**, 21016-05-7; **4**, 23861-68-9; **5**, 25158-10-5; **6**, 25109-60-8; **7**, 25158-11-6; **8**, 25109-61-9; **9**, 23861-69-0; **10**, 23861-74-7; **11**, 23861-70-3; **12**, 25109-64-2; **13**, 25109-65-3; **14**, 25109-66-4; **15**, 25109-67-5; **16**, 25109-68-6.

Acknowledgments.—Appreciation is expressed to Professor F. Ramirez for timely suggestions and assistance in the preparation of this manuscript, Mr. J. Kobliska for microanalysis, Dr. J. Gove for nmr interpretations, Dr. T. Mead for mass spectra data, and Mr. J. Morath for vapor phase chromatographic analysis.

Molecular Rearrangements. X.[1] The Boron Trifluoride Etherate Catalyzed Rearrangements of *trans*-2,3-Diphenyl-2,3-epoxypropionitrile and Its *p*- and *p'*-Methyl Derivatives

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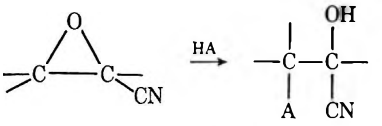
Received February 17, 1970

The syntheses of *trans*-2,3-diphenyl- (**1a**), *trans*-2-phenyl-3-(*p*-tolyl)- (**1b**), and *trans*-3-phenyl-2-(*p*-tolyl)-2,3-epoxypropionitrile (**1c**) are presented. Boron trifluoride etherate catalyzed rearrangement of **1a** and **1c** leads exclusively to the product of phenyl migration, α-cyanodiphenylacetaldehyde (**5**) and α-cyanophenyl-*p*-tolylacetaldehyde (**5**), respectively, while **1b** yields 47% **5** and 53% phenyl-*p*-tolylpyruvonitrile (**7a**), the products of *p*-tolyl and phenyl migration, respectively. Treatment of **7a** with base yields the stable enol form, **7b**. The catalyzed rearrangements of **1a–1c** are discussed in terms of a stepwise, ionic mechanism. Thermally, **1b** and **1c** produce *trans* → *cis* isomerization only.

There have been several reported studies of the rearrangements of α-cyano epoxides.[3] Cyano group migration has been observed in the formation of α-cyano ketones in a few cases where the intermediate α-cyano epoxide has been produced by treatment of an α-halocyanohydrin with base. Acid (protonic or Lewis) promoted rearrangements of α-cyano epoxides generally lead to α-substituted cyanohydrins as the products. In our general study of the chemistry of α-electronegatively substituted epoxides we have investigated the thermal and boron trifluoride etherate



catalyzed rearrangements of *trans*-2,3-diphenyl-2,3-epoxypropionitrile (**1a**), *trans*-2-phenyl-3-(*p*-tolyl)-2,3-epoxypropionitrle (**1b**), and *trans*-3-phenyl-2-(*p*-tolyl)-2,3-epoxypropionitrile (**1c**). These substrates were chosen because of our previous success in demonstrating exclusive chlorine migration from the intermediate α-chloro epoxides in the epoxidation of *trans*-α-chlorostilbenes.[4]

Synthesis of 2,3-Diaryl-2,3-epoxypropionitriles.—The synthetic approach to **1a–c** involved the preparation of the *trans*-α,β-diarylacrylonitriles (**2**) followed by base catalyzed peroxidation. The *trans*-α,β-diarylacrylonitriles (**2a–c**) were readily prepared by the condensation of the appropriate arylacetonitrile and arylcarboxaldehyde in the presence of sodium ethoxide.[5] The *trans* configuration was assigned to these products on the basis of the observed ultraviolet spectra compared with those of *cis*- and *trans*-α,β-diphenylacrylonitrile (**2a**) previously reported[6] (Table I).

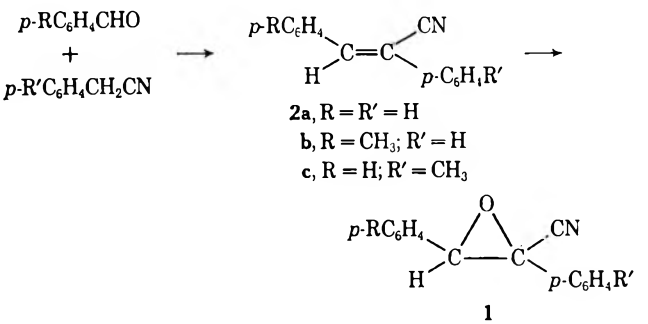


TABLE I
OBSERVED ULTRAVIOLET SPECTRA OF *cis*- AND *trans*-α,β-DIARYLACRYLONITRILES

	cis, λ_{max} (log ε)	*trans*, λ_{max} (log ε)
2a	224 (4.36), 295 (4.22)[6]	227 (4.27), 312 (4.41)[6]
2b		232 (4.13), 317 (4.40)
2c		229 (4.21), 317 (4.39)

Of the two literature methods for synthesizing **1a**, (1) treatment of desyl chloride with sodium cyanide in ethanol[7] and (2) basic peroxidation of **2a** with *t*-butyl hydroperoxide in the presence of benzyltrimethylammonium hydroxide,[8] the latter method was chosen since only *trans* isomer **1a** was obtained and in good yield. Applying this procedure to **2a–c** gave **1a–c** in

(1) For paper IX in this series, see R. N. McDonald and R. N. Steppel, *J. Org. Chem.*, **35**, 1250 (1970).

(2) Taken from the M. S. Thesis of D. G. Hill, 1969. A portion of these results were communicated in *Chem. Commun.*, 671 (1969).

(3) For a review of this and related rearrangements of α-substituted epoxides, see R. N. McDonald in "Mechanisms of Molecular Migrations," Vol 3, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., in press.

(4) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **85**, 4004 (1963).

(5) (a) A. Bistrzycki and E. Stelling, *Ber.*, **34**, 3089 (1901); (b) K. Hohenlohe-Oeringen, *Monatsh. Chem.*, **89**, 484 (1958); (c) S. Wawzonek and E. M. Smolin, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 715.

(6) C. F. Codington and E. Mostig, *J. Org. Chem.*, **17**, 1027 (1952).

(7) E. P. Kohler and F. W. Brown, *J. Amer. Chem. Soc.*, **55**, 4299 (1933).

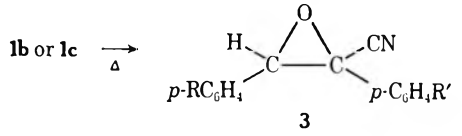
(8) G. B. Payne and A. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).

good yields. The *trans* configurations of **1a–c** were based on the comparison of the spectral data given in Table II.

Table II
Comparison of Some Infrared and Nmr Absorptions for 2,3-Diaryl-2,3-epoxypropionitriles

		Epoxide ring		
	ν (CN), μ	ν_{sym}, μ	ν_{asym}, μ	τ (H_a)
1a	4.47	7.87	11.30	5.98
1b	4.47	7.88	11.35	6.05
1c	4.40	7.90	11.45	6.02
3b	4.45	8.48	11.16	5.32

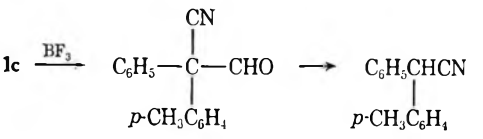
Attempted Thermal Rearrangement of 2,3-Diaryl-2,3-epoxypropionitriles.—α-Cyano epoxides **1b** and **1c** were each separately heated to 200° under full vacuum and passed through a 200-mm glass column filled with Pyrex helices heated to 350°. After four successive passes the nmr spectra of the product indicated that 40% of the starting material had been altered. The infrared and nmr spectra of the pure product gave conclusive evidence that only *trans* to *cis* isomerization had occurred in this thermolysis (see Table II). A similar isomerization had been observed when **1a** was photolyzed for short periods of time.[9]



3

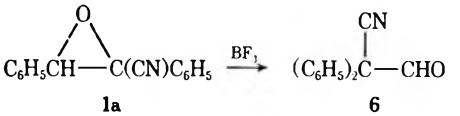
Boron Trifluoride Etherate Catalyzed Rearrangements of 2,3-Diaryl-2,3-epoxypropionitriles.—The boron trifluoride etherate catalyzed rearrangements of **1a–c** were chosen for study since it was felt that these might give a good opportunity to observe cyano group migration and greatly reduce the formation of α-fluorocyanohydrins, a major result when (1-cyanoethylidene)cyclohexane oxide is treated with excess boron trifluoride etherate.[10] The catalyzed rearrangement of **1a** and **1c** were first attempted in ether solvent but little or no rearrangement was observed over a short period of time. However, using benzene as solvent, complete rearrangement was observed almost immediately and the ratio of products was found to be quite independent of the concentration of catalyst used.

The boron trifluoride etherate catalyzed rearrangement of **1c** in benzene solution resulted in the formation of a single liquid product in 98% yield. The nmr spectrum (CCl_4, internal TMS[11]) of this liquid exhibited absorptions at τ 0.48 (s, 1), 2.68 (t, 5), 2.87 (s, 4), and 7.67 (s, 3), while the infrared spectrum showed characteristic absorptions at 4.45 (CN) and 5.75 μ (C=O). Chromatography of this liquid product on neutral alumina gave a 92% recovery of phenyl-*p*-tolylacetonitrile (**4**). The presence of the aldehyde function in the product, originally indicated from the nmr and infrared spectra, was established by a positive Tollens test, the product of this reaction followed by acidification being **4**, and preparation of the 2,4-dinitrophenylhydrazone derivative. These facts establish the structure of the product from the catalyzed rearrangement of **1c** to be α-cyanophenyl-*p*-tolylacetaldehyde (**5**), the easy decarbonylation during chromatography being due to a retrograde Claisen condensation which also occurred when **5** was treated with bases or distilled. Aldehyde **5** could be obtained in a fairly pure state if the rearrangement solution is only washed briefly with a dilute, aqueous solution of sodium carbonate for the work-up.



5 4

When a benzene solution of α-cyano epoxide **1a** was similarly treated with boron trifluoride etherate, the nmr spectrum of the product indicated incomplete rearrangement. The nmr spectrum of the crude product (99% recovery) showed that along with **1a** only α-cyanodiphenylacetaldehyde (**6**) was present; integration of the aldehydic proton *vs.* that of the total aromatic protons indicated that 37% **6** had been formed. The presence of **6** was confirmed by the presence of the carbonyl absorption at 5.77 μ in the infrared spectrum.



1a 6

With only a single mode of aryl migration established in the catalyzed rearrangements of **1a** and **1c**, we suspected that this same single process would be observed on similar treatment of **1b**. That this was not the case was immediately evident from the nmr spectrum of the rearrangement mixture which is recovered in 98% yield. Washing the rearrangement mixture with water until barely acidic, drying, and evaporation of the solvent gave the product residue whose nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 0.53 (s, 0.47, CHO), 2.70–2.95 (m, 9, aromatic), 4.88 (s, 0.53, methine), and 7.71 (d, 3, methyl). Addition of deuterium oxide to this sample resulted in no exchange of the protons. The infrared spectrum showed two nitrile absorptions at 4.50 (w) and 4.55 μ (m), and a broadened carbonyl stretching frequency centered at 5.85 μ (s).

If the benzene solution from the rearrangement of **1b** was washed with a saturated aqueous solution of sodium bicarbonate in the work-up procedure the nmr spectral absorption at τ 4.88, above, was lost. Addition of deuterium oxide resulted in no noticeable proton exchange even though the infrared spectra of the rearrangement product so obtained showed a strong hydroxyl absorption at 3.14 μ. The lack of observing the hydroxyl proton in the nmr spectrum could simply be due to its exchange rate in the sample.

These facts suggested that the rearrangement mixture from **1b** was composed of aldehyde **5** (47%) and a cyano ketone **7** (53%) which is readily and, apparently, completely converted to its enol by base treatment.

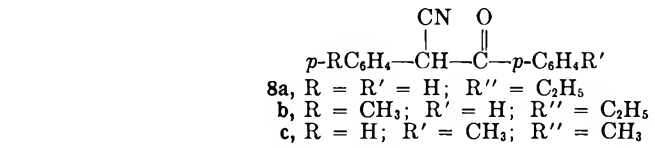
Our approach to the proof of structure of this cyano ketone product was to consider that it might be the product of either cyano or hydrogen migration from **1b**

(9) I. P. Stepanov, O. A. Ikonopistseva, and T. I. Temnikova, *J. Org. Chem., USSR*, **2**, 2216 (1966).

(10) G. Stork, W. S. Worrall, and J. J. Pappas, *J. Amer. Chem. Soc.*, **82**, 4315 (1960).

(11) Tetramethylsilane.

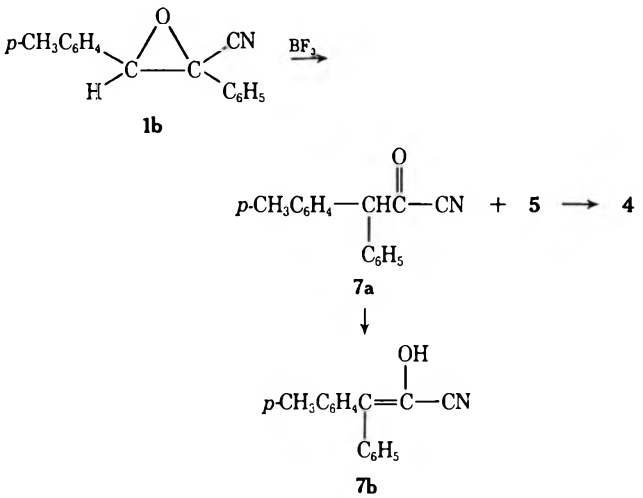
which would yield α-cyano-α-(*p*-tolyl)acetophenone (**8b**) or α-cyano-*p*-methyl-α-phenylacetophenone (**8c**), respectively. These two α-cyano ketones, along with α-cyano-α-phenylacetophenone (**8a**), were prepared by the condensation of the appropriate alkyl arylcarboxylate and arylacetonitrile in ether with sodium hydride. The spectral data for **8b** and **8c** did not agree with that of the unknown cyano ketone **7**. The only remaining



rearrangement to consider from **1b** would be phenyl migration leading to the formation of phenyl-*p*-tolypyruvonitrile (**7a**).

The separation of **5** and **7** by column chromatography on silica gel failed and on neutral alumina gave only nitrile **4**, the "decarbonylation" product from **5**, which could be hydrolyzed in 70% sulfuric acid to phenyl-*p*-tolylacetamide. Treatment of the mixture of **5** and **7** with a slight excess of 2,4-dinitrophenylhydrazine (**9**) gave only recovered **9** and the 2,4-dinitrophenylhydrazone of **5**; this derivative of **5** could be isolated in 41% yield (87% yield based on available **5**).

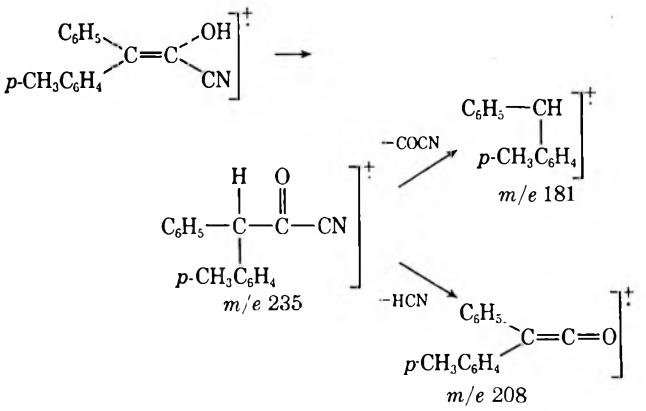
After several fruitless attempts, **7** was finally separated from **5** and its decomposition product **4** by extraction of an ether solution of **5** and **7** with a dilute, aqueous potassium carbonate solution. Upon rapid separation of layers, acidification, and ether extraction of the acidic layer, **7** was obtained as a crystalline solid. Compounds **4** and **5** were obtained from the original ether layer which were completely converted to **4** when chromatographed on neutral alumina.



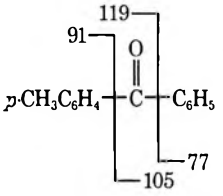
The infrared spectrum of **7** showed hydroxyl absorption at 3.09 μ and nitrile absorption at 4.50 μ with no evidence of a carbonyl stretch; a similar but more resolved infrared spectrum was obtained as a 15% solution of **7** in chloroform. The nmr spectrum ($CDCl_3$, internal TMS) of **7** exhibited a broad absorption at τ 4.05, assigned to the hydroxyl group of **7b**, which disappeared on addition of deuterium oxide. Other than the absorptions for the aromatic protons, two peaks were observed at τ 7.67 and 7.69 for the methyl protons. Our interpretation of these spectra is that we are dealing with the *cis* and *trans* isomers of **7b** and *not* with a measurable equilibrium mixture of **7a** and **7b**.

The ultraviolet spectrum of **7b** was similar to the spectra observed for α-cyano ketones **8a–c** but exhibited a greater molar absorptivity. This can be rationalized since Russell[12] has shown that the keto–enol tautomerism of **8a** occurs even in nonpolar solvents.

The 70-eV mass spectrum of **7b** was quite interesting. The fragmentations which are most informative and require our structural assignment of **7b** involve the losses of HCN (*m/e* 27) and COCN (*m/e* 54) from the parent ion radical ($M\cdot^+$, *m/e* 235); both processes show the required metastables. It seems reasonable to assume the ketonization occurs in $M\cdot^+$ which is analogous to the same reaction used to describe the most important fragmentations of phenol.[13]



Other peaks observed at 196, 165, 119 (base peak), and *m/e* 106 could not be explained by the fragmentation of **7**, **8b**, or **8c**, or other isomeric compounds. The presence of three of these peaks was rationalized by oxidation of **7b** occurring in the mass spectrometer at



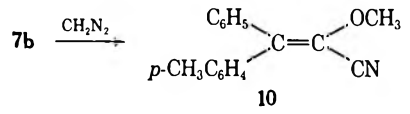
70 eV to give 4-methylbenzophenone. These peaks were found to decrease in intensity in successive spectra and completely disappeared when observed at 11 eV. The origin of the ion at *m/e* 165 is uncertain.

Further evidence for structure **7b** was obtained when it was hydrolyzed with 25% sulfuric acid or 5% aqueous sodium hydroxide at 100° to phenyl-*p*-tolylacetic acid, which may be the direct result of hydrolysis of enol **7b** itself or proceed by way of an equilibrium, **7a** ⇄ **7b**, and **7a** undergoing hydrolysis.

The methyl ether of enol **7b** was also prepared by reaction with diazomethane. The infrared and nmr spectra, and the elemental analysis were in agreement with the structure of the product as α-methoxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (**10**).

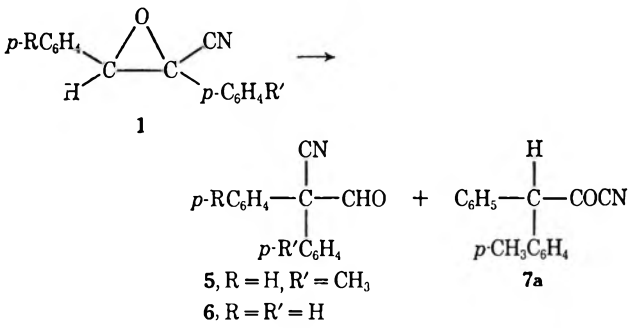
(12) P. B. Russell, *J. Amer. Chem. Soc.*, **74**, 2654 (1952).

(13) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 115.



10

To summarize the rearrangement results, **1a** and **1c** rearrange in the presence of boron trifluoride etherate in benzene solution exclusively by phenyl migration to yield the corresponding α-cyanodiarylacetaldehyde, **6** and **5**, respectively, while **1b** produces **5** (47%) and **7a**



1

5, R = H, R′ = CH_3
6, R = R′ = H

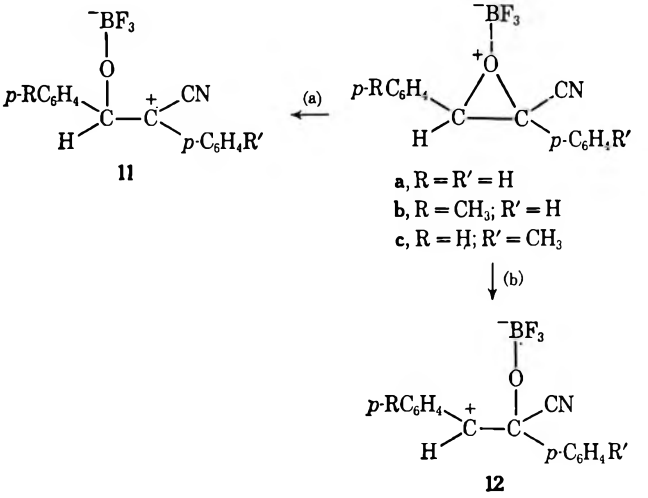
7a

(53%) by *p*-tolyl and phenyl migration, respectively. It should be noted that no evidence for cyano group migration was found.

If these catalyzed rearrangements occurred by a concerted mechanism, the stereochemistry of the transition state would be very nearly the same for **1a–c**. If we assume little or no charge buildup, then rearrangement of the best migrating group should be the major control on product formation, and similar distributions of products should be observed from the three α-cyano epoxides. With **1b**, since *p*-tolyl is a better migrating group than phenyl, we would expect that the resulting product, **5**, would predominate; the opposite situation is observed. Stereochemistry cannot be a factor since all are *trans*.[14] Also, arguments opposed to such concerted epoxide–carbonyl rearrangements have been presented.[4]

If, however, a stepwise rearrangement occurs involving epoxide ring opening followed by aryl migration, the effect of substituent groups in the aryl group should be influential in controlling the course of the rearrangements. This influence would appear to be greatest if the heterolytic epoxide ring opening is rate determining followed by a fast aryl migration step, the latter process being facilitated by concurrent generation of the carbonyl group.

If we assume that the unaccounted for 2% of starting material from the rearrangements of **1a** and **1c** went by way of intermediate **12**, then the replacement of hydrogen by methyl (R) in **12** would require a lowering of the transition-state energy in forming **12b** relative to **12a** or **12c** by $\Delta\Delta F^{\pm} \approx 2.3$ kcal/mol. This is equal to a rate factor of about 50 for the *p*-CH_3 *vs.* hydrogen substituent effect.[15] This does not seem too unreasonable since the same substituent effect in the aqueous acetone solvolysis of benzyl tosylates gives a rate factor of 30.[16] It should be surprising that the influence of substituents would be greater in the present case since the electron



11

a, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3

12

demand on the substituent is greatly increased in benzene as solvent as compared with aqueous acetone used in the benzyl tosylate solvolyses.

An interesting corollary arises if the stepwise mechanism and the discussion above are correct. This is that the cyano group in **11** is stabilizing to the carbonium ion center. If the cyano group destabilized the attached carbonium ion, we would expect to find ring opening (b) occurring in **1a–c** and a substituent effect as R′ of **11** is changed from hydrogen (**1a**) to methyl (**1c**). This is not observed; however, the results can be rationalized by cyano group stabilization of **11** swamping out the substituent, R′, effect.

Experimental Section[17]

trans-α-**Phenyl**-β-(*p*-**tolyl**)**acrylonitrile** (**2b**).—The method used here was that described for the synthesis of **2a**.[6c] The crude product from 39.7 g (0.33 mol) of *p*-tolualdehyde and 38.6 g (0.33 mol) of phenylacetonitrile was repeatedly recrystallized from ethanol to give 37.2 g (52%) of **2b**, mp 58.5–59.0° (lit.[5a] mp 61°). The infrared spectrum (KBr) exhibited nitrile absorption at 4.53 μ while the nmr spectrum (CCl_4, internal TMS) showed absorptions at τ 2.10–2.90 (m, 10, aromatic and vinyl) and 7.65 (s, 3, methyl).

trans-β-**Phenyl**-α-(*p*-**tolyl**)**acrylonitrile** (**2c**).—Using the same procedure as for the preparation of **2b**, 47.7 g (0.36 mol) of *p*-tolylacetonitrile and 41.7 g (0.39 mol) of benzaldehyde gave, after recrystallization from ethanol, 69.6 g (87%) of **2c**, mp 77.5–78.0° (lit.[5b] mp 74°). The infrared spectrum (KBr) exhibited nitrile absorption at 4.52 μ and the nmr spectrum (CCl_4, internal TMS) showed absorptions at τ 2.10–3.00 (m, 10, aromatic and vinyl) and 7.69 (s, 3, methyl).

trans-**2,3-Diphenyl-2,3-epoxypropionitrile** (**1a**).—The procedure for the preparation of **1a** has been described.[8] Crude **1a** (8.7 g) was recrystallized from methanol to give 5.0 g (59%) of **1a**, mp 70.0–70.5° (lit.[8] mp 70.0–70.5°). The nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 2.67 (s, 10, aromatic) and 5.98 (s, 1, epoxide ring).

trans-**2-Phenyl-3-(***p*-**tolyl)-2,3-epoxypropionitrile** (**1b**).—As per the procedure used to prepare **1a**, 41.6 g (0.19 mol) of **2b** gave, after recrystallization from methanol, 37.0 g (84%) of α-cyano epoxide **1b**. Further recrystallizations from a small volume of ether gave product with a melting point of 81.0–81.5°. The nmr spectrum (CCl_4, internal TMS) exhibited absorptions centered at τ 2.65 and 2.82 (m's, 9, aromatic), 6.05 (s, 1, epoxide ring), and 7.65 (s, 3, methyl).

(14) H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **77**, 6525 (1955).

(15) If 1% of the rearrangement of **1a** and **1c** go by way of **12** the rate factor would be about 100, $\Delta\Delta F^{\pm} \approx 2.7$ kcal/mol.

(16) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3445 (1953).

(17) All melting points were taken on a Kofler hot stage and are corrected; boiling points are uncorrected. Infrared, nmr, and ultraviolet spectra were recorded using P-E Model 137, Varian A-60, and Cary Model 11 spectrophotometers, respectively. Mass spectra were determined with an MS-9 mass spectrometer. Solution molecular weights were obtained with a Mechrolab osmometer, Model 301A, and microanalyses were performed by Galbraith Laboratories, Inc.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.65; H, 5.57. Found: C, 81.67; H, 5.44.

trans-**3-Phenyl-2-(*p*-tolyl)-2,3-epoxypropionitrile** (**1c**).—As per the procedure used to prepare **1a**, 24.1 g (0.11 mol) of **2c** gave, after recrystallization from methanol, 19.7 g (76%) of **1c**. Further recrystallizations from a small volume of ether gave product with a melting point of 77.8–78.2°. The nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 2.60–2.90 (m, 9, aromatic), 6.02 (s, 1, epoxide ring), and 7.68 (s, 3, methyl).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.65; H, 5.57. Found: C, 81.77; H, 5.64.

Boron Trifluoride Etherate Catalyzed Rearrangement of 1a.—Boron trifluoride etherate (0.28 ml, 2.0 mmol) was added to a solution of 1.00 g (4.25 mmol) of α-cyano epoxide **1a** in 13 ml of dry benzene. After standing for 10 min at room temperature, this reaction mixture was washed with water until the aqueous washings were barely acidic and dried ($CaCl_2$), and the solvent was removed under reduced pressure to give 0.99 g of crude product.

The infrared spectrum of this product showed absorptions at 4.45 (CN) and 5.77 μ (C=O) while the nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 0.45 (s, 0.37, aldehyde), 2.55–2.88 (m, 10, aromatic), and 5.95 (s, 0.63, epoxide ring). It was concluded that this product was a mixture of 63% starting material (**1a**) and 37% diphenyl-α-cyanoacetaldehyde (**6**). The combination of the spectra of **1a** and **6** account for every peak in the nmr and infrared spectra of this rearrangement mixture.

Boron Trifluoride Etherate Catalyzed Rearrangement of 1b.—To a stirred solution of 2.09 g (8.5 mmol) of α-cyano epoxide **1b** in 25 ml of dry benzene was added 0.55 ml (4.0 mmol) of freshly distilled boron trifluoride etherate. After 10 min, the solution was washed with water until barely acidic, dried ($CaCl_2$), and filtered. Evaporation of the solvent gave 2.04 g of rearrangement product. The infrared and nmr spectra of this product are given in the discussion.

If a sample of the epoxide was treated with boron trifluoride etherate in benzene (as above) but the benzene solution was evaporated under reduced pressure, a green residue was obtained which exhibited the same nmr and infrared spectra as observed above. However, if the benzene solution was treated with a saturated solution of sodium bicarbonate in the work-up procedure, the nmr spectrum remained identical except for the peak at τ 4.88 which disappeared. Addition of deuterium oxide resulted in no obvious change in the spectrum. The infrared spectrum of this sample now exhibited a strong hydroxyl absorption at 3.14 μ.

A 1.09-g sample of the original rearrangement product from **1b** was chromatographed on neutral, activity II–III alumina. Evaporation of the solvent from the various fractions gave only one fraction (petroleum ether–benzene) which solidified on standing. The crystalline solid, 0.40 g, was sublimed (60°, 0.05 mm), recrystallized from hexane, and resublimed to a final melting point of 61–62°. Molecular weight determination ($CHCl_3$) gave a value of 207 ± 2. The infrared spectrum (KBr) of this material exhibited nitrile absorption at 4.48 μ and the nmr spectrum (CCl_4, internal TMS) had absorptions at τ 2.75 (s, 5, aromatic), 2.90 (s, 4, aromatic), 5.05 (s, 1, methine), and 7.70 (s, 3, methyl). This data was in agreement with the structure phenyl-*p*-tolyacetonitrile (**4**) (lit.[18] mp 61–62°) for this product.

Utilizing the method of Shine[19] for the preparation of 2,4-dinitrophenylhydrazones; 0.50 g (2.13 mmol) of rearrangement product from **1b** was added to 13 ml of a 0.168 *M* solution (2.18 mmol) of 2,4-dinitrophenylhydrazine in diglyme followed by 3 drops of concentrated hydrochloric acid. Evaporation of the solvent under reduced pressure left a bright yellow-red residue. Fractional recrystallization from ethanol–ethyl acetate gave a difficult to purify residue and excess 2,4-dinitrophenylhydrazine. Only one 2,4-dinitrophenylhydrazone was indicated as being present.

Repeating the above procedure using 7 ml (1.17 mmol) of 2,4-dinitrophenylhydrazine reagent; 0.36 g (41% yield) of the 2,4-dinitrophenylhydrazone was obtained after recrystallization from ethanol–ethyl acetate. Repeated recrystallization from ethanol–ethyl acetate gave an analytical sample with mp 178–178.5°.

Anal. Calcd for $C_{22}H_{17}N_5O_4$: C, 63.61; H, 4.13; N, 16.86. Found: C, 63.86; H, 4.02; N, 16.93.

(18) H. A. Michael and J. Jeanpretre, *Ber.*, **25**, 1616 (1892).

(19) H. J. Shine, *J. Org. Chem.*, **24**, 252 (1959).

The infrared and nmr spectra indicated the product to be α-cyanophenyl-*p*-tolylacetaldehyde (**5**) 2,4-dinitrophenylhydrazone. The nmr spectrum ($CDCl_3$, internal TMS) exhibited peaks at τ −1.15 (broad s, 1, NH), 0.19 (d, 1, aromatic), 1.6–1.8 (q, 1, aromatic), 1.82 (s, 1, aromatic), 2.10 (s, 1, methine), 2.57 (s, 5, aromatic), 2.73 (s, 4, aromatic), and 7.63 (s, 3, methyl). The infrared spectrum exhibited absorptions at 3.09 (NH), 4.46 (C≡N), and 6.20 μ (C=N).

A 2.0-g sample of the original rearrangement mixture in 50 ml of ether was rapidly extracted with three portions of 5% aqueous potassium carbonate. The chilled basic solution was immediately acidified and extracted three times with ether. The ether extracts were combined, washed with water, and dried ($CaCl_2$). Evaporation of the ether left an oil (1.0 g) which solidified on addition of carbon tetrachloride. Recrystallization from cyclohexane gave 0.64 g of product, mp 111–112° (sealed tube). A sample was taken and purified further by slow sublimation at 70° (0.05 mm), followed by two recrystallizations from cyclohexane, mp 114–115° (sealed tube). An nmr spectrum of the sample indicated no change in purity. The product was resublimed and submitted for analysis.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.27; H, 5.64.

The product is assigned the structure of α-hydroxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (**7b**) from this and its spectral data. The infrared spectra (KBr and $CHCl_3$ solution) of **7b** have been presented in the discussion while the nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions centered at τ 4.05 [broad, 1, hydroxyl (removed with D_2O)], 2.70 and 2.85 (m, 9, aromatic), and 7.68 (d, 3, methyl). The ultraviolet spectrum (ethanol) of this compound exhibited absorption maxima at 290 (log ϵ, 4.23) and 235 nm (log ϵ 4.08). The mass spectrum has been discussed.

Boron Trifluoride Etherate Catalyzed Rearrangement of 1c.—To a stirred solution of 2.03 g (8.5 mmol) of **1c** in 25 ml of dry benzene was added 0.55 ml (4.0 mmol) of freshly distilled boron trifluoride etherate. After 10 min, the solution was washed with water, until barely acidic, dried ($CaCl_2$), and filtered. An oil (1.99 g) was obtained after evaporation of excess benzene. The nmr spectrum (CCl_4, internal TMS) of this oil indicated complete rearrangement; absorptions at τ 0.48 (s, 1, aldehyde), 2.68 (t, 5, aromatic), 2.87 (s, 4, aromatic), and 7.67 (s, 3, methyl) were observed in the nmr spectrum. The infrared spectrum exhibited absorptions at 4.45 (CN) and 5.75 μ (CO).

The oil (0.20 g, 0.85 mmol) was chromatographed on neutral alumina, activity II–III. Evaporation of the solvents gave only one fraction (0.16 g) which solidified upon standing. The solid was sublimed at 60° (0.05 mm), to give the product (92%) with a melting point of 60–61°. The infrared and nmr spectra were identical with those previously obtained for phenyl-*p*-tolylacetonitrile (**4**).

A 0.50-g sample of rearrangement product from **1c** was added to 15 ml of a 0.168 *M* solution of 2,4-dinitrophenylhydrazine in diglyme followed by 3 drops of concentrated hydrochloric acid. The solution was cooled and a residue formed on addition of water. Recrystallization from ethanol–ethyl acetate gave 0.48 g (55%) of the 2,4-dinitrophenylhydrazone, mp 178.0–178.5°. The infrared and nmr spectra were identical with those of α-cyanophenyl-*p*-tolylacetaldehyde (**5**) 2,4-dinitrophenylhydrazone.

Purification of **5** was difficult owing to the ease of decarbonylation in the presence of base. Attempted bisulfite addition and distillation also resulted in quantitative yields of phenyl-*p*-tolylacetonitrile. If the crude aldehyde dissolved in benzene was washed once with a saturated solution of sodium bicarbonate followed by water, dried, and solvent evaporated, the purest **5** was obtained. The infrared spectrum exhibited absorptions at 4.45 (CN) and 5.75 μ (C=O). The nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 0.45 (s, 1, aldehyde), 2.72 (t, 5, aromatic), 2.68 (s, 4, aromatic), and 7.67 (s, 3, methyl).

Treatment of 0.75 g (3.2 mmol) of **5** with Tollens reagent[20] produced a silver precipitate which was filtered and washed with hot water and methanol, and the combined filtrates were acidified. The solution was cooled and filtered, and the crystals obtained were sublimed at 60°, (0.05 mm) giving 0.43 g (65%) of nitrile **4**, mp 60–61°.

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 163.

Phenyl-*p*-tolylacetamide.—Phenyl-*p*-tolylacetonitrile (0.40 g, 1.93 mmol) was hydrolyzed in 10 ml of 75% sulfuric acid at 100° for 11 hr. The cooled solution was poured over ice and extracted with ether. The ether layers were combined, extracted three times with a 5% solution of potassium carbonate, and washed with water. The etheral solution was dried and excess solvent was removed leaving a crystalline product (0.14 g). The infrared and nmr spectra indicated the product to be phenyl-*p*-tolylacetamide, mp 155.7–156° (lit.[21] 151°). The infrared spectrum exhibited characteristic absorptions at 6.05 (C=O) and 3.20 μ (NH_2). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 2.75 (s, 5, aromatic), 2.88 (s, 4, aromatic), 3.70–4.50 (broad s, 2, NH_2), 5.13 (s, 1, methine), and 7.70 (s, 3, methyl).

Hydrolysis of α-Hydroxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (7b).

1. **With Aqueous Sulfuric Acid.**—α-Hydroxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (0.20 g, 0.89 mmol) was hydrolyzed in 10 ml of 25% aqueous sulfuric acid at 100° for 6 hr. The solution was cooled and extracted with ether. The combined ether extracts were extracted with 5% aqueous potassium carbonate followed by water. Evaporation of the ether layer left a residue (2 mg) which was not further investigated. After acidification of the carbonate extracts with 10% hydrochloric acid and extraction with ether, the ether layer was washed with water, dried ($CaCl_2$), and evaporated to yield 0.14 g of an oil which soon solidified. Recrystallization from cyclohexane gave 90 mg (45%) of phenyl-*p*-tolylacetic acid, mp 114.5–115° (lit.[22] mp 115–116°). The infrared and nmr spectra obtained were identical with those of an authentic sample.

2. **With 5% Aqueous Sodium Hydroxide.**—α-Hydroxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (0.20 g, 0.89 mmol) was hydrolyzed with 10 ml of 5% aqueous sodium hydroxide at 100° for 6 hr. After the cooled solution was extracted with ether, the basic solution was acidified with 10% sulfuric acid and extracted again with ether. The ether extracts of the acidified solution were combined, washed, and dried, and the excess solvent was evaporated. The solid obtained (0.17 g) was recrystallized from cyclohexane to yield 0.16 g (80% yield) of phenyl-*p*-tolylacetic acid, mp 114–115°.

α-Methoxy-β-phenyl-β-(*p*-tolyl)acrylonitrile (10).—An excess of diazomethane was added to 0.30 g (1.28 mmol) of α-hydroxy-β-phenyl-β-(*p*-tolyl)acrylonitrile in ether. After 3 hr, the excess diazomethane and ether were removed under vacuum to obtain an oil whose nmr spectrum indicated a good yield of the methyl vinyl ether. The oil was taken up in ether and extracted with a dilute solution of sodium bicarbonate to rid the solution of any enol that might be present. The solid obtained upon evaporation of ether was sublimed three times (60°, 0.05 mm) and recrystallized twice from pentane interchangably until the product appeared pure from the nmr spectrum. An analytical sample of **10** was obtained with mp 79.5–80.5°.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.91; H, 6.07. Found: C, 82.01; H, 6.08.

The infrared spectrum exhibited a nitrile absorption at 4.58 μ. The nmr spectrum (CCl_4, internal TMS) exhibited absorptions at τ 2.73 (s, 5, aromatic), 2.94 (m, 4, aromatic), 6.26 (s, 3, methoxyl), and 7.70 (s, 3, methyl).

α-Cyano-α-phenylacetophenone (8a).—To a well-stirred solution of 6.1 g (0.10 mol) of a 40% sodium hydride dispersion in 50 ml of dry ether, 5.84 g (0.05 mol) of phenylacetonitrile was added dropwise. The etheral solution was heated under reflux for 0.5 hr, cooled, and ethyl benzoate (7.50 g, 0.05 mol) was added dropwise. This mixture was stirred overnight and then hydrolyzed by the slow addition of water and extracted with ether. The aqueous layer was cooled, acidified (10% H_2SO_4), and extracted with ether. The combined ether extracts were washed and dried ($CaCl_2$), and the ether was removed under reduced pressure. Compound **8a** (7.9 g) was recrystallized from ether–cyclohexane to give 7.0 g (64%) of product, mp 91.5–92.0° (lit.[23] mp 91–92°).

The infrared spectrum exhibited absorptions at 4.47 (CN), and 5.95 μ (CO). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 1.95–2.18 and 2.40–2.85 (complex m, 9, aromatic) and 4.33 (s, 1, methine). Addition of deuterium oxide resulted in no exchange with deuterium. The ultraviolet spectrum[12] exhibited absorption maxima at 291 (log ϵ 4.12) and 249 nm (log ϵ, 3.97) in ethanol.

α-Cyano-α-(*p*-tolyl)acetophenone (8b).—The procedure described for the synthesis of **8a** was employed here. Recrystallization of the crude product from ether–cyclohexane gave 9.5 g (81%) of **8b**, mp 94.0–94.5°.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 82.02; H, 5.56.

The infrared spectrum exhibited absorptions at 4.48 (CN) and 5.95 μ (CO). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 1.95–2.17 and 2.42–2.97 (complex m, 9, aromatic), 4.37 (s, 1, methine), and 7.73 (s, 3, methyl). Addition of dueterium oxide resulted in no exchange with deuterium. The ultraviolet spectrum in ethanol exhibited an absorption maximum at 293 nm (log ϵ 4.14).

α-Cyano-*p*-methyl-α-phenylacetophenone (8c).—The procedure used in the preparation of **8a** was employed. From 5.84 g (0.05 mol) of phenylacetonitrile and 7.50 g (0.50 mol) of methyl *p*-toluate 7.7 g (66%) of **8c** was obtained after recrystallization from ether–cyclohexane, mp 104–104.5°.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.78; H, 5.71.

The infrared spectrum exhibited absorptions at 4.45 (CN) and 5.97 μ (C=O). The nmr spectrum ($CDCl_3$, internal TMS) exhibited absorptions at τ 2.05–2.30 and 2.50–2.90 (complex m, 9, aromatic), 4.37 (s, 1, methine), and 7.65 (s, 3, methyl). Addition of deuterium oxide resulted in no exchange with deuterium. The ultraviolet spectrum in ethanol exhibited an absorption maximum at 290 nm (log ϵ 4.12).

Near Thermal Rearrangement of 1b.—α-Cyano epoxide **1b** (2.0 g, 8.6 mmol) was heated at 200° under full vacuum and passed successively through a 200-mm column containing Pyrex helices heated to 350° by a coil furnace. The rearrangement was followed by nmr spectroscopy. The crystalline product was

Times through column	% rearranged
1	11
3	27
4	40

recrystallized from methanol to remove some of the epoxide (0.43 g). The residue obtained was chromatographed on neutral alumina, activity II–III. Elution with cyclohexane–carbon tetrachloride gave 0.61 g of recovered epoxide, 0.52 g of a mixture of epoxide and isomerized product, and 0.14 g of thermally isomerized product. Three successive sublimations gave 0.12 g of pure isomerized epoxide, mp 85.5–86°.

The infrared and nmr spectra indicated the product to be *cis*-2-phenyl-3-(*p*-tolyl)-2,3-epoxypropionitrile. The infrared spectrum exhibited absorption at 4.45 μ (CN); other bands present at 8.48 and 11.13 μ were attributed to the symmetric and asymmetric stretch of the epoxide ring.[24] The nmr spectrum (CCl_4, internal TMS) exhibited peaks at τ 2.70 (s, 5, aromatic), 3.00 (s, 4, aromatic), 5.32 (s, 1, epoxide ring), and 7.77 (s, 3, methyl).

Neat Thermal Rearrangement of 1c.—The procedure for the thermal rearrangement of this compound was the same as described above for **1b**. The per cent of rearranged product, as determined by nmr spectroscopy, is given below. It was concluded that *trans* to *cis* isomerization must be occurring also for this compound.

Times through column	% rearranged
1	11
2	20
3	28
4	40

Registry No.—**1a**, 15115-82-9; **1b**, 25125-18-2; **1c**, 25125-28-4; **2b**, 25125-29-5; **2c**, 25125-30-8; **3b**, 25125-31-9; **5**, 25125-32-0; 2,4-dinitrophenylhydrazone of **5**, 25125-33-1; **7b**, 25125-34-2; **8a**, 5415-07-6; **8b**, 25124-91-8; **8c**, 25124-92-9; **10**, 25124-93-0; phenyl *p*-tolylacetamide, 25124-94-1.

(21) T. Zincke, *Ber.*, **10**, 997 (1877).

(22) A. McKenzie and S. T. Widdows, *J. Chem. Soc.*, 708 (1915).

(23) W. Wislicenus, H. Eichert, and M. Marquardt, *Justus Liebigs Ann. Chem.*, **436**, 92 (1924).

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1941, p 118; K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 36.

Acknowledgment.—The authors thank Dr. R. G. Cooks for determining the mass spectrum and the National Science Foundation (GP-7818) for support of this research.

Condensation of Cyclic Olefins with Paraformaldehyde and Hydrogen Chloride

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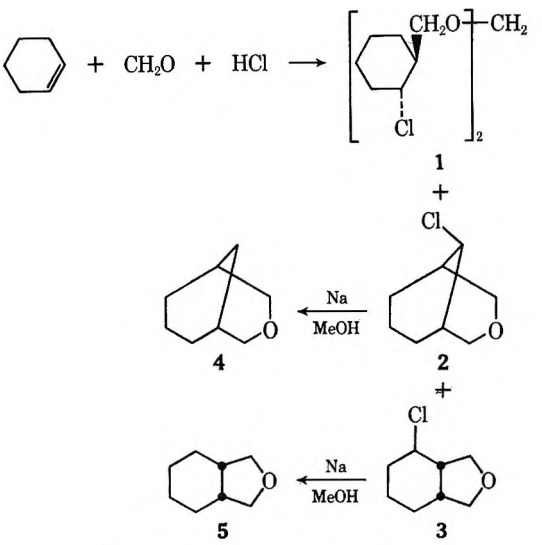
Condensation of cyclohexene with paraformaldehyde and hydrogen chloride at −60 to −70° gave a good yield of a mixture of two bicyclic chlorinated ethers along with a small amount of the formal of *trans*-2-chlorocyclohexanemethanol (1). The structure of the principal component (80% of the mixture) was established by chemical degradation, synthesis, and nmr as *trans*-9-chloro-*cis*-3-oxabicyclo[3.3.1]nonane (2), and the minor component was identified as *trans*-6-chloro-*cis*-3-oxabicyclo[4.3.0]nonane (3). Under similar conditions, cyclopentene gave 2-chlorocyclopentanemethanol (7) (60% yield) and a mixture of two isomeric bicyclic chlorinated ethers (32%) in a ratio of 2:1. These were separated and identified as 6-chloro-*cis*-3-oxabicyclo[3.3.0]-octane (8) and 8-chloro-3-oxabicyclo[3.2.1]octane (9), respectively. Calculated nmr spectra were obtained which were useful in establishing the stereochemistry and nature of ring fusion in both the 3-oxabicyclononanes and 3-oxabicyclooctanes.

A number of investigators have studied the sulfuric acid catalyzed reaction of cyclohexene and formaldehyde in acetic acid solution.[1-3] The reaction leads to a complex mixture of products, but the major constituents are derivatives of *trans*-2-hydroxymethylcyclohexanol and none of the *cis* isomer is found. Blomquist[1] identified *trans*-9-hydroxy-*cis*-3-oxabicyclo[3.3.1]nonane as a minor by-product and Dolby[3] later isolated and identified small quantities of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane from a similar reaction. In a related study of the reaction of cyclohexene, paraformaldehyde, and hydrochloric acid, Volynskii[4] identified the formal of *trans*-2-chlorocyclohexanemethanol (1) as the major product and found 5% each of *trans*-9-chloro-*cis*-3-oxabicyclo[3.3.1]nonane (2) and *trans*-6-chloro-*cis*-3-oxabicyclo[4.3.0]nonane (3).[5] The stereochemistry of 2 and 3 was elucidated by conversion to the known hydroxy compounds.

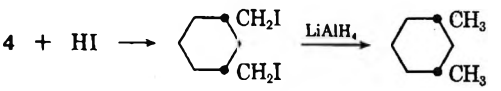
In previous articles[6-8] we described a novel modification of the Prins reaction in which various olefin types were treated with paraformaldehyde and hydrogen halides at low temperatures. Extension of this modified Prins reaction to include the condensation of cyclohexene and cyclopentene with paraformaldehyde is considered in this report. As a number of bicyclic compounds became available during the course of this work, an opportunity was afforded to consider some aspects of theoretical calculations of the nmr spectra of these bicyclic systems.

Introduction of hydrogen chloride into a paraformaldehyde–cyclohexene mixture (1.5:1 mol ratio) in methylene chloride at −60 to −70° gave, in addition to a substantial quantity of cyclohexyl chloride and a small amount of 1, 65–75% yields of a mixture of two bicyclic chlorinated ethers. The structure of the principal component (80% of the mixture) was established by elemental analysis, chemical degradation, and its nmr spectrum as *trans*-9-chloro-*cis*-3-oxabicyclo-[3.3.1]nonane (2) and the minor component was assigned the structure of *trans*-6-chloro-*cis*-3-oxabicyclo-[4.3.0]nonane (3) (Scheme I). The structures of the

SCHEME I



basic ring systems were established by removal of the chlorine from the mixture of bicyclics with sodium and methanol to give *cis*-3-oxabicyclo[3.3.1]nonane (4) and *cis*-3-oxabicyclo[4.3.0]nonane (5) in the same 4:1 ratio. These were separated by preparative glpc; elemental analyses, mass spectra, and nmr spectra were in complete agreement with the assigned structures. Chemical confirmation of 4 as *cis*-3-oxabicyclo[3.3.1]nonane



(1) A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.*, **79**, 6025 (1957).

(2) E. Smissman and R. A. Mode, *ibid.*, **79**, 3447 (1957).

(3) L. J. Dolby, *J. Org. Chem.*, **25**, 2971 (1962).

(4) N. P. Volynskii, G. D. Gal'pern, and A. B. Urin, *Zh. Org. Khim.*, **2**, 1043 (1966); *Chem. Abstr.*, **65**, 15306 (1966).

(5) In naming 2 as *trans*-9-chloro-*cis*-3-oxabicyclo[3.3.1]nonane, Volynskii[4] differs from earlier investigators by designating the ring fusion as *cis*. We are not aware of any derivatives of *trans*-3-oxabicyclo[3.3.1]nonane; hence it might appear that this is unnecessary. Inspection of molecular models of 3-oxabicyclo[3.3.1]nonane suggests that a *trans* fusion is possible, though strained, and to avoid possible ambiguity we will use the nomenclature of Volynskii.

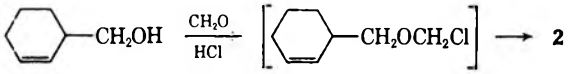
(6) P. R. Stapp, *J. Org. Chem.*, **34**, 479 (1969).

(7) P. R. Stapp, *ibid.*, **34**, 1143 (1969).

(8) P. R. Stapp and D. S. Weinberg, *ibid.*, **34**, 3592 (1969).

was provided by conversion to *cis*-1,3-dimethylcyclohexane *via* cleavage with hydriodic acid and lithium aluminum hydride reduction. Capillary gas chromatography of the product showed that the retention time eliminated all isomers except 1,1-, *cis*-1,3-, and *trans*-1,4-dimethylcyclohexane from consideration; final confirmation as *cis*-1,3-dimethylcyclohexane was furnished by dehydrogenation to *m*-xylene.[9]

Low-temperature crystallization of the bicyclic chloride fraction from methanol readily gave pure **2** on a preparatively useful scale. Chemical evidence for assignment of the chlorine atom to the unreactive 9 position was supported by its inertness to nucleophilic reagents; **2** was recovered unchanged after a 6-hr treatment with excess potassium hydroxide in refluxing 2-propanol or heating with ammonia (18 mol) at 2000 psig and 200°. Earlier work[6,10] has shown that 4-chlorotetrahydropyrans are produced from homoallylic alcohols by treatment with paraformaldehyde and hydrogen chloride, presumably *via* an intermediate unstable chloromethyl ether. A similar condensation of 2-cyclohexenemethanol[11] gave synthetic **2** identical with that obtained from the cyclohexene reaction.

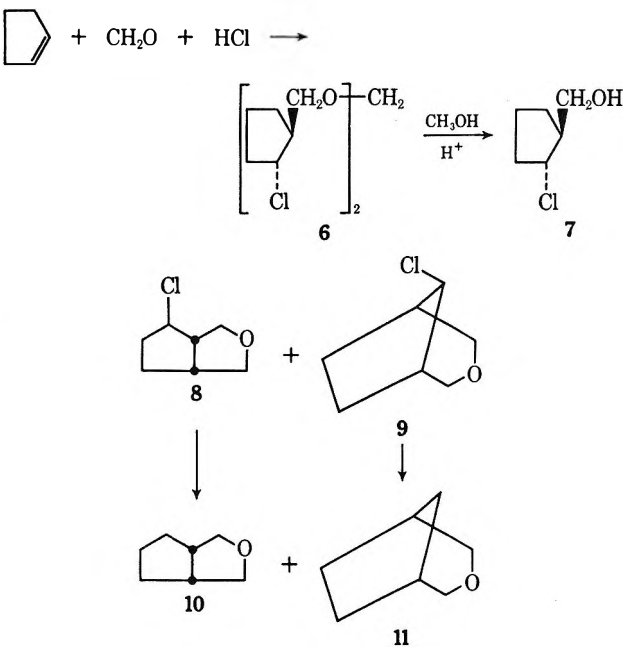


Pure **3** was obtained by preparative glpc of the enriched mother liquors from crystallization of **2**. Formulation of **3** as the *trans*-6-chloro isomer was based on the mode of formation and the nmr spectrum which showed a chemical shift for the proton α to the chlorine in the region of −235–240 Hz. The chemical shift of the proton α to the chlorine atom in **2** was observed downfield at −265–270 Hz. Since the conformation of the *cis*-3-oxabicyclo[3.3.1]nonane system has been established as chair–chair,[12] it is of interest that the proton chemical shift observed corresponds so closely to the shift of an equatorial hydrogen α to a chlorine atom.[13] A proton equatorial to the cyclohexane ring is expected for the *trans*-9-chloro configuration.

Cyclopentene gave a somewhat different distribution of products than did cyclohexene under the same reaction conditions (Scheme II).

Only a small quantity of cyclopentyl chloride was formed, and the major product (60% yield) was characterized as the formal of 2-chlorocyclopentanemethanol (**6**) by elemental analysis and the infrared spectrum. Methanolysis gave 2-chlorocyclopentanemethanol (**7**) which yielded a sharply melting 3,5-dinitrobenzoate. Attempts to determine the stereochemistry of both the free alcohol and the ester were inconclusive. The complexity of the nmr spectrum of **7** indicated that a mixture of isomers was present, with the principal constituent comprising an estimated 75–85% of the total. This is in agreement with earlier work[8] which established that 2-butenes condensed with paraformaldehyde and hydrogen chloride with 70–80% stereoselectivity. In view of the well-documented formation of *trans* derivatives from cyclohexene, it appears logical to assign the *trans* configuration to the major component. A mixture of two bicyclic chlorinated ethers was also formed (32% yield) in a ratio of 2:1. These were separated by preparative glpc and assigned the structures 6-chloro-*cis*-3-oxabicyclo-[3.3.0]octane (**8**) and 8-chloro-3-oxabicyclo[3.2.1]octane (**9**) by elemental analysis and their nmr spectra. Reduction of **8** and **9** with sodium and methanol provided, respectively, *cis*-3-oxabicyclo-[3.3.0]octane (**10**) and 3-oxabicyclo[3.2.1]octane (**11**), a crystalline solid. The *cis* fusion in **10** was established by cleavage with hydriodic acid and reduction to *cis*-1,2-dimethylcyclopentane and by comparison with the nmr spectrum of an authentic sample.[14]

SCHEME II



The nmr spectra of the bicyclics were uniformly consistent with the proposed structures in terms of chemical shifts and relative areas of the different proton types; however, some distinctive features were noted in the resonances from the methylene protons α to the oxygen atom, hereafter referred to as α methylene resonances. The complexity of these α methylene resonances varied significantly among the various bicyclic ethers; for example, the 3-oxabicyclooctanes gave more complex α methylene spectra when a chemical bond existed directly between bridgehead carbon atoms. A similar condition did not prevail among the 3-oxabicyclononanes, which gave spectra that were deceptively simple. Since the structure of the bicyclics had been reasonably established with the exception of **9** and **11**, which were assigned by analogy, the nmr spectra of the α methylene resonances were then closely examined for criteria that could support the proposed structures and for information that would prove constructive in later analyses.

The complexity of the α methylene resonances in the various bicyclic ethers is undoubtedly a result of so-called virtual coupling;[15] however, such an oversim-

(9) W. J. Hines and D. E. Smith, *Anal. Chem.*, **36**, 2250 (1964).
(10) J. Colonge and P. Boisde, *Bull. Soc. Chim. Fr.*, **23**, 824 (1956).
(11) A. T. Blomquist, J. Verdol, C. L. Adami, J. Wolinsky, and D. D. Phillips, *J. Amer. Chem. Soc.*, **79**, 4976 (1957).
(12) R. J. Bishop, L. E. Sutton, M. J. T. Robinson, and N. W. J. Pumphrey, *Tetrahedron*, **25**, 1417 (1969).
(13) R. V. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).
(14) L. N. Owen, Imperial College of Science and Technology, personal communication, 1969.
(15) J. I. Musher, and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

plification without qualification can lead to a loss of information, particularly with regard to the present compounds, which give obvious virtual coupling in only one of two analogous situations. The α methylene multiplets from **2**, **4**, **9**, and **11** can be treated approximately as AB portions of equivalent ABX systems if we choose temporarily to ignore the perturbations introduced from vicinal bridgehead (H_X) coupling with other hydrogen nuclei.[16] The AB portion of an ABX system can be easily recognized by a characteristic set of eight lines;[17] thus the α methylene resonances of **10** are clearly too complex for an ABX approximation, although the analogous compound, **5**, apparently fits neatly into the realm of ABX possibilities with eight distinctly recognizable transitions. Since the possibility exists for substantial vicinal coupling between the bridgehead hydrogens in **5** and **10**, the α methylene resonances were considered as AB components of AA'BB'XX' systems. (With zero values for $J_{AA'}$ and $J_{BB'}$ the AA'BB'XX' system reduces to the ABX case when $J_{XX'}$ is also zero.) The nmr spectra of the isomeric pairs of bicyclic ethers **4**, **5**, **10**, and **11** are reproduced in Figures 1 and 2 with expanded α methylene multiplets shown in the insets. Calculated spectra (using computer program NMRIT) for **4** and **11** which were obtained from ABX analyses that adequately represent the observed multiplets are also included. The calculated spectra shown for **5** and **10** were obtained after identifying the eight-line ABX portion of the multiplet and obtaining the ABX parameters. The ABX case was then expanded to an AA'BB'XX' analysis with the introduction of only $J_{XX'}$. A systematic variation of $J_{XX'}$, while holding the remaining parameters constant, permits a determination of the effect of bridgehead coupling on the incipient spectra of the α methylene protons. The effect of such coupling is shown in Figure 3. The calculated spectra for **5** and **10**, included in the insets of Figures 1 and 2, respectively, are the best representations of the observed multiplets. The bridgehead coupling constant, $J_{XX'}$, is in the range 7–10 Hz for **10** and 0–2 Hz for **5**. The valleys between the eight-line spectrum of **5** are somewhat filled suggesting a finite XX' coupling constant. The relatively high bridgehead coupling constant for **10** is in the range generally found for *cis* coupling in five-membered rings.[18] The *trans* bridgehead coupling, by analogy, should be quite small. A 100-HMz spectrum of *trans*-3-oxabicyclo[3.3.0]octane[19] contained an eight-line multiplet with no unusual broadening or splitting. The opposite relationship, found in the bicyclics containing fused cyclohexane rings, is supported by the fact that J_{trans} has been noted to be larger than J_{cis} in six-membered-ring systems.[20] The relatively unobscured eight-line multiplet for **5** is therefore consistent with the structure *cis*-3-oxabicyclo[4.3.0]nonane. Likewise the structure of **10** as *cis*-3-oxabicyclo[3.3.0]octane is strongly supported by the nmr spectrum.

(16) A. Alikhan, S. Rodmar, and R. A. Hoffman, *Acta Chem. Scand.*, **21**, 63 (1967).

(17) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York 1959, p 132.

(18) H. A. Sable, W. M. Ritchey, and J. E. Nordlander, *J. Org. Chem.*, **31**, 3771 (1966).

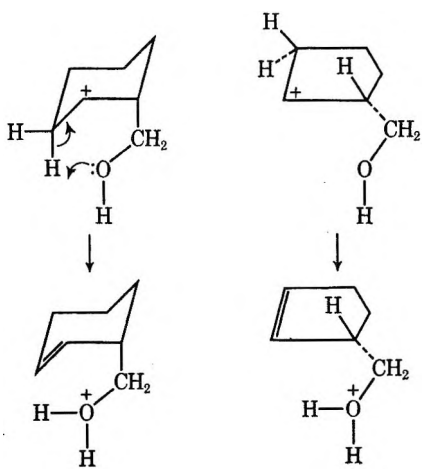
(19) We are indebted to Professor L. N. Owen for furnishing a copy of this spectrum.

(20) Reference 17, p 394.

The identification of more than the expected eight lines for an α methylene multiplet can be used to establish the existence of a chemical bond directly between the bridgehead carbon atoms if the possibility of such an effect arising from perturbations from strong vicinal coupling with other nuclei is precluded. An extension of the ABX treatment for **2** and **9** to the ABXCYZ case, which includes all possible vicinal bridgehead coupling constants, gives only a slight splitting of the AB portion (0.01–0.03 Hz) for vicinal coupling constants up to 10 Hz. The splitting observed in **10** must, therefore, result predominantly from vicinal coupling directly between the bridgehead hydrogens. The complexity or broadness of the α methylene multiplets thus offers a means for determining the stereochemistry of ring fusion and the existence of a methylene or higher order bridge in these bicyclic ethers.

The corresponding chloro derivatives **2**, **3**, **8**, and **9** offered additional evidence for the structures of the parent bicyclic ring systems. The α methylene multiplets for **2** and **9** were not so collapsed as those in **4** and **11**, and ABX fits were easily obtained with the same sets of coupling constants calculated from the nmr spectra of the parents. The α methylene spectra for the chloro bicyclics are reproduced in Figure 4. Structurally equivalent sets of α methylene protons are indicated by the proposed structures for bicyclic pairs **2** and **4**, and **9** and **11**. The fact that satisfactory ABX fits were possible with only chemical shift changes supports the existence of equivalent sets of α methylene protons in each of the chlorine derivatives.

Complex α methylene multiplets could be anticipated for **3** and **8** because the α methylene protons are not structurally equivalent and the possibility for strong bridgehead coupling exists in each case. As expected, more than eight lines were observed for the α methylene resonances of **8**; unfortunately, overlap with the multiplet from proton α to the chlorine atom in **3** prevented an exact determination of the numbers of lines. The multiplet was complex in support of the proposed structure, as illustrated in Figure 4.



It has been previously suggested[6] that 4-chlorotetrahydropyrans are produced from 1 olefins, paraformaldehyde, and hydrogen chloride by cyclization of the unstable chloromethyl ether of an intermediate homoallylic alcohol. The proposal that the homoallylic

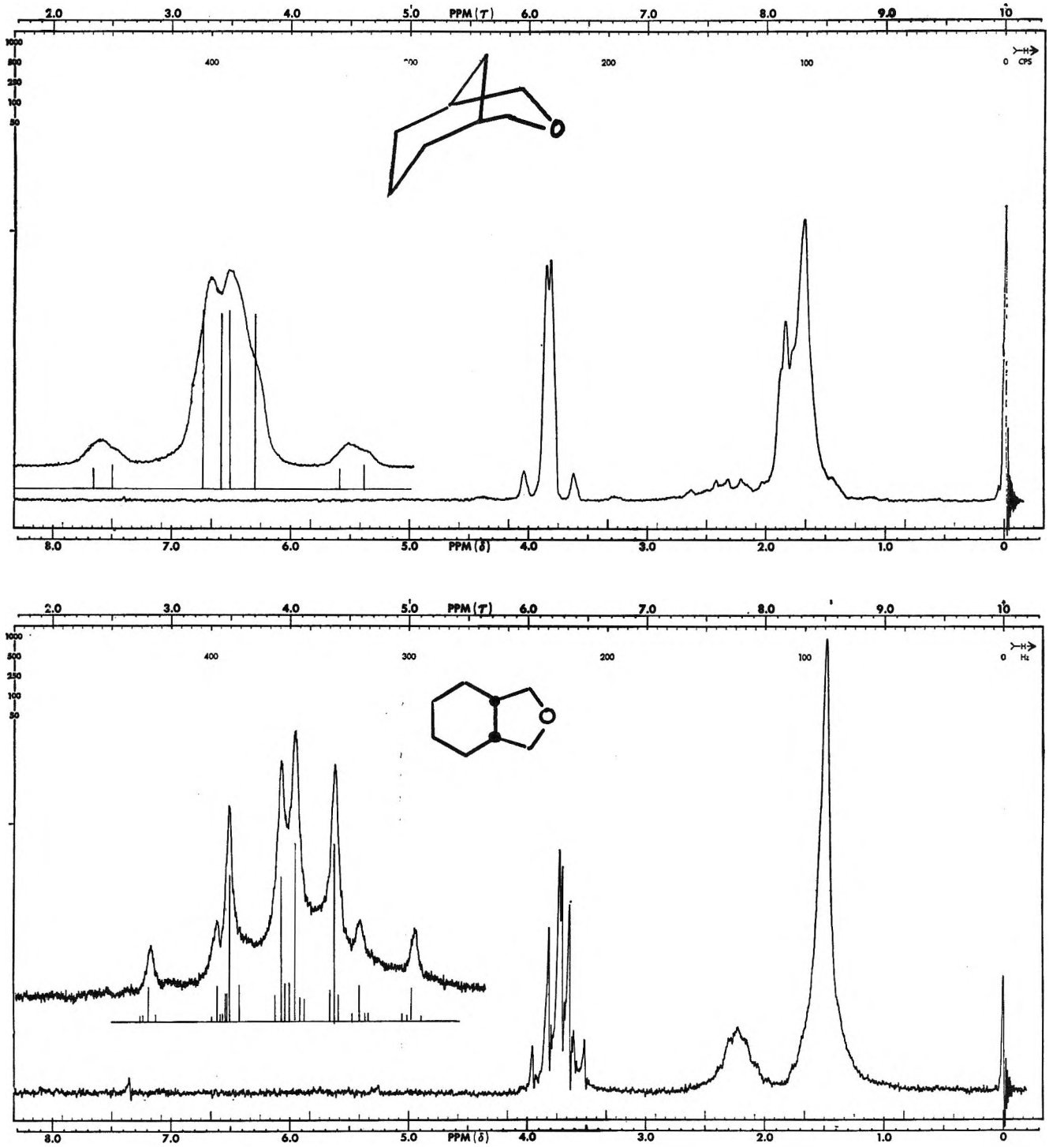


Figure 1.—Nmr spectra of *cis*-3-oxabicyclo[3.3.1]nonane (4) and *cis*-3-oxabicyclo[4.3.0]nonane (5). Calculated spectra shown in insets are from an ABX analysis of 4, δ_{AB} = 8.8 Hz, W_X = 137.0, $|J_{AB}|$ = 11.0, $|J_{AX}|$ = 2.7, and $|J_{BX}|$ = 1.7 Hz, and an AA'BB'XX' analysis of 5 with $W_A = W_{A'} = -218.7$, $W_B = W_{B'} = -228.4$, and $W_X = W_{X'} = -135.0$ Hz, $|J_{AB}| = |J_{A'B'}| = 7.9$, $|J_{AX}| = |J_{A'X'}| = 5.0$, $|J_{BX}| = |J_{B'X'}| = 6.9$, and $|J_{XX'}| = 3.0$ Hz ($J_{AA'} = J_{BB'} = 0$ Hz).

alcohol was formed by a cyclic deprotonation of the adduct of the olefin with protonated formaldehyde was supported by isolation of the intermediate under certain conditions. The isomeric 2-butene adducts did not deprotonate readily, and chloride ion capture occurred to give the chloro alcohols as the major products.[8] Consideration of the geometry of the protonated formaldehyde adducts with cyclopentene and cyclohexene suggests that deprotonation to the homoallylic alcohol would be far more facile with cyclohexene; thus, more bicyclic product is expected from cyclohexene, and trapping of the intermediate carbonium ion by chloride would result in preferential production of the chloro alcohol from cyclopentene. The isolation of significant quantities of tetrahydrofuran derivatives, *e.g.*, **3** and **8**, was somewhat unexpected since none was found in the earlier work with 1 olefins. In addition, allyl chloromethyl ethers are known to be very difficult to cyclize.[10] Examination of molecular models of the isomeric pairs of bicyclics qualitatively supports the assumption that the least strained bicyclic system is formed from both cyclohexene and cyclopentene.

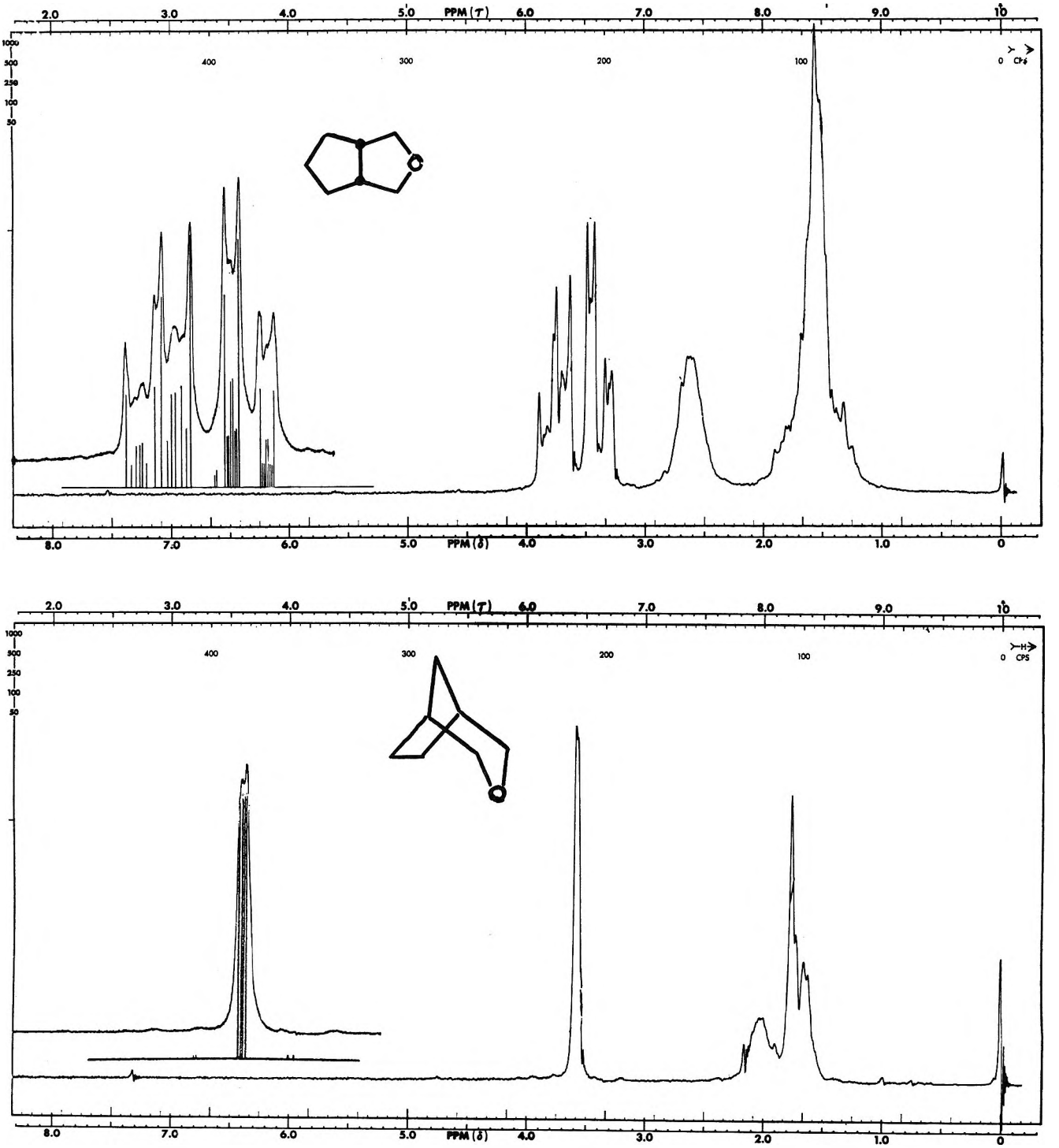


Figure 2.—Nmr spectra of *cis*-3-oxabicyclo[3.3.0]octane (**10**) and 3-oxabicyclo[3.2.1]octane (**11**). Calculated spectra shown in insets are from an AA'BB'XX' analysis of **10**, $W_A = W_{A'} = -224.2$, $W_B = W_{B'} = -202.6$, and $W_X = W_{X'} = -158.0$ Hz, $|J_{AB}| = |J_{A'B'}| = 9.3$, $|J_{AX}| = |J_{A'X'}| = 7.6$, $|J_{BX}| = |J_{B'X'}| = 3.5$, and $|J_{XX'}| = 9.0$ Hz ($J_{AA'} = J_{BB'} = 0$ Hz), and an ABX analysis of **11**, $\delta_{AB} = 4.0$ Hz, $W_X = -112.0$ Hz, $|J_{AB}| = 11.0$, $|J_{AX}| = 0.5$, and $|J_{BX}| = 2.7$ Hz.

Experimental Section[21]

Reaction of Cyclohexene with Paraformaldehyde and Hydrogen Chloride.—Hydrogen chloride was passed into a stirred mixture of 139 g (4.5 mol) of 97% paraformaldehyde, 246 g (3.0 mol) of cyclohexene, and 500 ml of methylene chloride at −60 to −70° for 4 hr. After standing overnight, the reaction mixture was washed twice with water, then with saturated sodium carbonate solution, dried ($MgSO_4$), and filtered, and the solvent was removed. Fractionation gave 128 g (36%) of cyclohexyl chloride, bp 36–42° (17 mm), 202 g (65.5% crude yield) of bicyclic products, bp 85–120° (12 mm), and 41 g of residue containing the formal of the chloro alcohol. The residue was refluxed for 3 hr with 200 ml of methanol and 10 ml of concentrated hydrochloric acid; after distillation there was obtained 31 g (79%) of *trans*-2-chlorocyclohexanemethanol, bp 75–77° (0.8 mm), $n^{20}D$ 1.4897, lit.[4] bp 113° (15 mm), $n^{20}D$ 1.4910, lit.[22] bp 103–104° (14 mm), $n^{25}D$ 1.4771.

(21) All melting and boiling points are uncorrected. Olefins used were Phillips Petroleum Company Pure Grade materials. Glpc analyses were carried out on a Perkin-Elmer Model 720 gas chromatograph using 5 ft and 10 ft × 0.25 in. columns of 20% Ucon LB-550-X on Chromosorb P. Nmr data were obtained on a Varian Model A-60 spectrometer in chloroform-*d* with tetramethylsilane as an internal standard. Calculated spectra were obtained with computer program NMRIT (IBM SHARE Library No. 3165).

(22) M. Mousseron, J. Jullien, and F. Winternitz, *Bull. Soc. Chim. Fr.* **15**, 878 (1948).

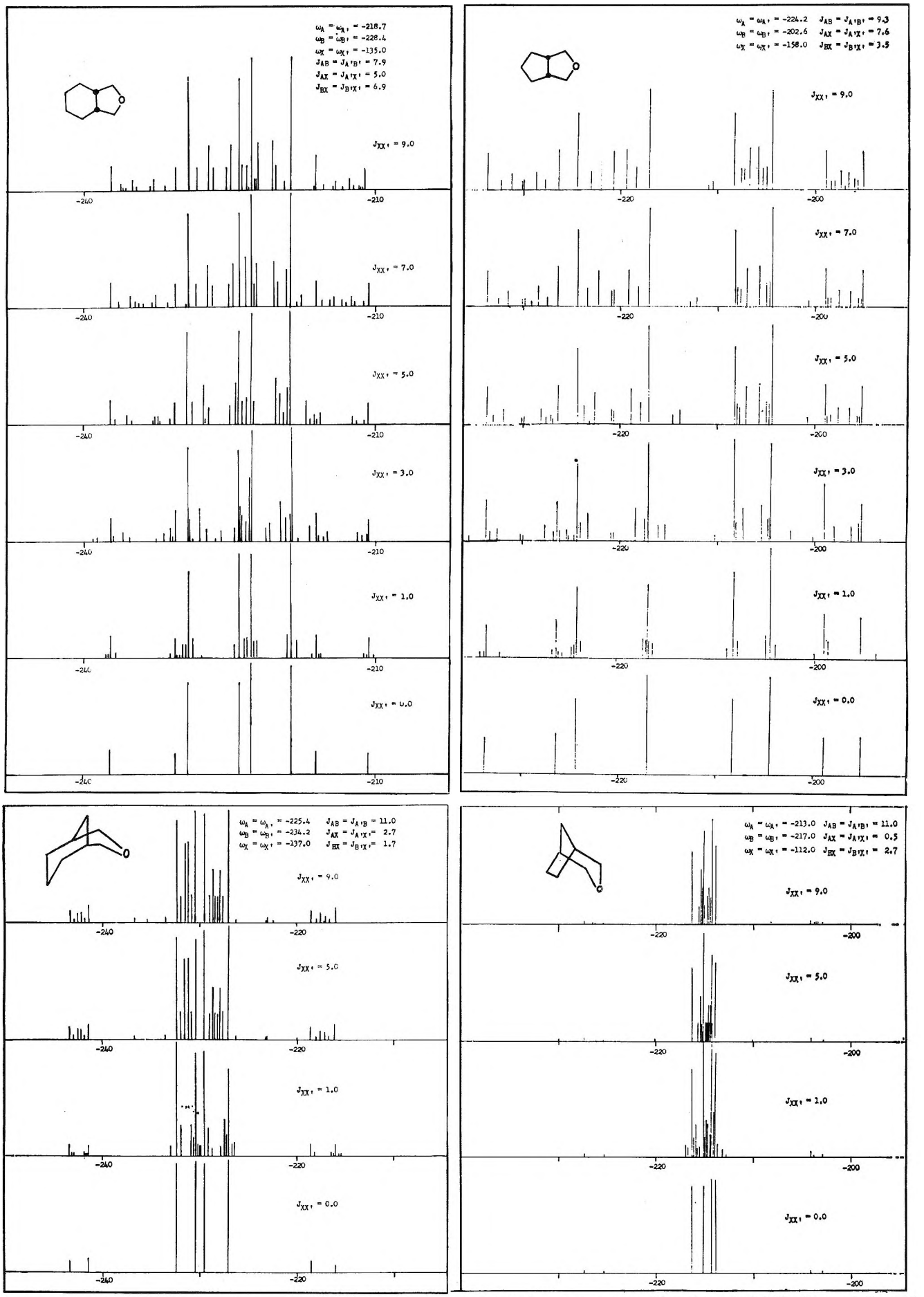


Figure 3.—Calculated line spectra from AA'BB'XX' analyses of α-methylene resonances of 3-oxabicyclo[3.2.1]octane, *cis*-3-oxabicyclo[3.3.1]nonane, *cis*-3-oxabicyclo[4.3.0]nonane, and *cis*-3-oxabicyclo[3.3.0]octane with changes only in $J_{XX'}$, the bridgehead coupling constant.

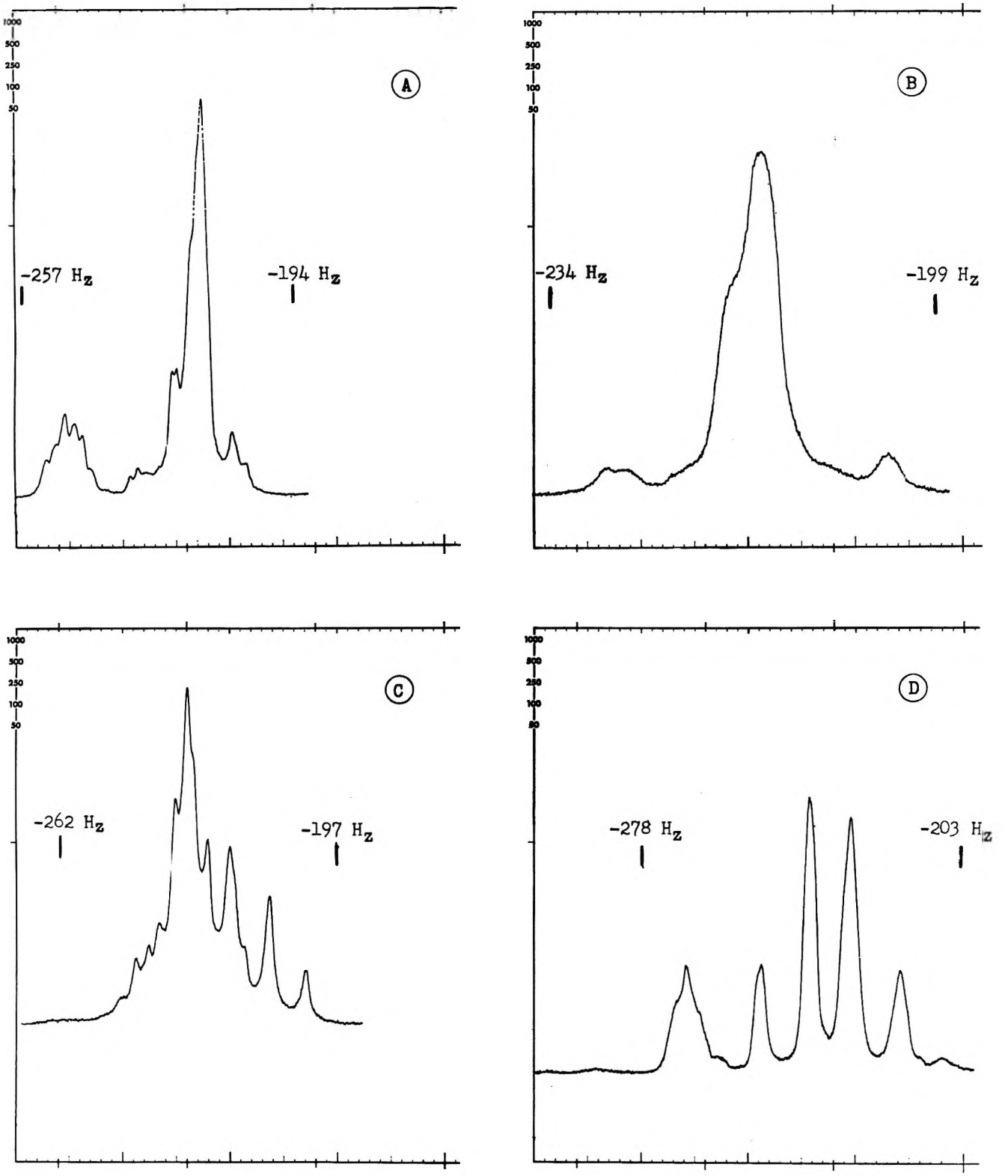


Figure 4.—α methylene resonance region for (A) 6-chloro-*cis*-3-oxabicyclo[3.3.0]octane (**8**), (B) 8-chloro-3-oxabicyclo-[3.2.1]octane (**9**), (C) *trans*-6-chloro-*cis*-3-oxabicyclo[4.3.0]nonane (**3**), and (D) *trans*-9-chloro-*cis*-3-oxabicyclo[3.3.1]nonane (**2**).

Anal. Calcd for $C_7H_{13}ClO$: C, 56.5; H, 8.8; Cl, 23.4. Found: C, 56.6; H, 9.0; Cl, 23.1.

The 3,5-dinitrobenzoate was obtained as colorless platelets, mp 85–86°, after two recrystallizations from 95% ethanol.

Anal. Calcd for $C_{13}H_{15}ClN_2O_6$: C, 47.2; H, 4.5; N, 8.5; Cl, 10.7. Found: C, 47.4; H, 4.4; N, 8.7; Cl, 10.5.

Reduction of Bicyclic Chlorides from Cyclohexene.—A solution of 32.1 g (0.2 mol) of the bicyclic chloride mixture (containing *ca.* 80% **2** and 20% **3** by glpc on the 5-ft Ucon column at 225°) in 300 ml of methanol was treated with 23 g (1.0 g-atom) of sodium cut into small pieces. After dilution with water, the product was extracted into ether and dried ($MgSO_4$); the ether was removed to give 20.8 g (83%) of a colorless, nearly solid product, which by glpc consisted of two isomers in a 4:1 ratio.

A portion of the product was separated by preparative gas chromatography on a 40 ft × $^3/_4$ in. Ucon column at 175°. The major component (**4**) eluted first and solidified; after purification by sublimation at 15 mm it melted at 141–143° (sealed tube), lit.[23] mp 135–138°, 120°.[1]

(23) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1959).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.1; mol wt, 126.1448. Found: C, 75.9; H, 11.3; mol wt, 126.1466 (high-resolution mass spectrometer).

The minor product (**5**), liquid, was submitted for elemental analysis.

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.1. Found: C, 75.8; H, 11.0.

Purification of *trans*-9-Chloro-*cis*-3-oxabicyclo[3.3.1]nonane (2).—Fractionation of a 175-g sample of mixed bicyclic chlorides through an efficient column gave 121 g of a center cut, bp 90–96° (1 mm), which partly solidified. Two recrystallizations from a minimum amount of methanol at 0° provided pure **2** as a crystalline solid with a camphor-like odor, mp 115–117°, lit.[4] mp 116.5–118°, in about 60% recovery.

Anal. Calcd for $C_8H_{13}ClO$: C, 59.8; H, 8.1; Cl, 22.1. Found: C, 59.8; H, 8.3; Cl, 22.0.

Preparative separation of **3** from the mother liquors was accomplished on the 40-ft Ucon column at 175°.

Cleavage of *cis*-3-Oxabicyclo[3.3.1]nonane (4).—A mixture of 5.5 g of *cis*-3-oxabicyclo[3.3.1]nonane and 50 ml of 47% hydriodic acid was refluxed for 2 hr, diluted with water, and extracted into ether (25 ml). The ether solution was dried ($MgSO_4$) and added dropwise to 1.0 g of lithium aluminum hydride in 50 ml of tetrahydrofuran. The mixture was refluxed for 3 hr during which time the ether was distilled out. The excess hydride was decomposed with water and the solution was filtered. Fractionation gave 3.1 g of liquid, bp 118–125°, which by glpc on a 150-ft squalane capillary column was found to contain more than 90% of a single isomer, *cis*-1,3-, *trans*-1,4-, or 1,1-dimethylcyclohexane. Dehydrogenation over platinum on carbon at 305° gave *m*-xylene in greater than 85% purity by glpc on the same column.

Synthesis of *trans*-9-Chloro-*cis*-3-oxabicyclo[3.3.1]nonane (2) from 2-Cyclohexenemethanol.—Hydrogen chloride was passed into 50 g of 2-cyclohexenemethanol[11] (*ca.* 80% isomeric purity) and 18 g of 97% paraformaldehyde in 200 ml of methylene chloride at −65° for 3 hr. Work-up and distillation gave 47.5 g of crude product, bp 74–88° (6 mm). Crystallization from methanol gave 24.6 g (45%) of colorless crystals, mp 112–116°, which was identical by infrared and nmr with the sample obtained from cyclohexene.

Reaction of Cyclopentene with Paraformaldehyde and Hydrogen Chloride.—Reaction of 272 g (4.0 mol) of cyclopentene and 186 g (6.0 mol) of 97% paraformaldehyde with hydrogen chloride in 500 ml of methylene chloride was carried out for 4 hr. Work-up and distillation gave 143.8 g of material, bp 81–96° (32 to 8 mm) and 247 g (66%) of crude formal, bp 127–154° (0.9 mm). A center cut of the formal fraction, bp 145–147° (0.5 mm), $n^{20}D$ 1.4921, was submitted for elemental analysis.

Anal. Calcd for $C_{13}H_{22}Cl_2O_2$: C, 55.6; H, 7.8. Found: C, 55.8; H, 7.9.

Methanolysis of the formal gave *trans*-2-chlorocyclopentanemethanol, bp 74–76° (2.5 mm), $n^{20}D$ 1.4875, in 70% yield.

Anal. Calcd for $C_6H_{11}ClO$: C, 53.5; H, 8.2. Found: C, 53.8; H, 8.3.

The 3,5-dinitrobenzoate was obtained as colorless platelets from absolute ethanol, mp 105–106°.

Anal. Calcd for $C_{13}H_{13}ClN_2O_6$: C, 47.5; H, 4.0; N, 8.5. Found: C, 47.4; H, 4.0; N, 8.3.

Purification of Bicyclic Chlorides from Cyclopentene.—The low-boiling material from the reaction was refractionated through an efficient column to give a center cut, bp 84–86° (15 mm), which was analyzed.

Anal. Calcd for $C_7H_{11}ClO$: C, 57.4; H, 7.5; Cl, 24.3. Found: C, 57.3; H, 7.5; Cl, 24.1.

Separation of **8** and **9** was accomplished on the 40-ft column at 125°.

Sodium and Methanol Reduction of Bicyclic Chlorides from Cyclopentene.—A solution of 50 g (0.34 mol) of the bicyclic chloride mixture in 300 ml of methanol was treated with 46 g (2.0 g-atom) of sodium. Ether extraction followed by distillation gave 23.1 g (61%) of colorless liquid, bp 62–64° (47 mm), which by glpc on a 10-ft Ucon column at 175° contained two compounds in the proportion of 1:2, respectively, in order of elution. The isomers were separated on a preparative scale on the 40-ft Ucon column at 125°.

The minor component, a solid, mp 109–110°, was identified as 3-oxabicyclo[3.2.1]octane.

Anal. Calcd for $C_7H_{12}O$: C, 75.0; H, 10.7. Found: C, 74.8; H, 10.6.

The major component, a liquid, was identified by nmr as *cis*-3-oxabicyclo[3.3.0]octane.

Anal. Calcd for $C_7H_{12}O$: C, 75.0; H, 10.7. Found: C, 74.9; H, 10.9.

Registry No.—**2**, 25236-89-9; **3**, 7639-11-4; **4**, 280-71-7; **5**, 13149-01-4, **6**, 25236-93-5; **7**, 25236-94-6; **7** (3,5-dinitrobenzoate), 25236-95-7; **8**, 25236-96-8; **9**, 25236-97-9; **10**, 5117-83-9; **11**, 279-83-4; hydrogen chloride, 7647-01-0; *trans*-2-chlorocyclohexane methanol (3,5-dinitrobenzoate), 25237-00-7.

Acknowledgment.—We wish to thank Mrs. Joy Buell for recording the nmr spectra, Mr. W. E. Koch for carrying out the capillary glpc separations and dehydrogenation experiment, Mr. C. G. Long for carrying out the preparative glpc separations, and Messrs. G. R. Herrington and W. F. Bowen for their technical assistance.

Electrostatic Participation by Carboxylate Groups in Forming α-Lactones

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Rates of hydrolysis for α-bromophenylacetic acid and six of its *meta*- and *para*-substituted derivatives have been measured in aqueous sodium bicarbonate at two or more temperatures. The substantial negative value for the Hammett ρ (−2.94) and the large positive activation enthalpies and entropies indicate a zwitterion-like transition state for the ionization of Br^- from $ArCHBrCO_2^-$. Rate-structure correlations show that the order of (electrostatic) participation by the α-CO_2^- group is tertiary bromide > secondary bromide > primary bromide, which is just opposite to that observed for covalent participation. It is suggested that the α-CO_2^- group exerts an electron-withdrawing inductive effect. This is counteracted in the hydrolysis reaction by electrostatic participation, which provides "ionizing power" sufficient to level the effects of adding water or salts to the medium for this carbonium ion reaction.

The observation that the solvolysis of α-bromopropionate ion in dilute basic media is independent of base concentration and occurs with retention of configuration[1] is generally regarded as classical example of neighboring group participation.[2-8] It was originally suggested that this was an SN1 reaction, and that configuration was retained in a zwitterion intermediate.[1] Most subsequent investigators have, however, favored an α-lactone intermediate to account for the stereochemistry.[2-8] Even if an α-lactone is accepted an an intermediate the question as to whether the transition state for halide ion release is lactone-like or zwitterion-like remains unanswered. This question is difficult to answer.[3] If the α-CO_2^- group initiates an intramolecular nucleophilic displacement the transition state will be lactone-like, but the stereochemistry can also be explained if ionization of the C–Br bond is merely facilitated by the presence of the negative charge on the carboxylate group and ionization is followed by a rapid collapse to an α-lactone. The rate of bromide ion release for the hydrolysis of $CH_3CHBrCO_2^-$ is actually retarded by ninefold, relative to $CH_3CHBrCH_3$. The latter is much more sensitive to the ionizing power of the solvent, however, so that when the comparison is made in methanol $CH_3CHBrCO_2^-$ is about 20-fold faster.[8] Although these data have been interpreted as "good evidence that the rate-determining step of the solvolysis involves direct intramolecular displacement by the carboxylate group,"[8] this conclusion is difficult to accept until the electrostatic effect of the α-CO_2^- group has been assessed. The small rate increases observed on increasing the polarity of the medium through increased water content or on addition of salts is in the direction predicted for a zwitterion-like transition state, but is smaller than might have been anticipated. At first sight one might have expected a reaction involving a lactone-like transition state to be retarded by an increased polarity or the medium, but Grunwald and Winstein got around this difficulty by assuming that the α-lactone itself "has very high ionic character," and that a lactone-like transition state would be expected to have increased ionic character, relative to the ground state.[3] Their conclusion was that the transition state is lactone-like, and most authors have accepted this interpretation.[6-8] On the other hand, Gould has interpreted the small positive salt effect as evidence that C–Br bond breaking is the slow step, and that the α-lactone is formed in a rapid subsequent step.[5] In order to obtain additional information concerning the nature of the transition state in the solvolysis of α-halo carboxylates we have examined substituent effects on the hydrolysis rates in the $ArCHBrCO_2^-$ system.[9] These results are reported in the present paper and are compared in the following paper with a similar study of the $ArCHBrCH_2CO_2^-$ and $ArCHBrCHBrCO_2^-$ systems.

Results

The rate of hydrolysis of α-bromophenylacetic acid and six of its *meta*- and *para*-substituted derivatives in aqueous sodium bicarbonate were measured at two or more temperatures. The reactions were followed by potentiometric determination of bromide ion released, at intervals. Reactions of each compound was found to be of first order in bromoacetate ion and of zero order in base. Plots of log $[ArCHBrCO_2^-]$ *vs.* *t* were found to be linear to at least three half-lives; rate constants were evaluated from the slope of the least squares "best fit" by multiplying by 2.302. The results are summarized in Table I.

The product of the reaction was in each instance the corresponding mandelic acid (>95%).

The values at 25° differ somewhat from those reported by Kemp and Metzger.[9] Their values, obtained by titration of liberated acid in 0.681 *M* acetone at ionic strength of 0.551 using excess sodium hydroxide, were consistently higher than those obtained by us (H, +6.5%; *p*-Cl, + 9.6%; *m*-NO_2, +36%; *p*-NO_2, +35%). For the parent and *p*-Cl compounds correction for salt effect[9] brings the two sets of data closely in line. For the *m*-NO_2 and *p*-NO_2 compounds there is a hydroxide contribution to the rate.[9] When this and the salt effect are taken into consideration, the agreement is reasonably good.

For the parent compound and its *p*-Cl derivative our enthalpies of activation (determined from the rates at four temperatures) are 1.2 and 1.4 kcal/mol higher

(1) W. A. Cowdry, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937); 1243 (1938).

(2) S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 1576 (1939); S. Winstein, *ibid.*, **61**, 1635 (1939).

(3) E. Grunwald and S. Winstein, *ibid.*, **70**, 841 (1948).

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 524.

(5) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 270.

(6) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 116.

(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 142.

(8) B. Capon, *Quart. Rev.* (*London*), **18**, 75 (1964).

(9) After this investigation was essentially complete a similar study was reported by K. C. Kemp and D. Metzger, *J. Org. Chem.*, **33**, 4165 (1968).

TABLE I

KINETIC DATA FOR THE HYDROLYSIS OF α-BROMOPHENYLACETIC ACIDS (0.006 *M*) IN AQUEOUS SODIUM BICARBONATE (0.066 *M*)

Bromoacetic acid	Registry no.	*T*, °C[a]	$10^6 k$,[b,c] sec^{-1}	$\Delta H^{\pm}$, kcal/mol[d]	$\Delta S^{\pm}$, eu
p-Methylphenyl	25297-16-9	0.0	351		
		25.0	19,700	25.5	19
m-Methylphenyl	25297-17-0	0.0	5.84		
		25.0	601	28.4	22
		40.7	5720		
Phenyl	4870-65-9	0.0	2.8		
		25.0	293	27.8	18
		40.7	3000		
		50.0	8700		
p-Chlorophenyl	3381-73-5	0.0	1.58		
		25.0	150	27.9	17
		40.8	1650		
		50.0	4980		
m-Chlorophenyl	3381-74-6	25.0	15.9	29.8	20
		40.8	238		
		50.0	797		
m-Nitrophenyl	21986-02-7	25.0	3.06	28.3	11
		50.0	121		
		61.0	620		
p-Nitrophenyl	4578-72-7	25.0	1.65	29.3	13
		50.0	81.7		
		61.0	367		

[a] The values for runs at 25° are the mean of three combinations of concentrations of $ArCHBrCO_2^-$ and $NaHCO_3$, *e.g.*, 0.006 *M* *vs.* 0.066 *M* or 0.036 *M* and 0.003 *M* *vs.* 0.036 *M*. The standard deviations did not exceed ±3% for any of the seruns. [b] All reactions were followed to three half-lives or beyond. [c] Correlation coefficients (*r*) were in every instance 0.997 or better. [d] Correlation coefficients (*r*) for the Arrhenius plot were in every instance 0.9994 or better.

than those reported and our entropies of activation are 3–4 eu higher. For *m*-NO_2 there is close agreement in the enthalpies from the two investigations, but our $\Delta S^{\pm}$ value is *ca.* 4 eu lower in this instance.

A Hammett plot of the data obtained at 25° using σ^+ values for *p*-Cl and *p*-Me substituents gave $\rho = -3.42$ (correlation coefficient = 0.979). A considerably larger $\sigma^+_{p\text{-Me}}$ value (*ca.* −0.55 rather than −0.311) would be required to fit the line.[10] Excluding the *p*-Me substituent $\rho = -2.94$ at 25° ($r = 0.995$). This compares with a value of −2.66 obtained by Kemp and Metzger.[9]

The ρ values determined at 40.8 and 50.0° from plots excluding the *p*-Me substituent were −2.83 ($r = 0.999$) and −2.64 ($r = 0.999$), respectively.

The effect of solvent on the rate was determined for $PhCHBrCO_2^-$ at 25° using aqueous ethanol. The slope (m) is 0.17 for a Grunwald–Winstein plot of log k *vs.* Y (for five points, $r = 0.999$; log $k_0 = -4.24$). A small solvent effect has been reported for $CH_3CHBrCO_2^-$,[3] and for $ArCHBrCO_2^-$.[9]

Discussion

Substituent Effects.—The substantial negative ρ value (−2.94) and the better fit of the data with σ^+ constants rather than σ constants for *p*-Me and *p*-Cl substituents provide strong evidence for the development of appreciable ionic character in the C–Br bond during hydrolysis of $ArCHBrCO_2^-$. As has been pointed out by Kemp and Metzger, the incipient benzylic cation in this reaction is more sensitive to substituent effects than are the incipient cations derived in the solvolyses of benzyl chlorides in aqueous alcohol or aqueous acetone ($\rho = -2.2$ and −1.8), or benzyl tosylates in aqueous ethanol ($\rho = -2.2$), but are much less sensitive than the incipient benzyl cations derived from the formolyses of benzyl bromides or benzyl tosylates ($\rho = -5.5$ and −6.0).[9] The effects are comparable with those observed in the hydration of styrenes ($\rho = -3.4$[11a]), the hydration of α-methylstyrenes ($\rho = -3.2$[11b]), and the dehydration of 2-aryl-2-propanols ($\rho = 3.1$[11b]) which are pictured as having the "positive charge partially on the incoming (or outgoing) proton and partially delocalized into the arene system."[11b] For $ArCHBrCO_2^-$ the developing positive charge is partially neutralized by the negative charge on the carboxylate group. Therefore, the data seem to require a zwitterion-like transition state where participation is electrostatic in nature, rather than an α-lactone-like transition state where participation involves covalent bond formation.

It would be desirable to have information concerning the size and sign of ρ for other systems reacting by electrostatic or covalent bonding participation. The only systems studied to date which can be used as models are participation by carbanions in the Ramberg–Bäcklund reaction[12] (for $ArCHBrSO_2CH_3$, $\rho = +1.27$; for $ArCHBrSO_2CH_2Ph$, $\rho = +1.55$; for $ArCHClSO_2CH_2Ph$, $\rho = +1.64$) and participation by alkoxide ion in the formation of styrene oxides (for the reaction $ArCHBrCH_2OH + HO^-$, $\rho = -1.13$).[13] The positive ρ values for the Ramberg–Bäcklund reaction suggest that covalent participation by a carbanion is aided by electron-withdrawing groups. On the other hand, the sizable negative ρ for styrene oxide formation suggests that with the more weakly nucleophilic oxide ion the carbon atom being attacked may develop appreciable positive character. It is not certain whether the latter is an example of covalent or electrostatic participation. More data are needed, therefore, to give a clear-cut interpretation to the meaning of the sizable negative ρ for $ArCHBrCO_2^-$ hydrolysis, but we favor electrostatic participation since it appears to give the more consistent overall picture of the hydrolyses in the $ArCHBrCO_2^-$, $ArCHBrCH_2CO_2^-$, and $ArCHBrCHBrCO_2^-$ systems, as will be brought out below and in the succeeding paper.

Activation Parameters.—The activation parameters for the $ArCHBrCO_2^-$ hydrolyses are noteworthy for the high activation enthalpies, and particularly for the large positive activation entropies (Table I). The latter are considerably more positive than the 0 to 10 eu range that is characteristic for most unimolecular (A-1, SN1) solvolyses,[14] and far greater than the 0 to −30 eu range into which bimolecular (A-2, SN2) sol-

(10) The apparent $\sigma^+_{p\text{-Me}}$ value for the hydrolysis of benzyl tosylates and chlorides is −0.63; see J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3445 (1953).

(11) (a) W. M. Schubert, B. Lamur, and J. R. Keeffe, *ibid.*, **86**, 4727 (1964); (b) N. C. Deno, F. A. Kish, and H. J. Peterson, *ibid.*, **87**, 2157 (1965).

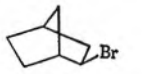
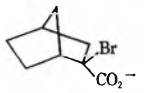
(12) M. D. Wolfinger, Ph.D. Dissertation, Northwestern University, June 1968. These are overall ρ values measured in 40% aqueous dioxane. If corrected for the influence of the substituent on the sulfone ⇄ sulfone carbanion equilibrium the values should be decreased by about 0.5 unit.

(13) A. C. Knipe, unpublished results. This value would be decreased to *ca.* −1.01 if corrected for the influence of substituents on the $ArCHBrCH_2OH + HO^- \rightleftarrows ArCHBrCH_2O^- + H_2O$ equilibrium.

(14) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

TABLE II

KINETIC DATA FOR THE HYDROLYSIS OF α-HALO CARBOXYLATES AND RELATED ALKYL HALIDES

Halide	T, °C	k, sec⁻¹	$k_{CO_2^-}/k_H$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	Ref
CH_3Br	50	1.05×10^{-5}				a
$CH_2BrCO_2^-$	50	$(1.1 \times 10^{-6})^b$	0.1	24.6	−9.5	c
CH_3CH_2Br	55	1.8×10^{-5}				a
$CH_3CHBrCO_2^-$	55	$(4.2 \times 10^{-6})^b$	2.3	29.7	11.4	d
	25	4.17×10^{-7}				
$(CH_3)_2CHBr$	25	$(3.7 \times 10^{-6})^b$				e
$(CH_3)_2CBrCO_2^-$	25	1.21×10^{-4}	33	25.8	3.3	23
$PhCH_2Br$	50	$(\sim 2.5 \times 10^{-3})^f$				
$PhCHBrCO_2^-$	50	8.7×10^{-3}	3.5	27.8	18	Table I
$PhCHBrCH_3$	25	5.6×10^{-1}		19.2	5	g, h
	50	$(6.9)^g$				
	62	$(6.55 \times 10^{-1})^h$		21	−17	18
	62	$(7.25 \times 10^{-4})^h$	1.1	28	11	18

[a] S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, **73**, 2700 (1951). [b] Extrapolated. [c] C. A. Kingsbury, *ibid.*, **87**, 5409 (1965). [d] H. Heine, E. Becker, and J. F. Lane, *ibid.*, **75**, 4514 (1953). [e] K. T. Leffek, R. E. Robertson, and S. E. Sugamori, *Can. J. Chem.*, **39**, 1990 (1961). [f] Estimated from data obtained for $PhCH_2Cl$. [g] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 1602 (1957). [h] In 80% EtOH.

volyses usually fall.[14] Strongly positive $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values have been observed previously for the hydrolysis of α-bromoisobutyrate ions. The latter has been the subject of an unusually careful, quantitative study, which included a determination of the heat capacity of activation and the solvent deuterium isotope effect.[15] The conclusion of Robertson is that the hydrolysis of α-bromoisobutyrate ion almost certainly occurs by an SN1 mechanism.[15] The activation parameters for hydrolysis of $Me_2CBrCO_2^-$ ($\Delta H^{\ddagger}$, 28.96 kcal/mol; $\Delta S^{\ddagger}$, 20.6 eu) are remarkably similar to those of the $ArCHBrCO_2^-$ system (Table I). The evidence from activation parameters would appear, then, to strongly favor electrostatic participation rather than covalent participation by the carboxylate group of $ArCHBrCO_2^-$. According to this view the carboxylate grouping provides "ionizing power," perhaps by controlling intramolecular reorganization of solvent molecules, which makes this SN1 reaction immune to the large rate acceleration ordinarily observed on increasing the water or salt content of the medium.[16]

Correlation of Rate and Structure.—Participation of a neighboring group ordinarily leads to appreciable rate acceleration. For example, neighboring β O^-, SR, NH_2, and I groups cause rate accelerations over that of parent chloride (k/k_H) of 10^3- to 10^8-fold.[17] By comparison, the effect of the neighboring carboxylate group is very modest. Comparison of the rates of hydrolysis of various α-bromoalkanecarboxylates with the rates of hydrolysis of the parent alkyl bromides are summarized in Table II.

Examination of Table II shows that substitution of the carboxylate group for a hydrogen of methyl bromide causes a tenfold retardation in the hydrolysis rate. On the other hand, substitution into ethyl, isopropyl, benzyl, or *exo*-norbornyl bromides causes a moderate rate acceleration (between *ca.* 2- and 33-fold). The effect in the series $BrCH_2CO_2^-$, $CH_3CHBrCO_2^-$, $(CH_3)_2CBrCO_2^-$ is atypical in that it is greatest for the tertiary bromide and least for the primary bromide. This is just the reverse of usual participation effects,[17] and provides an additional argument for electrostatic rather than covalent participation. The greater participation in tertiary than in primary systems will be even more marked in solvents of lower ionizing power than in water. It is of interest to note that extensive rearrangement occurs during the solvolysis of *exo*-α-bromonorbornanecarboxylate ion,[18] which is suggestive of carbonium ion intermediate.

Comparison shows that for $PhCH_2Br$ substitution of a methyl group causes *ca.* a 2700-fold increase in hydrolysis rate, whereas substitution of a carboxylate group cause only *ca.* 3.5-fold increase. It seems most likely that for the latter electrostatic participation is being offset by an electron-withdrawing effect of the CO_2^- group.[19-22]

Another piece of qualitative evidence favoring electrostatic participation in the hydrolysis of $PhCHBrCO_2^-$ (SN1 mechanism) is the close similarity in the leaving group effects for the $PhCHXCO_2^-$ and Ph-

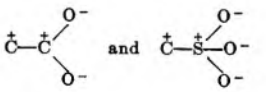
(15) B. N. Hendy, W. A. Redmond, and R. E. Robertson, *Can. J. Chem.*, **45**, 2071 (1967).

(16) See ref 15 for a detailed discussion of the possible role of the CO_2^- group in affecting solvation during the reaction. The remarkable insensitivity of the solvolyses of α-bromoalkanecarboxylate ions to solvent ionizing power may be judged by comparing the following k_{H_2O}/k_{MeOH} ratios: $CH_3CHBrCO_2^-$, 2.4 (at 50°); $(CH_3)_2CBrCO_2^-$, 2.4 (at 64°); $PhCHBrCO_2^-$, 6 (at 25°); *i*-PrBr, 270 (at 50°); *t*-BuBr, 1700 (at 25°). (The latter data are taken from ref 6, except for that for $PhCHBrCO_2^-$, which was calculated using $m = 0.17$.)

(17) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 828 (1948).

(18) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *ibid.*, **87**, 2204 (1965).

(19) In *meta* and *para* positions on the benzene ring the CO_2^- group appears to have a weak electron-releasing effect, as judged from its effect on the ionization constants of benzoic acids and the solvolysis rates of cumyl chlorides.[20] On the other hand, in the ionization of $ArPO_3H^-$,[21] the saponification of $ArCO_2Et$,[21] or the saponification of $ArOCOCH_3$[21] the CO_2^- appears to be electron withdrawing. Coulomb's law applied to



indicates a net repulsion by both the CO_2^- and SO_3^- groups to the development of an adjacent positive charge. The SO_3^- group is sufficiently electron-withdrawing to make $^-O_3SCH_2CO_2H$ a stronger acid by 0.7 pK_a units than CH_3CO_2H.[22]

(20) Y. Okamoto and H. C. Brown, *ibid.*, **80**, 4976 (1958).

(21) See the summary by V. van Bekkum, P. E. Verkade, and B. M. Wepter, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

(22) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 99.

$CHXCH_3$ systems ($k_{Br}/k_{Cl} \cong 12/1$ in each instance at 25° in water).[23,24] In contrast, the leaving group effects for covalent participation to form three-membered rings appears to be unusually large.[25]

Hydrolysis of optically active $PhCHBrCO_2^-$ or $PhCHClCO_2^-$ leads to essentially racemic mandelic acid.[29] This result can be rationalized either by assuming the formation of a zwitterion intermediate of lifetime long enough to permit racemization or of an α-lactone intermediate which racemizes, presumably *via* the zwitterion, prior to capture by solvent.

In the following paper it will be shown that participation by the carboxylate ion is more effective in accelerating the overall rate for β-CO_2^- than for α-CO_2^-. Since for covalent participation formation of a three-membered ring is always much more effective than formation of a four-membered ring, this is further support for the electrostatic participation hypothesis. (This takes no account, of course, of internal return, which would be much greater for the α-CO_2^- system.)

Experimental Section

Aryl α-Bromoacetic Acids.—These compounds were prepared by methods described in the literature.[10,30]

Kinetics of Solvolysis of α-Bromophenylacetic Acid Anions.—Reaction was initiated by adding a weighed amount of the bromo acid to a base solution (0.03–0.07 *M* $NaHCO_3$ in water or 0.016 *M* NaOH in ethanol–water mixtures) that had attained the temperature of the thermostated bath. The mixture was agitated until dissolution was complete. The time taken for dissolution of the acid was disadvantageous in cases where the reaction half-life was short. This was overcome by dissolving the material in acetone (2 drops) prior to addition, whereupon dissolution was immediate. Insensitivity of reaction rate to the small concentration of acetone was verified.

Aliquot parts (containing 0–6 microequivalents of bromide ion) were withdrawn at intervals and quenched in a solution of acetone (3 ml) and 0.25 *M* nitric acid (5 ml). Bromide ion was titrated potentiometrically with 0.0015 *N* $AgNO_3$ using an automatic constant rate buret (Sargent Model C) linked with a chart recorder. The electrode assembly comprised a silver indicator and calomel half-cell reference electrode. The end point was determined from the inflection of a volume *vs.* mV trace in the usual way. It was confirmed that the presence of unreacted material and of reaction products was without effect on the titrations.

Product Analysis.—The bromo acid (0.005 mol) was kept with aqueous 0.06 *M* sodium bicarbonate (250 ml) at 50° for ten half-lives. The reaction mixture was acidified (HCl) to pH 5 and evaporated to a 50-ml volume. The solution was saturated with sodium chloride and continuously extracted with ether during a 100-hr period. The extract was dried ($MgSO_4$) and evaporated. In each case the corresponding mandelic acid was isolated in not less than 96% yield (based on the mass of crude material which in general melted 5° below the literature value). The purified products were identified by ir, nmr, and mixture melting point.

α-Bromo-*m*-methylphenylacetic Acids.—A mixture of *m*-methylmandelic acid (3.32 g, 0.02 mol) and 48% hydrobromic acid (10 ml) was refluxed during 3 hr. The mixture was poured onto crushed ice (30 g) and extraction was with ether. The ether extract was washed with water to remove unreacted mandelic acid, dried, and evaporated to give the product (1.5 g., 33% yield). The bromo acid had bp 134° (0.5 mm).

α-Bromo-*p*-methylphenylacetic Acid.—α-Bromo-*p*-methylphenylacetic acid was prepared from *p*-methylmandelic acid (0.02 mol) in 25% yield, in the same way as the *m*-methyl analog. It had bp 145° (0.1 mm) and mp 83°.

Acknowledgment.—We are grateful to the National Science Foundation (GP 7065) for support of this investigation.

(23) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 1602 (1957).

(24) W. R. Bulcraig and H. M. Dawson, *J. Chem. Soc.*, 80 (1943).

(25) For the Ramberg–Bäcklund reaction of α-halo sulfones k_{Br}/k_{Cl} varies from 88 to 620 depending on the system, solvent, and temperature.[26] For ethylene oxide formation from $HOCH_2CH_2X$ initiated by base $k_{Br}/k_{Cl} \cong$ 88/1 in water, and *ca.* 153/1 in aqueous methanol, after correcting for the alcohol ionization constants.[27,28] For $ArCHXCH_2OH$ k_{Br}/k_{Cl} = 55 in water.[28]

(26) F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968).

(27) C. L. McCabe and J. C. Warner, *ibid.*, **70**, 4031 (1948).

(28) A. C. Knipe, unpublished results.

(29) (a) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **93**, 811 (1908); **95**, 777 (1909). (b) A. McKenzie and N. Walker, *ibid.*, **107**, 1685 (1916); A. M. Ward, *ibid.*, **118**, 1184 (1926).

(30) J. Krapcho, U. S. Patent 3,166,554 [*Chem. Abstr.*, **62**, 13157e (1965)]; B. Ekstrum, A. Gomes-Revilla, R. Mollberg, H. Thelin, and B. Stoberg, *Acta Chem. Scand.*, **19** (1), 281 (1965); K. Heyns and H. Schultze, *Justus Liebigs Ann. Chem.*, **611**, 55 (1958); B. Wladislaw and A. Giora, *J. Chem. Soc.*, 5747 (1965)].

Electrostatic Participation by Carboxylate Groups in the Hydrolysis of β-Bromo- and α,β-Dibromo-β-arylpropionate Ions

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The rates of bromide ion release from β-bromo-β-phenylpropionate ion and five of its *meta*- and *para*-substituted derivatives, $ArCHBrCH_2CO_2^-$ (1), have been measured in aqueous sodium bicarbonate solution at three or more temperatures. The sizable negative ρ (−3.24 at 25°) and the insensitivity of the rate to salt and solvent effects has been interpreted as evidence for electrostatic participation in bromide ion release by the β-CO_2^- leading to a zwitterion intermediate which partitions itself between styrene and β-lactone products. The positive activation entropies are consistent with this interpretation, as are correlations of rate with structure. Salt, solvent, and substituent effects similar to those of 1 were observed also for the rate of bromide ion release from *erythro*-α,β-dibromo-β-phenylpropionate ion and five of its *meta*- and *para*-substituted derivatives (ρ = −3.19 at 37.8°). Here the zwitterion intermediate decomposes mainly to β-bromostyrenes.

Beginning with Einhorn's isolation of a β-lactone from the reaction of β-bromo-*o*-nitrohydrocinnamic acid with sodium carbonate,[1] there have been numerous examples wherein β-halo carboxylates have been shown to undergo hydrolysis to give β-lactones as intermediates or as final products.[2] The hydrolysis of chlorosuccinate ions was demonstrated by Holmberg to involve β-lactone intermediates,[3] and these were

(1) A. Einhorn, *Ber.*, **16**, 2208 (1883).

(2) For reviews, see (a) H. E. Zaugg, *Org. React.*, **8**, 315 (1954); (b) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 116–119; (c) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 75 (1964).

(3) B. Holmberg, *J. Prakt. Chem.*, **88**, 553 (1913).

later isolated by Johansson.[4] Recently the formation of β-lactones from the hydrolysis of α-bromo-α-methylsuccinates and related compounds have been followed by nmr.[5] β-Lactone formation is generally stereospecific and involves inversion at the C–X center.[2]

When a β-aryl group is present, as in $ArCHBrCH_2CO_2^-$ or $ArCHBrCHBrCO_2^-$, debromodecarboxylation to form a styrene competes favorably with the formation of the β-lactone.[6,7] Alkene formation occurs to a lesser extent in other systems, such as α-methyl-β-halobutyrates,[6d] α,α-diphenyl-β-halopropionates,[8] and α,β-dibromosuccinates.[5] β-Lactones will react to give alkenes, but this reaction is slow compared with that whereby alkenes are formed from β-halo carboxylates. Therefore, it is generally agreed that β-lactones are not intermediates in the formation of alkenes by the solvolysis of β-halo carboxylates.[6,7] It has been suggested, instead, that alkene formation and β-lactone formation occur by separate pathways; a duality of mechanisms is possible for each. SN1-like and SN2-like transition states are possbile for β-lactone formation. E2-like and E1-like elimination mechanisms have been suggested as occurring simultaneously for alkene formation, E2 predominating in nonpolar media (acetone, ethanol) and E1 predominating in water. Most authors regard the β-hydroxy acids formed on hydrolysis of β-halo carboxylates by arising by hydrolysis of β-lactone intermediates.

In the previous paper[9] evidence was presented to show that in the hydrolysis of $ArCHBrCO_2^-$ the C–Br bond was extensively ionized in the transition state ($\rho = -2.9$) and that the rate was accelerated *ca.* fourfold relative to $ArCH_2Br$. It was suggested that the α-CO_2^- group was exerting its anchimeric effect on ionization through an electrostatic participation rather than through a conventional direct nucleophilic covalent participation. In other words the transition state was considered to be zwitterion-like rather than α-lactone-like. In the present paper the study has been extended to include the $ArCHBrCH_2CO_2^-$ and $ArCHBrCHBrCO_2^-$ systems and a similar conclusion has been reached.

Results

Substituent, Temperature, and Medium Effects on the $ArCHBrCH_2CO_2^-$ System.—Rates of liberation of bromide ion from a series of *meta*- and *para*-substituted β-bromo-β-arylpropionate ions were measured in the presence of excess sodium bicarbonate at three or more temperatures (Table I).

The effect of solvent was determined by measuring the rates in aqueous ethanol in the presence of excess 0.0006–0.006 *M* sodium hydroxide. (The rates were found to be independent of base concentration.) Solutions containing 10, 20, 40, 60, 80, and 100 mol per cent water were used in each instance, and duplicate kinetic runs were made. The data are summarized in Table II.

Lithium perchlorate was found to exert a small positive salt effect on the rate of liberation of bromide ion from *m*-$ClC_6H_4CHBrCH_2CO_2^-$: $k_{salt}/k_0 = 1.05$ (0.5 *M*), 1.06 (1.5 *M*), and 1.1 (2.5 *M*).

The distribution of products is shown in Table III.

Substituent, Temperature, and Medium Effects in the $ArCHBrCHBrCO_2^-$ System.—Rates of formation of β-bromostyrenes from a series of *meta*- and *para*-substituted α,β-dibromo-β-arylpropionate ions were measured in the presence of excess 0.033 or 0.066 *M* sodium bicarbonate at two or more temperatures by following the increase in absorbance at or near 257 nm (Table IV).

Trumbull and coworkers[7] report the following kinetic data obtained by a titration method in 89% (v/v) aqueous ethylene glycol in a phosphate buffer for the parent compound: $k^{35°}$ 8.6×10^{-5}; E_a, 32.0 kcal/mol; $\Delta S^{\ddagger}$ +23.1 eu. The presence of *ca.* 11% (v/v) ethylene glycol in their solution accounts for most of the discrepancy in the rate constant. There is, however, a serious discrepancy in the activation parameters. It should be noted in this connection that our rate mea-

TABLE I

KINETIC DATA FOR THE HYDROLYSIS OF β-BROMO-β-ARYLPROPIONATES, $YC_6H_4CHBrCH_2CO_2^-$

Y	Registry no.	T, °C	$10^5 k$,[a] sec^{-1}	$\Delta H^{\ddagger}$ kcal/mol[b]	$\Delta S^{\ddagger}$ eu[c]
H	25297-23-8	0.0	278	25.0	21.6
		4.70	665		
		9.55	1,480		
		25.0	14,000		
p-Cl	25356-16-5	4.70	365	22.6	12.2
		9.70	986		
		25.0	7,000		
m-Cl	25356-17-6	0.0	10.3	24.1	11.8
		4.75	23.8		
		9.8	58.1		
		25.0	594		
		32.7	1,380		
		38.4	2,650		
m-Br	25297-24-9	0.0	9.91	24.6	13.3
		25.0	500		
		32.7	1,360		
		38.4	2,630		
m-NO_2	25297-25-0	0.0	1.07	26.3	10.9
		25.0	72.8		
		41.5	714		
p-NO_2	25297-26-1	0.0	0.74	25.6	12.0
		25.0	46.2		
		41.4	416		

[a] Average of three or more runs carried to at least three half-lives. Standard deviations did not exceed ±2%. [b] E_a values were calculated from an Arrhenius plot by the method of least squares; correlation coefficients were 0.996 or better. [c] Calculated at 25°.

TABLE II

SOLVOLYSIS OF β-BROMOARYLPROPIONATE IONS IN AQUEOUS ETHANOL AT 25°

Substituent	Log k_0,[a] sec^{-1}	m[b]	r[c]
p-Cl	−2.4762	0.305	0.9985
m-Cl	−3.0041	0.23	0.9855
m-Br	−3.0021	0.224	0.9630
p-NO_2	−3.5141	0.080	0.9911

[a] Intercept on the ordinate. [b] Slope of a plot of log k *vs.* Grunwald–Winstein Y values. [c] Correlation coefficient.

(4) H. Johansson and S. M. Hagman, *Ber.*, **55**, 647 (1922).
(5) C. A. Kingsbury, *J. Org. Chem.*, **33**, 3247 (1968).
(6) (a) E. Erlenmeyer, *Ber.*, **13**, 303 (1880); (b) H. Johansson and S. M. Hagman, *ibid.*, **55**, 647 (1922); (c) S. J. Cristol and W. P. Norris, *J. Amer. Chem. Soc.*, **75**, 632, 2645 (1953); (d) E. Grovenstein, Jr., and D. E. Lee, *ibid.*, **75**, 2639 (1953).
(7) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Saunders, *J. Org. Chem.*, **27**, 2339 (1962).
(8) H. E. Zaugg, *J. Amer. Chem. Soc.*, **72**, 2998 (1950).
(9) F. G. Bordwell and A. C. Knipe, *J. Org. Chem.*, **35**, 2956 (1970).

TABLE III

PRODUCTS FROM THE HYDROLYSIS OF β-BROMO-β-ARYLPROPIONATES IN THE PRESENCE OF EXCESS SODIUM BICARBONATE

Substituent	T, °C	% β-lactone[a]	% styrene[a]	% recovery[b]
H	0	29	71	90
m-Br	25	43	57	94
		45	55	88
m-Cl	0	52	48	89
	25	49	51	95
	25	50	50	95
	25	46	54	95
	25	46[c]	54[c]	81[c]
	25	14[d]	86[d]	73[d]
	50	40	60	100
m-NO_2	25	73	27	84
		73	27	95
		74	26	95
p-NO_2	25	83	17	92
		87	13	98
		89	11	98

[a] Analysis by nmr (see Experimental Section). [b] Analysis by nmr using DMSO as a standard. [c] In 2 *N* $NaBH_4$. [d] Reaction mixture allowed to stand for 30 min before chloroform extraction. Hydrolysis of the β-lactone probably accounts for the low recovery and high styrene/lactone ratio.

TABLE IV

KINETIC DATA FOR THE HYDROLYSIS OF *erythro*-α,β-DIBROMO-β-ARYLPROPIONATES, $YC_6H_4CHBrCHBrCO_2^-$ (0.006 *M*), IN AQUEOUS SODIUM BICARBONATE (0.006 *M*)

Y	Registry no.	T, °C	10^5k,[a] sec^{-1}	$\Delta H^{\pm}$, kcal/mol[b]	$\Delta S^{\pm}$, eu[c]
p-Me	25297-27-2	25.0	564[d]	24.6	13.9
		37.0	3,300		
H	25297-28-3	25.0	3.22	26.8	11.0
		37.8	22.6		
		56.5	336[d]		
		63.1	692		
		70.5	1,560[d]		
		79.9	4,060		
m-MeO	25297-29-4	37.8	12.8	26.4	8.5
		56.5	176		
		63.1	382		
		70.5	845		
		79.9	2,380		
m-Cl	25297-30-7	56.5	17.9	27.0	5.7
		63.1	35.6		
		70.5	89.0[d]		
		79.9	287		
p-Cl	25297-31-8	56.5	244	24.2	2.8
		63.1	479		
		70.5	1,080[d]		
		79.9	2,990		
m-NO_2	25356-18-7	70.5	28.4		
		80.1	94.2		

[a] Single runs except where noted. [b] Calculated from E_a determined from the least-squares slope of an Arrhenius plot; correlation coefficients were 0.997 or better. [c] Calculated at 25°. [d] Average of two or more runs (standard deviation ±2%).

surements were made by a much simpler method, that the rates were determined over a range of 55° compared with 15°, and that the correlation coefficients for all of the compounds studied were high. (Analysis of the data of Trumbull and coworkers gave a correlation coefficient of 0.996.) Lithium perchlorate was found to exert a small positive salt effect on the rate of formation of β-bromostyrene from *erythro*-α,β-dibromo-β-phenylpropionate ion: k_{salt}/k_0 = 1.05 (0.5 *M*); 1.4 (1.5 *M*); 1.6 (2.5 *M*).

Attempts to determine solvent effects by measuring rates of reactions for $ArCHBrCHBrCO_2^-$ in aqueous ethanol in the presence of excess sodium acetate were not altogether successful. For p-Me the plot was linear from 0 to 60 mol % water (m = 0.5), but then curved upward; for $C_6H_5CHBrCHBrCO_2^-$ the plot curved steadily from 10 to 80 mol % water (mean m = 0.2); for m-Cl there was essentially no change in rate from 10 to 40 mol % water, and only a twofold increase in rate from 60 to 100 mol % water.

The Hammett ρ values for the $ArCHBrCH_2CO_2^-$ and $ArCHBrCHBrCO_2^-$ systems for a range of temperatures were evaluated from results for six substituents and are listed in Table V.

TABLE V

HAMMETT ρ VALUES FOR THE HYDROLYSIS OF $ArCHBrCH_2CO_2^-$ AND $ArCHBrCHBrCO_2^-$ AT VARIOUS TEMPERATURES

System	T, °C	ρ[a]	r
$ArCHBrCH_2CO_2^-$	0.0	−3.38	0.994
	25.0	−3.24	0.994
$(ArCHBrCHBrCO_2^-)$[b]	37.8	−3.19	0.979
		(−3.80)	(0.973)
	56.5	−2.95	0.989
		(−3.58)	(0.974)
	63.1	−3.85	0.986
		(−3.51)	(0.970)
	70.5	−2.69	0.987
		(−3.40)	(0.965)
	79.9	−2.54	0.987
		(−3.29)	(0.960)

[a] σ^+ values were used for p-Me and p-Cl since better correlation was obtained thereby; figures in parentheses were obtained by inclusion of p-Me points.[11] [b] Rates of reaction of the p-nitro derivative were extrapolated from results of Trumbull, *et al.*[7]

The Hammett ρ values were observed to be strongly solvent dependent (Table VI).

TABLE VI

VARIATION OF ρ WITH SOLVENT COMPOSITION IN THE SOLVOLYSIS OF β-BROMO-β-ARYLPROPIONATES AND α,β-DIBROMO-β-ARYLPROPIONATES IN AQUEOUS ETHANOL AT 25°

Mol % H_2O	ρ[a]	ρ[b]
100	−3.3	−3.3
80	−2.2	−2.6
60	−1.8	−1.9
40		−1.8
20	−1.2	−1.4
10	−1.1	−1.0

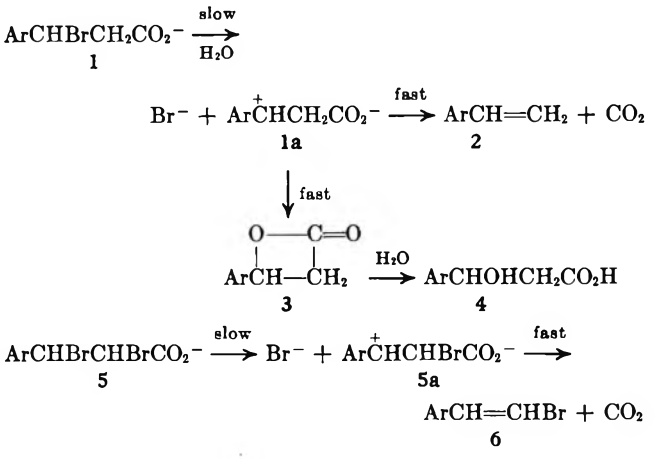
[a] Estimated from the relative rates of reaction of the p-Cl- and p-$NO_2C_6H_4CHBrCH_2CO_2^-$. [b] Estimated from the relative rates of $C_6H_5CHBrCHBrCO_2^-$ and its m-Cl derivative.

Discussion

Substituent, Salt, and Solvent Effects.—Comparison of the data in the previous section with that given in the preceding paper[9] shows that the substituent, salt, and solvent effects for hydrolysis of bromide ion from the $ArCHBrCO_2^-$, $ArCHBrCH_2CO_2^-$, and $ArCHBrCHBrCO_2^-$ systems are remarkably similar. In all

three systems, ρ is about -3, and, in all three systems the hydrolyses are relatively insensitive to salt effects and to changes in the ionizing power of the solvent. The sizable negative ρ shows that the C–Br bond is developing a high degree of ionic character in the transition state. It was concluded in the previous paper that these effects in the $ArCHBrCO_2^-$ system could be best interpreted as electrostatic participation by the carboxylate ion, which serves to facilitate the ionization and to produce a leveling influence on salt and solvent effects. We believe that this mechanism also offers the simplest explanation for the $ArCHBrCH_2CO_2^-$ and $ArCHBrCHBrCO_2^-$ systems, *i.e.* Scheme I.

SCHEME I



According to this interpretation the intermediate zwitterion **1a** partitions itself the styrene (**2**) and the β-lactone (**3**). The presence of electron-withdrawing groups promotes collapse to the β-lactone. Similar possibilities are available to zwitterion **5a**, but here the bromostyrene is essentially the only product, regardless of the substituent.

The change in ρ values with changes in solvent composition appears to be rather large, but there are relatively few data available for comparison.[10] Kochi and Hammond observed a similar but somewhat smaller change in the solvolysis of benzyl tosylates on increasing the water content of aqueous acetone, judging from the effect of one substituent (*p*-Me). Assuming their experimental value of -0.63 for $\sigma_{p\text{-Me}}$, the mole per cent water and respective ρ values were 29.0, -1.9; 44.8, -2.1; 55.0, -2.2; 62.0, -2.3; 67.0, -2.4; 74.1, -2.4; 76.6, -2.4.[11] Jaffé suggests a possible dependence of ρ on solvent ionizing power, Y, and this is borne out qualitatively by the Kochi and Hammond data. In the present instant ρ also increases (nonlinearly) with increasing values of Y. The lower sensitivity to substituent effects in less polar solvents for **1** and **5** could mean that the influence of electrostatic field of the carboxylate ion on the developing carbonium ion is greater in these solvents. It could, of course, also be explained by assuming a duality of mechanism.

A comparison of the rate of bromide ion release from $PhCHBrCH_2CO_2^-$ on hydrolysis (Table VII) shows it to be *ca.* 480 times as fast as that for $PhCHBrCO_2^-$. Similarly, $CH_3CHBrCH_2CO_2^-$ hydrolyzes 43 times as rapidly as does $CH_3CHBrCO_2^-$.[12] This order of reactivity is just opposite to that observed in covalent participations where the rates of formation of three-membered rings is much greater than that to form four-membered rings.[13] These results can be accounted for by electrostatic participation in which a β-CO_2^- is more effective than an α-CO_2^- because of less attenuation by the electron-withdrawing effect[9] of the CO_2^- group. It will be observed that substitution of either an α-CO_2^- or β-CO_2^- for hydrogen in the parent $PhCHBrCH_3$ is actually rate retarding. However, the relative insensitivity of the solvolyses of the β-bromoalkanecarboxylates to solvent ionizing power makes $k_{CO_2^-}/k_H$ = 95:1.0 when comparison is made in 80% ethanol (Table VII).

Introduction of a β-Br into $PhCHBrCH_3$ retards the solvolysis rate (in 80% EtOH) by *ca.* 1.5×10^4 (Table VII). A similar but somewhat smaller difference (*ca.* 4.3×10^3) is observed for the hydrolysis rates of *erythro*-$PhCHBrCHBrCO_2^-$ *vs.* $PhCHBrCH_2CO_2^-$. These differences can be ascribed to the retarding electron-withdrawing inductive effect of the β-Br on the ionization of the benzylic C–Br bond.[14]

Vaughan, Caple, Csapilla, and Scheiner have clearly demonstrated the existence of a rate accelerating electrostatic participation by β-CO_2^- through measurements made on systems where covalent participation is made impossible due to steric effects.[15] Some of their data are included in Table VII. Note that the *cis*-β-bromocyclopentanecarboxylate ion reacts 5.8 times as fast as the parent bromide.

Examination of Tables I and III shows that the hydrolyses of $ArCHBrCH_2CO_2^-$ and of $ArCHBrCHBrCO_2^-$ exhibit positive activation entropies. They are not as strongly positive as for $ArCHBrCO_2^-$, but are nevertheless more positive than the usual range for unimolecular (A-1, SN1) solvolyses (0 to 10),[16] and much more positive than those of the parent bromides (Table VII).

The commonly accepted view is that β-halo carboxylates react by three separate pathways: (a) intramolecular nucleophilic diplacement to form a β-lactone,[2] (b) a concerted E2-like debromodecarboxylation,[6] and (c) and E1-like debromodecarboxylation. The principal basis for these mechanisms is that they account for the stereochemistry.

For β-lactone formation covalent participation has been assumed on the basis of the modest rate enhancements observed and the overall retention of configuration in forming the β-hydroxy acid. We have seen, however, that electrostatic participation also can lead

(10) H. H. Jaffé, *Chem. Rev.*, **53**, 119 (1953).

(11) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3445 (1953).

(12) There are a number of instances wherein β-lactone formation is known to be preferred to α-lactone formation where the two processes are in direct competition. An early example is Holmberg's hydrolysis of $^-O_2CCH_2CHClCO_2^-$ from which a β-lactone was isolated.[2b,3,4]

(13) See A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).

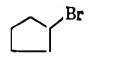
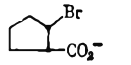
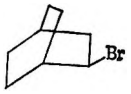
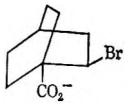
(14) The rate of bromide ion liberation from *threo*-α,β-dibromo-β-phenylpropionate ion is much faster than that for the *erythro* isomer, but exact kinetic data are lacking. It has been suggested that the *erythro* isomer reacts by a carbonium ion mechanism to the extent that it forms *trans*-β-bromostyrene (78%) and that the rate acceleration is due to a concerted elimination for the *threo* isomer.[6,7] For reasons stated below we prefer to assume that electrostatic participation leading to the formation of zwitterion occurs in each instance. One possible interpretation of the rate difference would be to assume a higher ground state energy for the *threo* isomer and zwitterion-like transition states of about equal energy.

(15) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, **87**, 2204 (1965).

(16) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

TABLE VII

KINETIC DATA FOR THE SOLVOLYSES OF β-BROMOALKANECARBOXYLATES AND RELATED COMPOUNDS

Bromide	T, °C	k,[a] sec⁻¹	$k_{CO_2^-}/k_H$	ΔS‡, eu	Ref
$PhCHBrCO_2^-$	25	2.93×10^{-4}		18	9
$PhCHBrCH_3$	25	5.6×10^{-1}		5	e
	25	$(1.91 \times 10^{-4})^b$		−7.7	e
	50	$(2.89 \times 10^{-3})^b$			e
$PhCHBrCH_2CO_2^-$	25	1.4×10^{-3}	0.25	22	f
	25	$(1.8 \times 10^{-2})^b$	95		
$PhCHBrCH_2Br$	55	$(1.90 \times 10^{-7})^c$			g
$PhCHBrCHBrCO_2^-$	25	3.22×10^{-5}			h
	55	$(5.4 \times 10^{-5})^d$	280		
$CH_3CHBrCO_2^-$	25	4.17×10^{-7}			i
$CH_3CHBrCH_2CO_2^-$	25	1.8×10^{-5}			j
	62	$(1.70 \times 10^{-5})^b$		−28	k
	62	$(9.73 \times 10^{-5})^b$	5.7	−8	k
		1.64×10^{-3}		10	
	62	$(6.65 \times 10^{-6})^b$		−25	k
	62	2.12×10^{-1}		20	k

[a] In water unless otherwise stated. [b] In 80% (v/v) EtOH–H_2O. [c] In 100% EtOH. [d] Estimated assuming $m = 0.5$. [e] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 79, 1602 (1957). [f] Table I. [g] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 70, 828 (1948). [h] Table IV. [i] J. F. Lane and H. W. Heine, *J. Amer. Chem. Soc.*, 73, 1348 (1951). [j] A. R. Olson and R. J. Miller, *ibid.*, 60, 2687 (1938). [k] Reference 15.

to rate acceleration,[15] and that, although overall retention of configuration is most readily explained by assuming a lactone intermediate, this does not preclude the formation of a zwitterion intermediate by loss of bromide ion followed by collapse to a β-lactone in a rapid step.[9]

The data in Tables I–III show that substitution of electron-withdrawing groups causes a sharp drop in overall rate which is accompanied by a gradual progressive shift in products from mainly olefin to mainly β-lactone. There also appears to be a decrease in sensitivity to solvent ionizing power with the substitution of electron-withdrawing groups, but there is no obvious trend in activation parameters. If the olefins and β-lactones are being formed by separate paths, *e.g.*, intramolecular displacement and E2 elimination, one might expect to see a curved Hammett plot and/or marked changes in activation parameters as the change from one reaction path to the other occurs. The constancy of the ρ value and of the activation parameters and their similarity to those in the $ArCHBrCO_2^-$ and $ArCHBrCHBrCO_2^-$ systems strongly suggests that all are forming similar (zwitterion) intermediates in the rate-determining step, and that these intermediates behave differently in the product-forming step. Ionization of the C–Br bond requires more assistance from carboxylate participation as the developing benzylic carbonium ions are made less stable through substitution of electron withdrawing groups. The resulting zwitterions collapse more rapidly to β-lactones in the latter instances (Table III).

The duality of mechanisms for $ArCHBrCHBrCO_2^-$ systems is based on the fact that, whereas the *erythro* and *threo* isomers undergo stereoselective *trans* elimination (E2-like) in nonpolar solvents,[6,7] in water the reactions become stereoconvergent. The change in stereochemistry has been attributed to a crossover to a carbonium ion (E1-like) mechanism. An alternative view would be that the β-CO_2^- facilitates the ionization of the C–Br by *trans* electrostatic participation to form a zwitterion, which in nonpolar (non stabilizing) solvents undergoes stereoselective loss of CO_2, but in stabilizing solvents (water) racemizes prior to loss of CO_2. Once again this interpretation is supported by the linearity of the Hammett plots and the relative constancy of the activation parameters. The salt and solvent responses also appear to be similar to those in the $ArCHBrCO_2^-$ and $ArCHBrCH_2CO_2^-$ systems.

Recently, Noyce and Banitt have studied the hydrolysis of *cis*- and *trans*-β-hydroxy-α-methyl-β-*m*-chlorophenylpropionic acid lactones in water at pH 6 and have obtained evidence that loss of carbon dioxide from the diastereomeric m-$ClC_6H_4C^+HCH(Me)CO_2^-$ zwitterions can be stereospecific.[17] The principal argument for a duality of mechanism in the debromodecarboxylation of $ArCHBrCHBrCO_2^-$ is negated if this conclusion is accepted for this system as well. At least until more definitive information becomes available it seems best to consider the ionizations of bromide ion from $ArCHBrCO_2^-$, $ArCHBrCH_2CO_2^-$, and $ArCHBrCHBrCO_2^-$ as all proceeding by similar reaction paths involving zwitterion-like transition states and zwitterion intermediates.

Experimental Section

Materials.—The β-bromo-β-phenylpropionic and *erythro*-β-phenyl-α,β-dibromopropionic acids were prepared by methods

(17) D. S. Noyce and E. H. Banitt, *J. Org. Chem.*, 31, 4043 (1966).

described in the literature.[18-23] Identification was by melting point, ir, and nmr.

The Kinetics of Reaction of β-Bromo-β-phenylpropionic Acid Anions.—Two analytical procedures were used to follow reactions of the β-bromo acid anions. (a) Reaction was initiated by adding a weighed amount of the bromo acid to a base solution (sodium bicarbonate in water or sodium hydroxide in ethanol–water mixtures) that had attained the temperature of the thermostated bath. The reaction was followed by potentiometric estimation of bromide ion released. Aliquot parts of the reaction mixture were titrated with silver nitrate at appropriate time intervals. The electrode assembly and titration procedure have been described previously.[9] It was confirmed that neither starting material or products interfered with the analytical method. (b) For those reactions leading to formation of the appropriate styrene in high yield it was convenient to follow the course of the reaction by observation of the increase in absorbance at 258 mμ. The substrates also had absorbance maxima at this wavelength, but with lesser extinction coefficients.

Reaction was initiated by addition of 5 μl of a solution (0.03 *M*) of the bromo acid in acetone to the solvent (3 ml) contained in a cuvette of 1-cm path length. The reaction vessel and contents had previously been allowed to attain the temperature of the thermostated cell compartment. In ethanol–water solution the wavelength at which the absorbance change was a maximum during the course of reaction was chosen by inspection and found always to be in the range of 245–255 mμ. All rate constants were evaluated by least-squares analysis of data recorded during a minimum time span of three reaction half-lives. The data were processed with the aid of a CDC 6400 computer at the Northwestern University Vogelback Computing Center.

Product Analysis.—The bromo acid (1 g) was stirred in a heterogeneous mixture of aqueous sodium bicarbonate (50 ml, 0.15 *M*) and chloroform (50 ml) at the appropriate temperature for 10 half-lives. The aqueous layer was saturated with sodium chloride and extracted with four 100-ml portions of chloroform. The combined chloroform extract was washed with water (50 ml), dried ($MgSO_4$), and evaporated to a volume of 1.5 ml by rotary evaporation at 25° (20 mm). DMSO (150 μl) was added and the nmr spectrum of the solution was recorded immediately. In every case the spectrum was that of a mixture of the appropriate lactone and styrene. The percentage composition of each product was evaluated from the integral and the overall recovery of products was evaluated with reference to the integral of the DMSO protons. The analyses were repeated in triplicate with good reproducibility as revealed in Table III.

Acknowledgment.—We are grateful to the National Science Foundation (GP 7065) for support of this investigation.

(18) E. Fourneau and J. R. Billeter, *Bull. Soc. Chim. Fr.*, **7**, 593 (1940).
(19) A. Basler, *Ber.*, **16**, 3002 (1883).
(20) G. Pravanitz, *ibid.*, **17**, 596 (1884).
(21) J. I. Jones and T. C. James, *J. Chem. Soc.*, 1600 (1935).
(22) H. Willstaedt, *Ber.*, **64B**, 2688 (1931).
(23) S. J. Cristol and H. P. Norris, *J. Amer. Chem. Soc.*, **75**, 632 (1953).

Silicon-Functional 1,2,5-Oxadisilacyclopentane Heterocyclics

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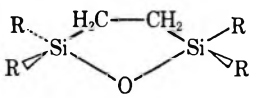
Ligand redistribution of appropriate alkoxy- or chlorosiloxane substrates at elevated temperatures afforded examples of the title heterocyclic system bearing easily solvolyzable substituents at one or both silicon sites. Also described are novel spirocyclic derivatives of the bidentate alkoxy ligand, $-OCMe_2CH_2CH_2CMe_2O-$.

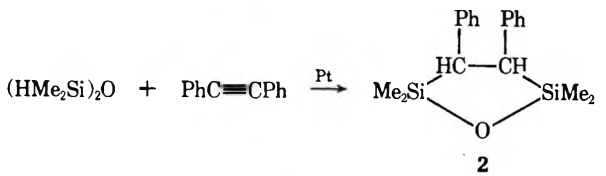
The first examples of the strained 1,2,5-oxadisilacyclopentane heterocyclic system, **1** (R = all combinations of Ph and CH_3), were reported by Merker[1] and



1

his coworkers who employed alkaline thermal siloxane rearrangement of appropriate polymeric substrates.

Other members of this interesting system (*e.g.*, **2**) have been reported[2] to form directly from certain hydrosilation reactions.



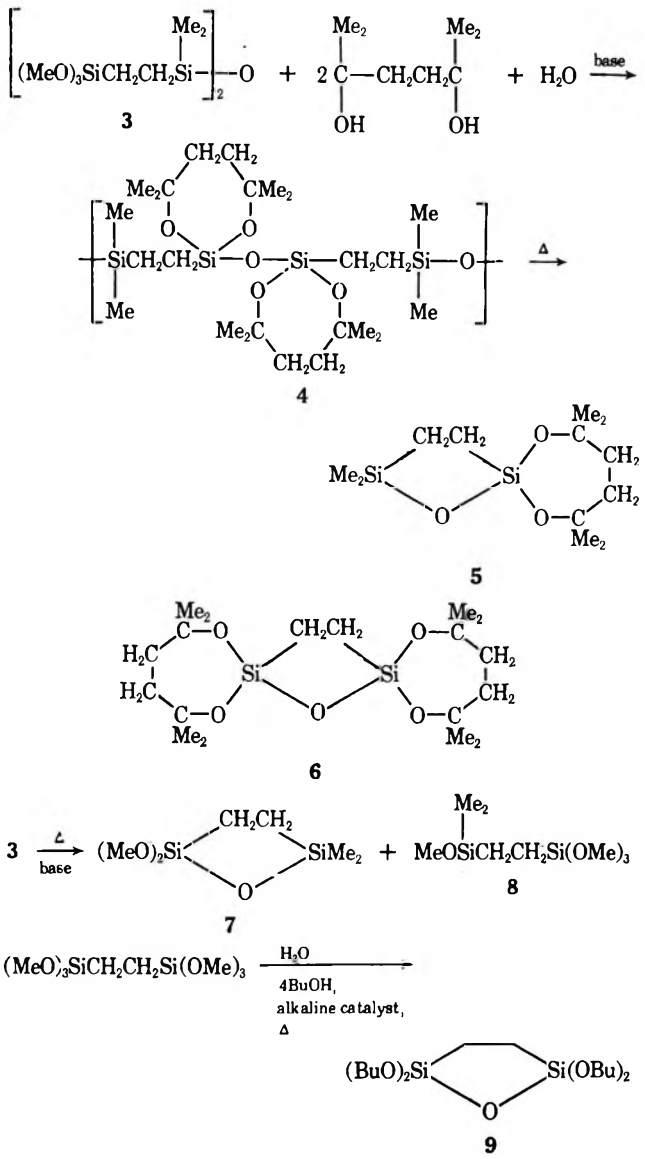
2

The previous literature contained no examples of this heterocyclic system containing easily hydrolyzable silicon substituents. We describe herein the first examples of chloro- and alkoxy-substituted 1,2,5-dioxasilacyclopentanes.[3]

Results and Discussion

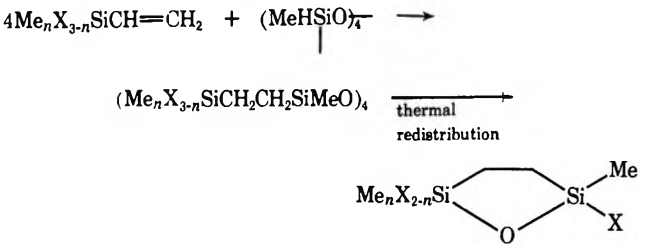
During an attempt to prepare a linear polymer (**4**) by the combined base-catalyzed partial hydrolysis and alkoxy exchange reaction of **3**, overheating occurred and the novel spirocyclic **5** distilled from the reaction mixture. By a very similar approach, using $(MeO)_3SiCH_2CH_2Si(OMe)_3$ rather than **3**, we were able to prepare very readily the related structure **6** containing *two* spiro sites. Although compounds **5** and **6** did indeed constitute representatives of the previously unknown alkoxy-functional 1,2,5-oxadisilacyclopentanes, it was of interest to attempt the synthesis of simpler examples bearing monodentate silicon ligands. With this objective, **3** was subjected to alkaline pyrolysis which did indeed afford good yields of **7** *via* alkoxy–siloxy redistribution as well as the expected by-product **8**. This type of synthesis is fairly general if the alkoxy ligand is selected with due regard for favorable volatility relationships among the species to be expected at equilibrium. Thus, **9** can be prepared in good yield *via* the reaction shown since it is the most volatile species

(1) (a) W. A. Piccoli, G. C. Haberland, and R. L. Merker, *J. Amer. Chem. Soc.*, **82**, 1883 (1960); (b) R. L. Merker and M. J. Scott, *J. Polym. Sci.*, **43**, 297 (1960).
(2) A. M. Polyakova, M. D. Suchkova, V. V. Korshak, and V. M. Vdovin, *Izv. Akad. Nauk. SSSR, Ser. Khim*, **7**, 1267 (1965).
(3) Information concerning the utility of such species may be found in U. S. Patent 3,427,338 (Feb 11, 1969) (C. L. Frye). Subsequent to the completion of our work, related acetoxy-substituted examples were disclosed in U. S. Patent 3,338,951 (Aug 29, 1967) (E. W. Khaub).



available from the simple redistribution of alkoxy and siloxy linkages and can consequently be preferentially removed from the higher boiling $(BuO)_3SiCH_2CH_2Si(OBu)_3$; with smaller alkoxy groups, the hexaalkoxydisilethane would be lower boiling than the tetraalkoxyheterocyclic, precluding this type of synthesis. At sufficiently high temperatures (*i.e.*, about 400°), the desired redistribution occurs even in the absence of any deliberately added catalyst; however, the addition of alkaline substances permitted a substantial decrease of the reaction temperature (250–350°).

This base-catalyzed 1,2,5-oxadisilacyclopentane synthesis is by no means free of complication. Since this heterocyclic system is strained, its formation presumably involves a rather large activation energy and is, therefore, favored by higher temperatures. The use of too much catalyst lowers the reaction temperature so drastically that other processes may predominate over strained-ring formation. Consequently, the choice of catalyst and its concentration can sometimes have a very marked effect on the nature of the resulting products. A particularly good example of the importance of catalyst concentration was provided by the redistribution of **3** to **7**. Relatively little catalyst (NaOMe) was employed the first time the reaction was run, resulting in an initial "cracking" temperature of approximately 285° and a fair yield (49%) of **7**. In a subsequent attempt, a much higher catalyst concentration was used, resulting in a much lower reaction temperature (200–250°) and volatile products which contained relatively little **7**. In this particular instance, base-catalyzed redistribution[4] of carbon–silicon bonds was sufficiently rapid at the higher catalyst levels to afford copious amounts of $Me_2Si(OMe)_2$ rather than the desired heterocyclic. Unwanted C–Si redistribution of this type is perhaps the most serious and common complication in the application of this method. To the extent that volatile "end-block-rich" species such as $Me_2Si(OMe)_2$ are distilled from the system the residue is depleted of end blocks resulting in ultimate gelation. Additional examples of this heterocyclic system bearing methoxy or chloro substituents were prepared by the following rather general procedure involving redistribution of appropriate hydrosilation adducts of vinylsilanes and $(MeHSiO)_4$.



10, X = MeO; n = 2
11, X = MeO; n = 0
12, X = Cl; n = 2
13, X = Cl; n = 0

Alkaline catalysis is of course precluded when chlorosilanes are involved; in these instances, catalysis with Lewis acids such as $FeCl_3$, $AlCl_3$, or $(BuO)_3B$ was attempted but no lowering of reaction temperature was observed.

Experimental Section

General.—The nmr data were obtained on a Varian Associates Model A-60 instrument using Me_4Si as an internal standard. The silane and siloxane reactants were obtained from a Dow Corning Corp. pilot plant and were checked for purity by vpc prior to use and distilled if necessary. The chloroplatinic acid catalyst solution used in the preparation of the hydrosilation adducts was prepared by dissolving 3.5 g of reagent grade $H_2PtCl_6 \cdot 2H_2O$ in 23.3 g of glacial acetic acid.

2,2,7,7,10,10-Hexamethyl-1,6,11-trioxa-2,5-disilaspiro[4.6]undecane (5).—Compound **3** was prepared *via* the chloroplatinic acid catalyzed hydrosilation reaction of 2 mol of vinyltrimethoxysilane with 1 mol of tetramethyldisiloxane. This adduct (43 g, 0.10 mol) was then combined with 2,5-dimethylhexane-2,5-diol (29.2 g, 0.20 mol), water (1.8 g, 0.10 mol), and a catalytic amount of NaOMe (0.05 g). Upon heating this mixture, hydrolysis and alcoholysis proceeded; after distilling 17.3 g of methanol from the system, the temperature was raised to 300–340°, whereupon cracking occurred. The fractions collected at a head temperature of 80–200° were combined and refractionated to yield product **5**: bp 55° (0.2 mm); ir (CCl_4) 10.7 μ (strained SiOSi). *Anal.* Calcd for $C_{12}H_{26}O_3Si_2$: C, 52.6; H, 9.5; Si, 20.5. Found: C, 52.3; H, 9.4; Si, 20.4.

2,2,5,5,11,11,14,14-Octamethyl-1,6,8,10,15-pentaoxa-7,9-disiladispiro[6.1.6.2]heptadecane (6).—1,2-Bis(trimethoxysilyl)-ethane was prepared from the chloroplatinic acid catalyzed hydrosilation reaction of CH_2=$CHSi(OMe)_3$ and $HSi(OMe)_3$. This adduct (18.6 g, 0.069 mol) was then heated with 2,5-dimethylhexane-2,5-diol, H_2O, and a trace of NaOMe as in the preceeding example. Cracking at 300–360° (0.2 mm) produced 25 g of distillate which, upon fractionation, afforded 12.4 g of **6**

(4) J. W. Ryan, *J. Amer. Chem. Soc.*, **84**, 4730 (1962).

(46% yield): bp 97° (0.05 mm); mp 78–80°; ir (CCl_4) 10.7 μ (strained SiOSi); nmr (CCl_4) τ 9.35 (s, 4, CH_2Si), 9.23 (s, 8, CH_2CMe_2), 8.78 and 8.70 (2 s, 24, C-CH_3); the C-CH_3 protons showed two singlets (12 protons in each) as a consequence of the two nonequivalent locations relative to the silethylene and siloxane adjacent ring elements. *Anal.* Calcd for $C_{18}H_{36}O_5Si_2$: C, 55.7; H, 9.28; Si, 14.47. Found: C, 55.9; H, 9.26; Si, 14.45.

2,2-Dimethoxy-5,5-dimethyl-1,2,5-oxadisilacyclopentane (7).—Compound **3** (98.5 g, 0.229 mol) containing NaOMe (0.05 g) underwent redistribution at a reaction temperature of 285–250° producing volatile products (88 g) which were distilled from the system. Careful refractionation afforded 21.7 g (49% yield) of pure **7**: bp 52° (15 mm); ir (CCl_4) 10.7 μ (strained SiOSi); nmr (CCl_4) τ 9.82 (s, 6, CH_3Si), 9.28 (m, 4, CH_2Si), 6.54 (s, 6, CH_2O). *Anal.* Calcd for $C_6H_{16}O_3Si_2$: C, 37.5; H, 8.34; Si, 29.24. Found: C, 37.6; H, 8.7; Si, 29.1.

An almost quantitative yield (55 g) of material believed to be the expected by-product $Me_2(MeO)SiCH_2CH_2Si(OMe)_3$ (**8**), was also obtained: bp 82° (7.5 mm). This material contains no strained siloxane moiety (as evidenced by the absence of absorbtion at 10.7 μ) and was identical (glc) with the hydrosilation adduct of $ViMe_2SiOMe$ and $HSi(OMe)_3$. When much larger amounts of NaOMe (*i.e.*, 0.8 g) were employed, redistribution occurred at somewhat lower temperatures (200–250°) and a major portion of the distillate was identified as $Me_2Si(OMe)_2$ by comparison with authentic material.

2,2,5,5-Tetra-*n*-butoxy-1,2,5-oxadisilacyclopentane (9).—1,2-Bis(trimethoxysilyl)ethane (54 g, 0.2 mol), 1-butanol (59 g, 0.8 mol), and isopropyl titanate (2 drops) were heated under a Nester–Faust spinning-band column. After collecting 25.5 g of methanol, water (3.6 g), additional 1-butanol (1.0 g), and KOH (0.25 g) were added to the reaction mixture. Heating was resumed and an additional 11.5 g of methanol was collected at 65°. A mixture of MeOH and *n*-BuOH (3.4 g) was collected over a range of 65–120°. The reaction mixture was then heated at 250–285°. The crude redistribution products (53.2 g) were collected at a head temperature of 175–185° (5 mm). Refractionation through the same band afforded 33.3 g (43% yield) of pure **9**: bp 119° (0.01 mm); ir (neat) 10.7 μ (strained SiOSi); nmr (neat) τ 6.27 (t, 8, CH_2O), 9.23 (s, 4, CH_2Si), 8.1–9.3 (m, 28, $CH_3CH_2CH_2CH_2O$). *Anal.* Calcd for $C_{18}H_{40}O_6Si_2$: C, 55.7; H, 10.3; Si, 14.45. Found: C, 55.7; H, 10.1; Si, 14.3.

1,2-Bis(tri-*n*-butoxysilyl)ethane (10.4 g) was also recovered from the fractionation: bp 150° (0.03 mm); ir (CCl_4) no line at 10.7 μ (*i.e.*, no strained SiOSi); nmr (neat) τ 6.31 (t, 12, CH_2O), 9.43 (s, 4, CH_2Si), 8.1–9.2 (m, 42, $CH_3CH_2CH_2CH_2O$). *Anal.* Calcd for $C_{26}H_{58}O_6Si_2$: C, 59.8; H, 11.1; Si, 10.8. Found: C, 59.8; H, 11.2; Si, 10.9.

2,2,5-Trimethoxy-5-methyl-1,2,5-oxadisilacyclopentane (11).—A suitable hydrosilation adduct was prepared by the gradual addition of $(MeHSiO)_4$ (360 g, 1.50 mol) to well-stirred, preheated (100°) $ViSi(OMe)_3$ (906 g, 6.1 mol) containing 12 drops of chloroplatinic acid solution; this caused the temperature to rise steadily to a maximum of 160°, whereupon the adduct was cooled to room temperature and stored in a polyethylene container. An aliquot of this adduct (108 g, 0.51 equiv of $SiCH_2CH_2Si$) was then heated with 0.1 g of BaO to a temperature of 380°, whereupon cracking commenced; a total of 80 g of volatile materials were distilled from the system. Glc analysis showed this material to contain approximately 36 g (34% yield) of compound **11** which was then isolated by fractional distillation: bp 61° (4.5 mm); ir (neat) 10.7 μ (strained SiOSi); nmr (CCl_4) τ 9.28 (m, 4, CH_2Si); 9.83 (s, 3, CH_3Si); 6.43, 6.48, 6.52 (3s, 9, CH_3O). *Anal.* Calcd for $C_6H_{16}O_4Si_2$: C, 34.6; H, 7.7; Si, 26.9. Found: C, 34.9; H, 7.6; Si, 27.0.

2-Methoxy-2,5,5-trimethyl-1,2,5-oxadisilacyclopentane (10).—The hydrosilation adduct for this redistribution reaction was prepared by gradually adding $(MeHSiO)_4$ (360 g, 1.50 mol) to refluxing $ViMe_2SiOMe$ (703 g, 6.06 mol) containing 4 drops of the chloroplatinic acid solution at such a rate as to avoid an excessive exotherm.

A 75-g (0.43 equiv of $SiCH_2CH_2Si$) aliquot of this adduct was then diluted with 75 ml of hydrogenated terphenyl (a commercially available heat transfer agent) and catalyzed with BuLi (1 ml of 1.6 *M* hexane solution.) Upon heating at a temperature of 300–355°, 69 g of volatile materials were distilled from the system and shown by glc analysis to contain 36 g (48% yield) of compound **10**, which was then isolated by fractional distillation: bp 30° (5.5 mm); ir (neat) 10.7 μ (strained SiOSi); nmr (CCl_4) τ 9.88 (2 poorly resolved singlets, 6, CH_3Si-CH_3), 9.81 (s, 3, CH_3SiOCH_3), 9.26 (m, 4, CH_2Si), 6.57 (s, 3, CH_3O). *Anal.* Calcd for $C_6H_{16}O_2Si_2$: C, 40.9; H, 9.1; Si, 31.6. Found: C, 40.7; H, 8.7; Si, 31.2.

2,2,5-Trichloro-5-methyl-1,2,5-oxadisilacyclopentane (13).—The hydrosilation precursor for this preparation was obtained by slowly adding $ViSiCl_3$ (333 g, 2.05 mol) to refluxing $(MeHSiO)_4$ (120 g, 0.5 mol) containing 12 drops of chloroplatinic acid solution as catalyst. Heating was continued until consumption of Si–H functionality was complete (as evidenced by disappearance of the characteristic infrared absorption at 4.5 μ). This adduct was then heated at 410–420° where cracking occurred, yielding 140 g of distillate before the contents of the reaction flask gelled. Refractionation afforded a cut boiling at 50–60° (4–5 mm) and believed to be compound **13**, which exhibited the strong infrared absorption at 10.7 μ, characteristic of the strained siloxane believed to be present. Subsequent analysis showed the material to be somewhat impure. *Anal.* Calcd for $C_3H_7Cl_3OSi_2$: C, 16.3; H, 3.16; Si, 25.3; Cl, 48.1. Found: C, 17.5; H, 3.33; Si, 24.6; Cl, 48.5.

Infrared examination showed the 10.7 band to decrease sharply within a few days, presumably owing to the near impossibility of maintaining this material acid free and the extreme sensitivity of these strained heterocyclics to acid-catalyzed polymerization. Because of the extreme reactivity of this material, no further characterization was attempted.

2-Chloro-2,5,5-trimethyl-1,2,5-oxadisilacyclopentane (12).—The hydrosilation adduct was obtained by slowly adding $(MeHSiO)_4$ (240 g, 1.00 mol) to refluxing $ViMe_2SiCl$ (490 g, 4.06 mol) containing 6 drops of chloroplatinic acid catalyst solution; as the exothermic reaction proceeded, the temperature gradually increased to a final value of 240°. Thermal redistribution of 151 g (0.84 equiv of $SiCH_2CH_2Si$) of this material at 360–380° for 6 hr afforded 123 g of distillate which boiled at approximately 120°, had the expected intense ir absorption at 10.7 μ, and is believed to have been compound **12**: nmr (CCl_4) τ 9.84 (s, 3, CH_3SiCH_3), 9.75 (s, 3, CH_3SiCH_3), 9.47 (s, 3, $ClSiCH_3$), 9.0 (m, 4, $SiCH_2CH_2$-Si). It was necessary to prevent contact of this material with atmospheric moisture since hydrolysis results in HCl and this highly strained system undergoes very facile acid catalyzed ring-opening reactions. If suitable precautions were taken, vpc analysis showed very little loss of product even after several days. *Anal.* Calcd for $C_5H_{13}OSi_2Cl$: C, 33.2; H, 7.2; Si, 31.1; Cl, 19.7. Found: C, 33.0; H, 7.5; Si, 31.5; Cl, 20.0.

Registry No.—**5**, 16881-69-9; **6**, 16930-89-5; **7**, 16881-66-6; **8**, 25383-60-2; **9**, 20325-53-5; **10**, 16881-67-7; **11**, 20238-72-6; **12**, 16881-68-8; **13**, 25383-65-7; 1,2-bis(tri-*n*-butoxysilyl)ethane, 18846-06-5.

Studies on the Bromination of *cis*- and *trans*-Piperylene

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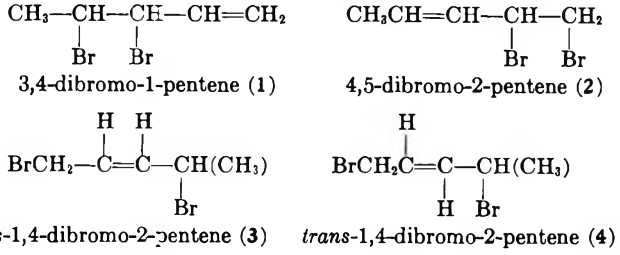
A study of the bromination of dilute (ionic conditions) and concentrated (radical conditions) solutions of *cis*- and *trans*-piperylene, and further investigations on the bromination of isoprene (concentrated solutions) are reported. The following products were formed in varying quantities depending on the conditions, in the bromination of *cis*- and *trans*-piperylene: 3,4-dibromo-1-pentene (*erythro*-**1a** and *threo*-**1b**), 4,5-dibromo-2-pentene (*cis*-**2a**, and *trans*-**2b**), *cis*-1,4-dibromo-2-pentene (**3**), and *trans*-1,4-dibromo-2-pentene (**4**). The principal differences in the bromination of the piperylenes in dilute and concentrated solutions are that, for the former conditions, bromine addition is completely stereoselective to give **1b** and **2a** from *cis*-piperylene, and **1a** and **2b** from *trans*-piperylene, whereas addition under the latter conditions is considerably less stereoselective. Detailed comparisons are made of the results of the brominations of butadiene, the piperylenes, and isoprene. Mechanistic interpretations of the results are suggested.

It has recently been shown that the addition of bromine to the 2-butenes is essentially stereospecific,[4] whereas bromination of certain styrene systems is only 83–88% stereospecific.[4,5] These data were interpreted as meaning that in the former case symmetrically bridged bromonium ion intermediates are involved which do not allow rotation around the 2,3 bond. The intermediates in the bromination of the styrenes are best described as unsymmetrically bridged bromonium ions, in which the carbonium ion is stabilized by interaction with the phenyl ring. Weak bonding between the bromine atom and the benzylic carbon atom permits rotation around the 1,2 bond and, hence, loss of stereospecificity. We felt that a determination of the stereoselectivity in the addition of bromine to *cis*- and *trans*-piperylene would provide insight into the nature of the intermediates in these reactions, and would allow a comparison to be made between a benzene ring and a vinyl group in terms of their relative abilities to interact with and disperse the charge from a bromonium ion. Loss of stereospecificity would be indicated by addition to the terminal double bond of a piperylene accompanied by isomerization of the 3,4 double bond, or by a nonstereospecific addition to the internal double bond, and would suggest extensive dispersal of charge across the allylic system.

Since a previous study on the bromination of butadiene had shown that addition could occur by either an ionic or radical mechanism depending upon the olefin concentration,[6,7] we needed to explore this problem with the piperylenes, and decided also to include isoprene since this aspect has not been investigated in a previous study of isoprene bromination.[8] Judging from results with butadiene, it was anticipated that bromination at 0.02 mol fraction of olefin would proceed entirely by an ionic mechanism and at 0.8 mol fraction by at least in part a radical mechanism.

Comparison of the results from the bromination of the piperylenes and isoprene might help elucidate factors affecting 1,2 and 1,4 addition. We also wished to determine whether the *cis* and *trans* double bonds would show a significant difference in reactivity as has been observed in the reaction of methanesulfenyl chloride with monoolefins.[9]

The structures of the dibromides which could theoretically be obtained from the bromination of piperylene are structures **1**–**4**. Isomer **1** can exist as either of two



diastereoisomers (**1a**, *erythro*, and **1b**, *threo*) and **2** can exist as either *cis*-**2a** or *trans*-**2b** isomers. The dibromides from isoprene have been described previously.[8]

Results and Discussion

The dibromides formed in the bromination of the piperylenes and isoprene under various conditions are summarized in Table I.

The results in Table II show that the stereoselectivity in the addition of bromine to *cis*- and *trans*-piperylene varies with the concentrations of the olefin.

Runs 1 and 6 (Table II) indicate that the bromination under ionic conditions is stereoselective within the limits of the analytical method. Addition to the terminal double bond occurs without isomerization of the internal *cis* or *trans* double bond and addition to the internal double bond (*trans* addition) yields one stereoisomer from the *cis* alkene and another from *trans*. This is in contrast to the bromination in carbon tetrachloride of the β-methylstyrenes where the addition was about 88–83% stereospecific,[4,5] but is in agreement with the results observed for *cis*- and *trans*-2-butene where at least 99.5% stereoselectivity was observed.[4] We interpret our results to mean that the intermediates in these diene additions are rather tightly bridged bromonium ions (see structures **5** and **7**) without appreciable delocalization of charge. We reject the possibility of the involvement of intermediates with charge delocalization (see structures **6** and **8**) on the basis of the following considerations. Delocalization of charge

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TABLE I

BROMINATION OF *cis*- AND *trans*-PIPERYLENE AND ISOPRENE, −15°

Run	Diene	Mol fraction of diene	Conditions[a]	Percentage of dibromides I	II	III	IV
1	*cis*-Piperylene	0.02		13	31		56
2	*cis*-Piperylene	0.8		3.5	23	0.5	73
3	*cis*-Piperylene	0.8	Inhibitor	3	23		74
4	*cis*-Piperylene	0.5	C_6H_5Et (solvent)	3.5	22.5	1	73
5	*cis*-Piperylene	0.5	C_6H_5Et (solvent), light	4.5	26	1.5	68
6	*trans*-Piperylene	0.02		0.5	35		64.5
7	*trans*-Piperylene	0.8		1	25	1	73
8	*trans*-Piperylene	0.8	Inhibitor	Trace	27	0.5	71.5
9	*trans*-Piperylene	0.5	C_6H_5Et (solvent)	1	27	Trace	72
10	*trans*-Piperylene	0.5	C_6H_5Et (solvent), light	2	27.5	2.5	68
11	Isoprene	0.02		23	2	2	73
12	Isoprene	0.8		10	6.5	9	74.5
13	Isoprene	0.5	C_6H_5Me (solvent)	13	6.5	6.5	74
14	Isoprene	0.5	C_6H_5Me (solvent), light	10	7	10	73

[a] The normal conditions are reported in the Experimental Section. Deviations are noted here. [b] I = 1 from piperylene and 3,4-dibromo-3-methyl-1-butene from isoprene, II = 2 from piperylene and 3,4-dibromo-2-methyl-1-butene from isoprene, III = *cis*-1,4-dibromides, IV = *trans*-1,4-dibromides.

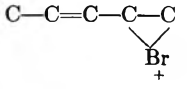
TABLE II

STEREOSELECTIVITY IN THE BROMINATION OF *cis*- AND *trans*-PIPERYLENE

Run[a]	Diene	Mol fraction of diene	Conditions[b]	Stereoisomers, % 1a	1b	2a	2b
1	*cis*-Piperylene	0.02			100	100	
2	*cis*-Piperylene	0.8		15	85	73	27
3	*cis*-Piperylene	0.8	Inhibitor	8	92	90	10
5	*cis*-Piperylene	0.5	C_6H_5Et (solvent), light	36	63	41	59
6	*trans*-Piperylene	0.02		100			100
7	*trans*-Piperylene	0.8		55	45	2	98
10	*trans*-Piperylene	0.5	C_6H_5Et (solvent), light	50	50	2	98

[a] The numbers of the runs in this table are identical with those in Table I. [b] See footnote *b* in Table I.

would result in a weakening of the carbon–bromine bond (see structure 8), rotation around the 3,4 bond would be expected (by analogy to the styrene systems[5]), and loss of stereospecificity would result. In the addition of bromine to the terminal double bond of either piperylene, if intermediates with delocalization of charge are involved (see structure 6), the π bonding between carbon atoms 3 and 4 would be reduced, and isomerization could occur. Isomerization would be particularly favored when the internal double bond has the *cis* con-



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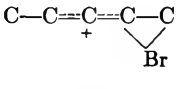

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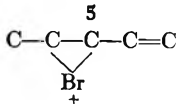

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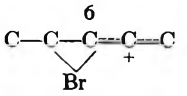

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figuration. In a previous study we showed that there is little, if any, delocalization of charge in the intermediates involved in the bromination of butadiene in methanol. The results reported in the present study support this earlier investigation.[10]

Runs 2 and 7 (Table II) indicate that the addition of bromine to *cis*- and *trans*-piperylene at high mole fraction is considerably less stereoselective than under ionic conditions. Evidence is presented in the Experimental Section to show that this effect is not due to rearrangement of the diene or of the dibromide products. The evidence for a radical mechanism for *cis*- and *trans*-piperylene under these conditions is not so clear as it was with butadiene. In the case of butadiene a radical mechanism was demonstrated by competitive bromination of ethylbenzene. However, with *cis*- and *trans*-piperylene no bromination of ethylbenzene, *cis*-1,2-dichloroethylene, or trichloroethylene occurred when the mole fraction of the radical scavenger and the dienes was 0.5.[11] The failure of these scavengers to compete for bromine under these conditions may be due to the greater reactivity of the piperylenes as compared with butadiene toward bromine atoms, the lower reactivity of the radicals formed in these reactions, or to a smaller radical component. On the basis of the very similar molecular structures of butadiene and the piperylenes, we feel that the latter are probably reacting in part by a radical mechanism at high mole fraction, but that a sufficiently sensitive method for detecting it has not been developed. In support of this assumption, we found that addition of the radical inhibitor, 2,6-di-*t*-butyl-4-methylphenol, to reaction at high concentration of diene resulted in considerable restoration of stereoselectivity (run 3, Table II).

If bromine does add to the piperylenes by a radical mechanism at high mole fraction, and considering the loss of stereospecificity as shown in Table II, the conclusion can be made that the intermediate radical resulting from attack by bromine atom at the terminal double bond must be a highly delocalized radical with sufficient weakening of the internal double bond to per-

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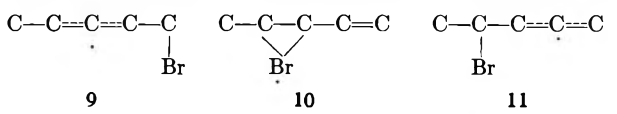
(11) Also, bromination of isoprene at high mole fraction in the presence of toluene or *n*-propylbenzene did not lead to benzyl bromide or α-bromopropylbenzene. However, α-bromoethylbenzene and benzyl bromide were formed during the bromination of the piperylenes in ethylbenzene and isoprene in toluene, respectively, at high mole fraction and under sun lamp irradiation.

mit rotation. (See structure **9**.) Also, if attack occurs at the internal double bond, a 3-membered, symmetrically bridged radical intermediate (see structure **10**) can hardly be involved, since loss of stereospecificity must occur by rotation around the 3,4 bond. The intermediate probably resembles structure **11**, with perhaps, a weak bond between the bromine atom and the neighboring allylic radical. Formation of **1** with much less



9 **10** **11**

stereoselectivity from *trans*-piperylene than from *cis*-piperylene may be due to the fact that the attack on the internal double bond of the *trans* isomer occurs mainly *via* a radical pathway, whereas the *cis* isomer has a significant ionic component to its addition.

The greater reactivity of the internal double bond toward ionic addition in *cis*-piperylene compared with *trans*-piperylene seems to be supported by the data in Table I. Runs 1 and 6 (Table I) suggest that the larger amount of internal addition obtained in *cis*-piperylene (13% *vs.* 0.5% for *trans*) is a true reflection of the reactivity of the *cis vs.* the *trans* double bond, since the bromonium ion obtained for each of these would be expected to afford nearly equal opportunity for 1,2 *vs.* 1,4 attack. This relative reactivity of 26:1 is similar to that observed by Thaler in the addition of methanesulfenyl chloride to alkenes, where *cis*-2-butene was found to be 18 times as reactive as *trans*-2-butene.[9]

The results in Table I show that chainging the mole fraction of diene from 0.02 to 0.8 affects significantly the proportions of dibromides formed. With butadiene the percentage of 1,4 addition was observed to change from 40% at 0.02 mol fraction to 80% at 0.4 mol fraction.[6] The piperylenes and isoprene also show similar changes although the percentage of 1,4-addition product is much larger at 0.02 mol fraction for the piperylenes and isoprene than for butadiene.

The data in Table I show that 1,2 addition in isoprene occurs primarily (11:1) at the methyl substituted double bond, but in the piperylenes at the unsubstituted double bond (*cis*, 2.5:1, and *trans*, 70:1). These data may not reflect the ratios of initial bromonium ion formation, since the source of 1,4-addition product is unknown. However, it is of interest to note that the sulfenyl halides, which give no 1,4 addition, yield similar 1,2-addition products with these dienes. Methanesulfenyl chloride adds to piperylene 86% at the unsubstituted bond and to isoprene 57% at the methyl substituted bond.[12]

Of the four dienes which we have studied, only isoprene yields a detectable quantity of *cis*-1,4-dibromide under ionic conditions. Apparently the ratio of *cis*- to *trans*-1,4-addition products formed under ionic conditions does not reflect the ratio of conformers (cisoid and transoid), since butadiene which has been shown to consist of 4% cisoid conformer gives no *cis*-1,4-dibromide.[13] It has been suggested[14] that the conformer population for *trans*-piperylene should be similar to butadiene, and again in this case no *cis*-1,4-dibromide was formed. However the appearance of *cis*-1,4-dibromide for butadiene and the piperylenes (and an increase in its amount for isoprene) seems to be characteristic of the free-radical reaction at high mole fraction. The ratio of *cis*-1,4-dibromide to *trans*-1,4-dibromide formed in the bromination of these dienes under radical conditions seems to reflect the ratio of cisoid to transoid conformers present in the diene. This particularly is true for butadiene, isoprene, and *trans*-piperylene. It is more difficult to explain how the *cis*-1,4-dibromide formed in the bromination of *cis*-piperylene can result from the cisoid conformer since this conformer probably does not exist. It is conceivable that a 1,4-bridged bromine radical may be involved in the *cis*-1,4-dibromide formation, since such a ring should open to give the *cis* isomer. However, we have no direct evidence that such an intermediate is formed.

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Experimental Section

Materials.—All solvents and reagents were obtained commercially in high purity unless otherwise indicated. Isoprene was Phillips Petroleum polymerization grade. The *cis*- and *trans*-piperylenes were shown by vpc to contain less than 1% of the other isomer.[15] The dienes were distilled immediately prior to use. Infrared spectra were obtained in carbon disulfide; nmr spectra are in carbon tetrachloride.

Bromination.—In the general procedure neat bromine was added dropwise (drop size, *ca.* 3 μl) at a rate of about 2 drops/min to well-stirred carbon tetrachloride solutions of the dienes. Reactions were done in the dark, under an atmosphere of dry nitrogen, at a temperature of −15°. Reaction volumes were about 0.8 ml for concentrated runs and 30 ml for dilute solution runs, although some brominations were done on a considerably larger scale. Reactions were carried to about 20% of completion. A more gradual and constant method of bromine addition was also employed, in which the bromine was run in from a small capillary beneath the surface of the solution (rate of addition, 0.07–0.2 ml/sec). Results obtained did not differ in a significant way from those obtained by dropwise addition. In reactions in which 2,6-di-*t*-butyl-4-methylphenol was used, it was present at a concentration of about 0.1 mol fraction. Two 100-W sun lamps placed 4 in. from the reaction mixture provided irradiation in illuminated runs. Under all conditions studied, reactions were very rapid and no bromine color was observed to develop in the solutions.

Yields of piperylene dibromides amounting to 85% at 0.02 mol fraction and 75% at 0.8 mol fraction were obtained. In large scale bromination the high boiling residue remaining after removal of the dibromides was about 10% of the calculated dibromide weight.

It was found by vpc that unreacted piperylenes had undergone no detectable rearrangement during the course of bromination.[15] An experiment was also performed to show that the piperylene dibromides did not undergo rearrangement during the bromination reaction. *cis*-Piperylene was brominated at 0.02 mol fraction; the dibromide ratios were determined by vpc. Most of the carbon tetrachloride was removed by suction and the resulting dibromide mixture was dissolved in cyclohexene so that the cyclohexene mole fraction was about 0.8. Bromination of this mixture was then done under the usual conditions. Analysis of the piperylene dibromide mixture after this treatment showed that the proportions of **1**, **2**, and **4** had not changed from the initial analysis and that **1** and **2** had substained no loss in stereoisomeric purity.[16]

(15) The piperylenes were analyzed on 6 ft × 0.25 in. columns packed with either silver nitrate–ethylene glycol or silver nitrate–benzyl cyanide on Chromosorb W. Less than 1% of either isomer in over 99% of the other can be readily detected.

(16) These conditions should approximate those of 0.8 mol fraction piperylene bromination. In an experiment in which a mixture of *cis*-piperylene and cyclohexene (both about 0.5 mol fraction) was brominated, the cyclohexene to piperylene dibromide ratio was near unity. The addition to piperylene under these conditions was less stereoselective (40%, **1a**, and 35%, **2b**) than when piperylene was brominated at 0.8 mol fraction in carbon tetrachloride.

Procedure for Analysis of Products.—The vpc analyses of the products were accomplished with an Aerograph 90 P-3 chromatograph and an F & M 700 chromatograph. Ratios of **1**, **2**, **3**, and **4** were determined under the following conditions, designated column A: flow rate (He), 300 ml/min; column dimensions, 5 ft × 0.25 in., stainless steel; temperature, 48°; composition, 2.5% SE-30 on 60–80 mesh DMCS Chromosorb W. The retention times of **1**, **2**, **3**, and **4** are, respectively 2.4, 3.4, 4.0, and 5.7 min. Conditions for separation of **1a** from **2b** and **2a** from **2b**, designated column B, are flow rate (He), 70 ml/min; column dimensions, 10 ft × 0.125 in., stainless steel; temperature, 38°; column composition, 3.5% SE-30 on 80–100 mesh DMCS Chromosorb W. Retention times for **1a**, **1b**, **2a**, and **2b** are, respectively, 17.5, 18.5, 26.0, and 27.6 min.

Dibromide mixtures were analyzed immediately after completion of reaction with no intermediate isolation steps. Detectable rearrangement did not occur under the conditions of analysis as shown by the fact that dibromide mixtures which were collected from the chromatograph and reinjected did not show a change in composition.

The percentages of the dibromides are based directly on the peak areas. Chromatography of know mixtures of **1**, **2**, and **4** gave area ratios which did not differ from the actual weight ratios by an amount greater than the uncertainty of the vpc analysis. The percentages of dibromide mixtures as obtained by column A were reproducible for reactions run under the same conditions to less than ± (percentage of dibromide × 0.05) except where a dibromide occurred in very small amounts. In analysis of stereoisomer mixtures with column B, the separation was not as complete. Because of the tailing of **2a**, small amounts of **2b** (<5%) could have escaped detection. For the same reason, and because **1** is formed to the extent of only 1% in low mole fraction brominations of *trans*-piperylene, small amounts of **1b** could have escaped detection. It is estimated that less than 2% of **1a** or **2a** could have been detected in the presence of the other isomer.

Identification of Products.—Chromatograms (column A) from low mole fraction brominations of *cis* -or *trans*-piperylene showed three peaks (1, 2, and 4) with an additional peak 3, occurring in small amounts in products from bromination at high mole fraction. Vpc (column B) showed that peaks 1 and 2 from low mole fraction runs consisted of single components but peaks 1 and 2 from high mole fraction runs were resolved into two peaks. Identification of these peaks were achieved in part distillation of a bromination product. Piperylene was brominated at *ca.* 0.1 mol fraction in dichloromethane and the product after removal of the solvent under vacuum was fractionated through a 20-cm Nester–Faust spinning-band column at a pressure of 0.5 mm and pot temperature, 50–70°. Fractions corresponding to vpc peaks 1, 2, and 3 were obtained with the following purities as shown by vpc: 1, >99%; 2, 93% (2% 1 and 5% 4); 4, 95% (5% 2).[17] Chromatograph analysis of these fractions on column B showed that 1 was 96% **1b** and 4% **1a**, and 2 was 82% **2b** and 18% **2a**. Unless otherwise stated nmr, ir, and other measurements were made with these fractions.

3,4-Dibromo-1-pentene (1).—The component corresponding to vpc peak 1 was assigned structure **1** on the following basis. In addition to alkene absorption bands at 3100 cm^{-1} and 1640 cm^{-1}, the ir spectrum showed strong absorption bands at 934 and 985 cm^{-1}, the latter two bands being typical of the proposed terminal vinyl structure.[18] The nmr spectrum[19] was distinctly different from that of the other three compounds under consideration, all three of which gave nmr spectra which were very similar in their gross features. In this compound absorptions could be assigned to three separate vinyl hydrogens, and two different methine hydrogens: nmr δ 1.76 (d, 3, CH_3), 4.31 (double quartet, 1, $BrCHCH_3$), 4.71 (dd, 1, $BrCHCH{=}CH_2$), 5.19 (d, 1, *cis*-HCH=CH), 5.28 (d, 1, *trans*-HCH=CH), 5.95 (octet, 1, $CH_2{=}CH$). The apparent coupling constant between the hydrogens of carbons 3 and 4 was found to be 4.0 Hz. On this basis **1b** may be reasonable assigned the *threo* structure, the expected structure resulting from *trans* addition to the *cis* double bond. The most stable conformer of the *threo* dibromide have the hydrogens *gauche* with an expected coupling constant of about 4 Hz, but the most stable *erythro* conformer has the hydrogens *anti* and consequently an expected coupling constant of 9–11 Hz.[5]

4,5-Dibromo-2-pentene (2).—The nmr of peak 2 was consistent with structure **2**: nmr δ 1.78 (d, 3, CH_3), 3.64 [1, d, BrC(H)H], 3.75 [1, d, BrC(H)H], 4.65 [double quartet, 1, $BrCH_2C(H)Br$], 5.3–6 (m, 2, CH=CH). The most significant evidence for assignment of structure **2** to vpc peak 2 is that the compounds corresponding to this peak have different structures depending upon whether *cis*- or *trans*-piperylene was brominated at low mole fraction. The ir spectrum of peak 2 collected from vpc of the product of bromination of *trans*-piperylene showed, in addition to absorption bands at 3040 and 1660 cm^{-1}, a strong absorption band at 958 cm^{-1} characteristic of the *trans* double bond. Peak 2 collected from vpc of the product resulting from bromination of *cis*-piperylene showed absorption bands in its ir at 3040 and 1660 cm^{-1} with its most prominent absorption band at 753 cm^{-1} rather than 958. This absorption band would be expected for the *cis*-CH=CH group.

trans-**1,4-Dibromo-2-pentene (4).**—The compound corresponding to vpc peak 4 showed an nmr spectrum consistent with this structure: nmr δ 1.78 (d, 3, CH_3), 3.92 (d, 2, CH_2Br), 4.62 [quintet, 1, $HC(Br)CH_3$], 5.76 (m, 2, CH=CH). The ir spectrum showed the characteristic *trans* absorption at 962 cm^{-1} as well as bands at 3010 and 1670 cm^{-1}.

cis-**1,4-Dibromo-2-pentene (3).**—**3**, prepared by independent synthesis, was shown to have a retention time identical with that of peak 3. 2-Pentyne-1,4-diol, $n^{22}D$ 1.4809 (lit.[20] $n^{17}D$ 1.4819), was prepared by the method of Gouge[20] and hydrogenated in a Parr apparatus using the Lindlar catalyst to *cis*-2-pentene-1,4-diol, $n^{21}D$ 1.4706 (lit.[20] $n^{18}D$ 1.4668 by Raney nickel reduction of the alkyne). Treatment of the diol with PBr_3 according to the method of Valette[21] yielded **3**, bp 40–43 (0.4 mm). Vapor phase chromatography showed that this product was contaminated with 10% **2** and 5% **4**. The ir spectrum was similar to that of **4** with absorption bands at 3040 and 1670 cm^{-1} and a weak absorption band at 958 cm^{-1}, possibly due to **2** and **4** contamination; the prominent feature was the strong *cis* absorption (CH=CH) band at 776 cm^{-1}, similar to the *cis*-**2a** absorption at 753 cm^{-1}. This absorption band is completely lacking in the spectrum of **4**. The gross features of the nmr spectrum were similar to those of **4** but splitting patterns for methine and methylene hydrogens were more complex: nmr δ 1.79 (d, 3, CH_3), 4.0 (m, 2, CH_2Br), 4.97 (double quartet, 1, CH_3CHBr), 5.4–6.0 (m, 2, CH=CH).

Equilibrium of Isomers.—Further proof that the dibromides are interrelated in the manner proposed is shown by the fact that, when isolated samples of each isomer were heated in sealed tubes for several days at 80°, identical mixtures were obtained in every case. This equilibrium mixture was shown by vpc to consist of 1% **1a**, 1% **1b**, 5% **2a**, 27% **2b**, 6% **3**, and 60% **4**.

Registry No.—*cis*-Piperylene, 1574-41-0; *trans*-piperylene, 2004-70-8; **1a**, 25296-34-8; **1b**, 25356-02-9; **2a**, 25356-03-0; **2b**, 25296-35-9; **3**, 25356-04-1; **4**, 25296-22-4.

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(17) Fraction 1 was obtained by brominating *cis*-piperylene; 2 was obtained from a mixture of piperylenes, mainly *trans*.

(18) For a discussion of the positions of absorption bands in the infrared, see L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1957.

(19) d = doublet; dd = double doublet; m = multiplet.

(20) M. Gouge, *Ann. Chim. (Paris)*, **6**, 648 (1951).

(21) A. Valette, *ibid.*, **3**, 644 (1948).

Metal Hydride Reductions of *endo*-Tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (*endo*-Dicyclopentadienone)[1]

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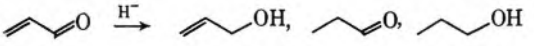
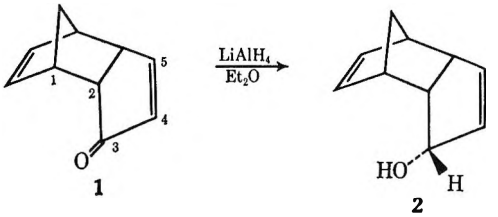
Reduction of the title compound **1** with aluminum hydride in ether and sodium borohydride in methanol gave exclusively the dienol **2** and the dihydro alcohol **4**, respectively. Reduction with lithium tri-*t*-butoxyaluminum hydride in ether gave predominantly the dihydro ketone **3** while lithium aluminum hydride in ether under various conditions gave mixtures of all three reduction products. Evidence consistent with the formation of a carbon–aluminum bond in the precursor to the dihydro alcohol **4** was obtained by lithium aluminum deuteride reduction. An internally consistent sequence of reactions is proposed to account for the various products.

The reduction of α,β-unsaturated ketones by various metal hydrides can produce an allylic alcohol, a saturated ketone, or a saturated alcohol depending on the substrate, the metal hydride, and the reaction conditions.[2,3] Brown and Hess[3w] have recently summarized

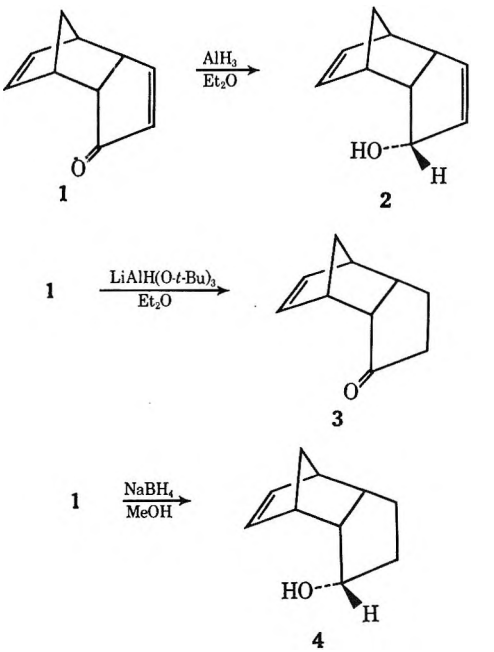


some of the more pertinent data in this area. During the course of our work on reactions in the 1,3-bishomocubyl system,[4] we carried out the lithium aluminum hydride ($LiAlH_4$) reduction of the cyclopentenone derivative **1**.[3g,5] Since appreciable quantities of by-products in addition to the dienol **2** were formed in some cases, we have examined this reduction in more detail and have examined the use of other metal hydrides.



Results

Reduction of the ketone **1** with aluminum hydride, lithium tri-*t*-butoxyaluminum hydride, and sodium borohydride gave either exclusively or mainly the allylic alcohol **2**, the dihydro ketone **3**, and the dihydro alcohol **4**, respectively. $LiAlH_4$ reduction of the ketone



1 gave mainly carbonyl reduced product **2** along with varying amounts of **3** and **4** depending on the reaction conditions. These results are summarized in Table I. The stereochemistry of these reductions was not studied in detail except for the case of the 0.017 *M* $LiAlH_4$ reduction to the dienol **2**. In this reaction the ratio of *syn*-hydroxyl product **2** to the epimeric *anti*-hydroxyl product **5** was 93:7. In the other reductions leading to the dienol **2** or the dihydro alcohol **4**, the epimeric purity was not determined. However, in each case the *syn*-hydroxyl products, **2** and **4**, probably were formed in greater than 90% epimeric purity by analogy with the above result and also since spectral data on the products obtained did not indicate any appreciable amounts of the *anti*-hydroxyl epimers.

(1) For a preliminary report of this work, see W. L. Dilling and R. A. Plepys, *Chem. Commun.*, 417 (1969).

(2) For reviews, see (a) W. G. Brown, *Org. React.*, **6**, 469 (1951); (b) V. M. Micovic and M. L. Mihailovic, "Lithium Aluminum Hydride in Organic Chemistry," Naukna Knjiga, Belgrade, Yugoslavia, 1955; (c) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 290, 930, 964; (d) W. Klyne, "The Chemistry of Steroids," Methuen and Co. Ltd., London, 1957, p 97; (e) N. G. Gaylord, *J. Chem. Educ.*, **34**, 367 (1957); (f) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 270; (g) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 135; (h) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 40.

(3) (a) F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3484 (1948); (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952); (c) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind. (London)*, 1482 (1954); (d) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955); (e) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957); (f) C. Djerassi and W. Rittel, *J. Amer. Chem. Soc.*, **79**, 3528 (1957); (g) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); (h) D. Kupfer, *ibid.*, **15**, 193 (1961); (i) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962); (j) J. A. Zderic and J. Iriarte, *J. Org. Chem.*, **27**, 1756 (1962); (k) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963); (l) M. E. Cain, *J. Chem. Soc.*, 3532 (1964); (m) R. C. Cookson, N. S. Isaacs, and M. Szelke, *Tetrahedron*, **20**, 717 (1964); (n) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964); (o) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 6514 (1965); (p) P. R. Story and S. R. Fahrenholtz, *ibid.*, **87**, 1623 (1965); (q) J. E. Baldwin, *J. Org. Chem.*, **31**, 2441 (1966); (r) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966); (s) P. L. Southwick, N. Latif, B. M. Fitzgerald, and N. M. Zaczek, *J. Org. Chem.*, **31**, 1 (1966); (t) L. A. Paquette and O. Cox, *J. Amer. Chem. Soc.*, **89**, 5633 (1967); (u) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968); (v) J. A. Waters and B. Witkop, *ibid.*, **90**, 758 (1968); (w) H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969); (x) F. G. Cowherd and J. L. von Rosenberg, *J. Amer. Chem. Soc.* **91**, 2157 (1969).

(4) (a) W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969); (b) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Amer. Chem. Soc.*, **91**, 3404 (1969).

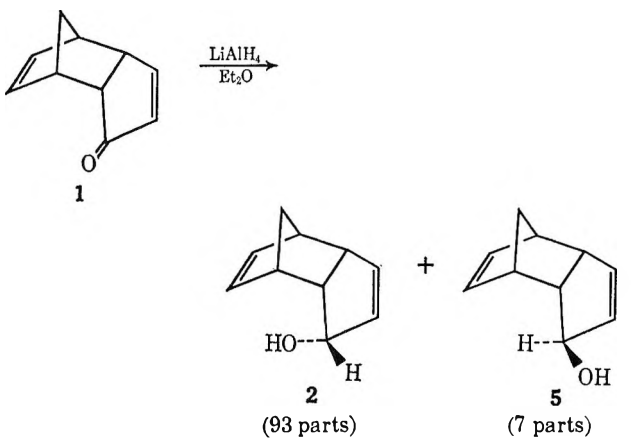
(5) (a) H. Hock and F. Depke, *Chem. Ber.*, **84**, 356 (1951); (b) K. Alder and F. H. Flock, *ibid.*, **87**, 1916 (1954); (c) M. Rosenblum, *J. Amer. Chem. Soc.*, **79**, 3179 (1957).

TABLE I

PRODUCT COMPOSITION FROM METAL HYDRIDE REDUCTIONS OF *endo*-TRICYCLO[5.2.1.0^{2,6}]DECA-4,8-DIEN-3-ONE (1)

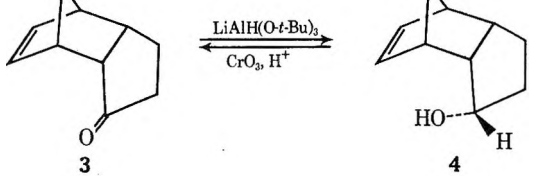
Reducing agent and conditions[a]	Overall yield, %	Product distribution, % 2[b]	3	4
AlH_3 ($3LiAlH_4 + AlCl_3$)[c] in Et_2O[d]	76	100	...[e]	...[e]
$LiAlH(O\text{-}t\text{-}Bu)_3$ ($LiAlH_4 + 3\ t\text{-}BuOH$)[f] in Et_2O[d]	70	1	83	16
$NaBH_4$ in MeOH[d]	72	...[g]	...[g]	100
$LiAlH_4$ (0.017 *M*) in Et_2O[h] (normal addition)[d]	89	97	...[i]	3
$LiAlH_4$ (0.087 *M*) in Et_2O[h] (normal addition)[d]	94	65	17	18
$LiAlH_4$ (0.079 *M*) in Et_2O[h] (inverse addition)[j]	96	74	26	...[i]

[a] More than 2 equiv of hydride/mol of ketone 1 was used in all experiments except that with 0.017 *M* $LiAlH_4$ where 1 equiv was used. Reactions carried out either at 0° or *ca.* 25° for 0.5–several hours. [b] Includes any epimeric dienol 5 which was not separated from 2 by the analytical procedure. [c] Prepared according to the procedure of Jorgenson.[3i,19] [d] Ketone 1 added to hydride solution. [e] Less than 2% by gc analysis. [f] Prepared according to the procedure of Brown and McFarlin.[20] [g] Probably less than 5% formed. [h] The initial ketone 1 concentration was 0.067 *M*. [i] Less than 1% by gc analysis. [j] Hydride solution added dropwise over 1 hr to ketone 1 solution.

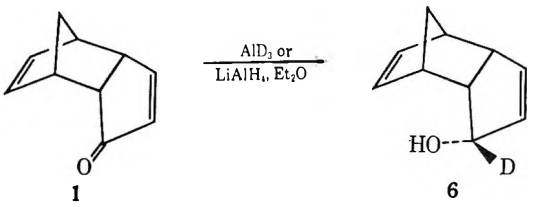


Attempted reduction of the dienone 1 with $LiAlH_4$ in hexane as described by Snyder[6] led to very slight reduction and gave mainly intractable material.[7]

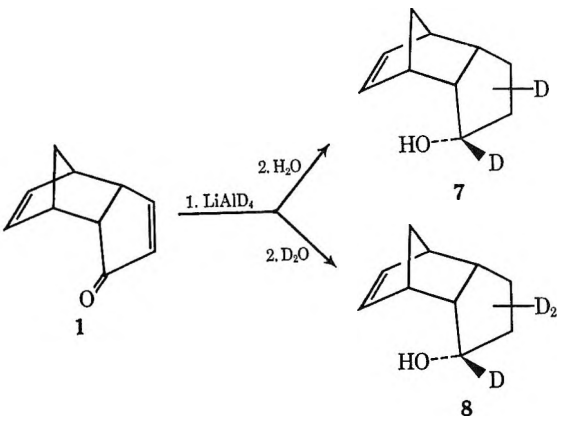
The structures of the ketone 3 and dihydro alcohol 4 were determined by infrared, ultraviolet, nmr, and high-resolution mass spectroscopy (see Experimental Section). In particular, the infrared and ultraviolet spectra of the ketone 3 exhibited bands characteristic of a cyclopentanone derivative.[8] Further structural evidence for 3 and 4 was provided by lithium tri-*t*-butoxyaluminum hydride reduction of the ketone 3 to 4 and reconversion of the alcohol 4 to 3 by Jones oxidation.[9] The reduction of 3 to 4 would be expected to proceed *via* hydride attack from the *exo* side of the carbonyl group and produce the *endo* alcohol 4 as the major product.[3p,w,10] The relative nmr chemical shifts of the proton on the hydroxyl-bearing carbon atom (–CHOH–) of the alcohols 2, 4, and 5[3g] are in agreement with this assignment. This proton in the *anti*-dienol 5 (−3.96 ppm) is shielded with respect to the corresponding proton of the *endo*-dienol 2 (−4.59 ppm), probably owing mainly to the anisotropy of the C-1–C-2 single bond. The chemical shift for this proton in the dihydro alcohol 4 is −4.29 ppm as expected when the double bond is saturated. The chemical shift of the corresponding proton of the epimer of 4 would be expected to be *ca.* −3.7 ppm.



Reduction of the dienone 1 with aluminum deuteride or lithium aluminum deuteride ($LiAlD_4$) gave the expected monodeuterated dienol 6. The dihydro alcohol



7 produced in the $LiAlD_4$ reaction under conditions which maximized its yield (entry 5, Table I) contained two deuterium atoms as shown by mass spectrometry. Hydrolysis with deuterium oxide gave a trideuteriodienol 8. In both cases nmr analysis indicated that one



of the deuterium atoms was on C-3 while the others were on one or more of the secondary carbon atoms, presumably C-4 and C-5. The O–D was washed out with ordinary water.

Discussion

A reaction sequence consistent with these results is shown in Scheme I. The ketone 1 apparently undergoes both 1,2 and 1,4 reduction by $LiAlH_4$ to give intermediates 9 and 10, respectively. In contrast to the $LiAlH_4$ reduction of cinnamaldehyde, where an alkoxyaluminum hydride from cinnamyl alcohol is an intermediate in the formation of the dihydro alcohol, hydro-

(6) E. I. Snyder, *J. Org. Chem.*, **32**, 3531 (1967).

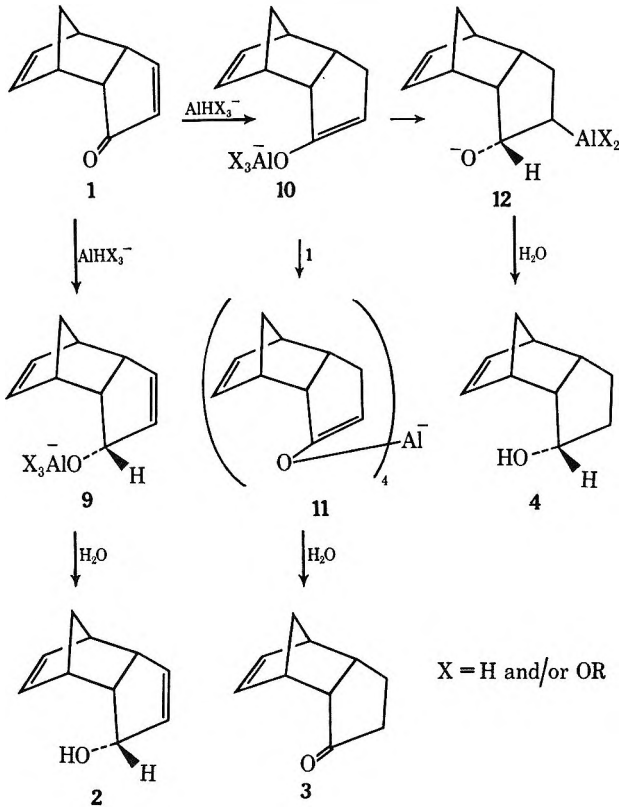
(7) Use of hexane as the solvent prevents reduction of the double bond in methyl cinnamate.[6]

(8) (a) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 202; (b) W. D. Kumler and A. C. Huitric, *J. Amer. Chem. Soc.*, **78**, 3369 (1956).

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

(10) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

SCHEME I



cinnamyl alcohol,[3a,i] the allylic alcohol **2** is inert to the reaction conditions.

The enolate **10** can undergo either further reaction with ketone **1** to give ultimately the tetraalkoxyaluminum ion **11**, or intramolecular aluminum hydride addition to the double bond to give the alkylaluminum species **12**. Alternatively, the latter reaction could be replaced by an intermolecular reaction of an aluminum hydride species with the keto tautomer of **10**. The intramolecular transformation of **10** to **12** is somewhat analogous to the $LiAlH_4$ reduction of an enol acetate to a saturated alcohol described by Dauben and Eastham.[11] The ordinary water and deuterium oxide hydrolysis of the salt produced by reaction with $LiAlD_4$ is consistent with the formation of a carbon aluminum bond in **12**.

The absence of any carbon–carbon double-bond reduction of **1** by aluminum hydride is readily explained as due to initial coordination of the electrophilic aluminum hydride to the carbonyl oxygen atom and hydride transfer to the carbonyl carbon atom.[3i] The other nucleophilic reducing agents in Table I apparently can transfer a hydride ion to the 5 position in a manner analogous to a Michael addition.

Tri-*t*-butoxyaluminum hydride attacks ketone **1** almost exclusively at C-5, possibly for steric reasons, and leads to a tetraalkoxy species **10** which on hydrolysis gives only ketone **3**. The small amount of dihydro alcohol **4** may arise from attack on the enolate **10** or its keto tautomer by another aluminum hydride ion. Since the ketone **3** reacts readily with lithium tri-*t*-butoxyaluminum hydride to give alcohol **4**, the ketone **3** must not be formed until after hydrolysis. Story and Fahrenholtz[3p] and Brown and Hess[3w] have reported analogous results with similar cyclopentenone derivatives.

Contrary to expectation,[2h] sodium borohydride also leads almost exclusively to initial 1,4 reduction which produces the boron analog of **10**. Owing to the protic solvent, this intermediate is converted to ketone **3** which in turn is reduced to the dihydro alcohol **4**. The results of Brown and Hess[3w] are completely in accord with this reaction.[12]

The amounts of 1,2 and 1,4 reduction of **1** with $LiAlH_4$ are apparently concentration dependent with higher hydride concentrations favoring 1,4 reduction. The relatively large amount of 1,4 reduction obtained with inverse addition, conditions which should lead to a very low hydride concentration, may be due to a very rapid reaction in the vicinity of the concentrated hydride solution as it contacts the ketone solution. This concentration dependence could be due to the 1,4 reduction's having a higher order dependence on hydride concentration than the 1,2 reduction has. Alternatively, aggregation of the $LiAlH_4$ in ether could account for the concentration dependence.[13] With a low ketone **1** concentration (normal addition), the conversion of intermediate **10** to **12** is competitive with further reaction of **10** with ketone **1**. At a high ratio of ketone **1** to $LiAlH_4$ (inverse addition), the reaction of **10** with excess ketone **1** wins out leading to relative large amounts of ketone **3**. The predominant formation of the *syn*-hydroxyl epimers, **2** and **4**, is expected on the basis of steric approach control.[10,16]

Experimental Section

General.—Melting points were determined in capillary tubes and are corrected. Infrared spectra were recorded using a Perkin-Elmer 337 double grating spectrometer by Mr. F. L. Beman and coworkers. The ultraviolet absorption spectra were obtained by Mr. Beman and coworkers with a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained by Mr. Beman and coworkers with a Varian A-60 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal TMS. Mass spectral analyses were performed by Dr. L. A. Shadoff, Mrs. W. L. Dilling, and Miss W. J. Plagens on either a magnetically scanning 90° sector spectrometer using an electron ionizing voltage of 75 eV and a vaporizer temperature of 200° (unless specified otherwise), or an Atlas CH4B (EFO4B ionization source) with direct probe sample introduction, or a high-resolution Consolidated Electrodynamics 21-110B spectrometer. Microanalyses were determined by Mr. L. E. Swim and coworkers. Gas chromatographic (gc) analyses were performed with a F & M 500 gas chromatograph using a 10 ft × 0.25 in. column packed with 20% Apiezon L on acid-washed Chromosorb W at 150° with a helium flow rate of 150 ml/min unless specified otherwise. Under these conditions, the retention times of the reduction products were 14.0 min, **2**;

(11) W. G. Dauben and J. E. Eastham, *J. Amer. Chem. Soc.*, **70**, 3484 (1948).

(12) Brown and Hess[3w] reported that reduction of *endo*-tricyclo[5.2.1.$0^{2,6}$]-dec-4-en-3-one with sodium borohydride in refluxing ethanol gave 100% *endo,syn*-tricyclo[5.2.1.$0^{2,6}$]decan-3-ol while Cowherd and von Rosenberg[3x] reported that reduction of the same ketone with sodium borohydride under unspecified conditions gave *endo,syn*- and *endo,anti*-tricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-ol in a 9:1 ratio, respectively.

(13) The degree of association [*n* of $(LiAlH_4)_n$] was 1.58 at 0.05 *M*, 2.27 at 0.5 *M*, 2.85 at 1.0 *M*, and 3.64 at 2.0 *M* as determined by boiling point elevation in diethyl ether.[14] Wiberg[15] reported that 0.08 *M* $LiAlH_4$ in ether is dimeric and that at 0.8 *M* it is trimeric.

(14) C. B. Roberts, Dow Chemical Co., private communication.

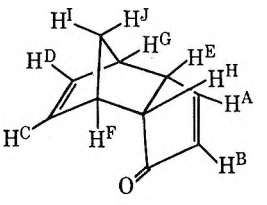
(15) E. Wiberg, *Angew. Chem.*, **65**, 16 (1953).

(16) Brown and Hess[3w] reported 100% *anti* attack by sodium borohydride on *endo*-tricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one. Rothberg[17] reported 99% *anti* attack on *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-3-one by $LiAlH_4$. Replacement of the *endo* hydrogen atoms at C-8 and C-9 by the C-8–C-9 double bond as in **1** and **3** should lead to slightly increased ease of *syn* attack by the hydride.

(17) I. Rothberg, unpublished results quoted by H. C. Brown and W. J. Hammor, *J. Amer. Chem. Soc.*, **89**, 1524 (1967).

17.0 min, **3**; 18.2 min, **4**. Compounds **3** and **4** were not completely resolved. Operation of the column at higher temperature caused partial decomposition of the dienol **2**. The *anti*-hydroxy epimer **5** was not separated from **2** under the gc conditions used. Product distributions were determined from gc peak areas (height times width at half-height) assuming equal thermal conductivities on a molar basis.

endo-**Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one** (**1**).—This ketone was prepared according to the chromic acid oxidation procedure of Alder and Flock[5b] as modified by Woodward and Katz.[3g] Material for the following experiments was purified by vacuum sublimation at 110° (0.5 mm) and recrystallization from hexane, mp 59–63°. A more highly purified sample for spectral data was obtained by recrystallization four more times from hexane (1% impurity by gc): mp 65.5–67.5° (lit. mp 58–59°,[18] 58–60°,[3n] 59.0–59.5°,[5c] 65.3–65.6°,[3g] 80°[5b]); $\nu_{max}^{CCl_4}$ 3075 (w) and 3055 (w) (=C—H), 2980 (s), 2945 (m) and 2880 (m) (C—H), 1715 (vs, C=O), 1585 (s, C=C) cm^{-1}; $\nu_{max}^{CS_2}$ 723 (s, *cis* H's) cm^{-1}; λ_{max}^{hexane} 218.5 mμ (ε 8890, π → π*), 314 (sh, 17.0), 327 (26.8), 341.5 (32.3, n → π*), 358 (25.5), 376 (9.6); λ_{max}^{MeOH} 226.5 mμ (ε 7420, π → π*), 321.5 (36.1, n → π*); nmr spectrum (CCl_4) a doublet of doublets centered at −7.25 (H^A, 1.0 H, J_{AB} = 5.7, J_{AE} = 2.6 cps), a multiplet at −6.0 to −5.6 (H^{B,C,D}, 2.9 H), an eight-line



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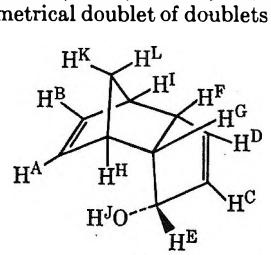
multiplet centered at −3.36 (H^E, $J_{EH} \sim 5.5$, J_{EG} = 4.1, J_{AE} = 2.6 cps) overlapping with a multiplet at −3.3 to −3.05 (H$^{F\text{ or }G}$) (2.0 H total), a multiplet at −3.05 to −2.8 (H$^{G\text{ or }F}$, 1.0 H), an unsymmetrical doublet of doublets centered at −2.68 (H^H 1.1 H, J_{EH} = 5.4, J_{FH} = 4.9 cps), and an unsymmetrical doublet of triplets centered at −1.77 (H$^{I\text{ or }J}$, J_{IJ} = 8.4, $J_{FI} \approx J_{GI}$ or $J_{FJ} \approx J_{GJ}$ = 1.6 cps) overlapping with another unsymmetrical doublet of triplets centered at −1.57 ppm (H$^{J\text{ or }I}$, J_{IJ} = 8.5, $J_{FJ} \approx J_{GJ}$ or $J_{FI} \approx J_{GI}$ = 1.4 cps) (2.0 H total); mass spectrum *m/e* 39 (relative intensity 23.1, $C_3H_3^+$), 40 (10.9, $C_3H_4^+$), 51 (14.9, $C_4H_3^+$), 65 (26.2, $C_5H_5^+$), 66 (81.5, $C_5H_6^+$), 77 (10.3, $C_6H_5^+$), 78 (14.0, $C_6H_6^+$), 91 (28.2, $C_7H_7^+$), 103 (17.1, M$^+$ − C_2H_3O or C_3H_7), 115 (31.3, M$^+$ − CH_3O), 117 (100.0, M$^+$ − CHO or C_2H_5), 118 (50.6, M$^+$ − CO or C_2H_4), 131 (19.8, M$^+$ − CH_3), 132 (11.4, M$^+$ − CH_2), 146 (27.5, M$^+$) (some relative intensities variable).

endo,syn-**Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol** (**2**).—Material prepared by the lithium aluminum hydride (0.063 *M* in ether) reduction of the dienone **1**, according to the procedure of Woodward and Katz,[3g] was purified by recrystallization four times from pentane and sublimation at 60° (0.15 mm): mp 82.5–85° (lit. mp 85.0–85.5°,[3n] 85.0–85.8°[3g]); $\nu_{max}^{CCl_4}$ 3620 (m, free O—H), 3500 (m, br, bonded O—H), 3060 (m, =C—H), 2975 (s) and 2945 (s), 2910 (m) and 2880 (m) (C—H), 1625 (w, cyclopentenyl C=C), 1585 (w, norbornenyl C=C) cm^{-1}; $\nu_{max}^{CS_2}$ 728 (s, *cis* H's) cm^{-1}; nmr spectrum (CCl_4) an unsymmetrical doublet of doublets centered at −6.11 (1.0 H, H$^{A\text{ or }B}$, J_{AB} = 5.6, $J_{AH\text{ or }BI}$ = 2.5 cps), an unsymmetrical doublet of doublets centered at −5.68



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(H$^{B\text{ or }A}$, J_{AB} = 5.6, $J_{BI\text{ or }AH}$ = 3.1 cps) overlapping with a singlet at −5.50 (H^C, H^D) (2.9 H total), a doublet of doublets (with further splitting evident) centered at −4.59 (1.0 H, H^E, J_{EG} = 8.5, J_{CE} = 1.1 cps), an unsymmetrical doublet of doublets centered at −3.23 (1.0 H, H^F, J_{FG} = 7.3, J_{FI} = 4.1 cps), a multiplet at −3.1 to −2.6 with a maximum at −2.87 (3.0 H, H^G, H^H, H^I), a singlet at −2.06 which disappeared on shaking the solution with D_2O (1.0 H, H^J), and two overlapping unsymmetrical doublets of triplets centered at −1.55 (H$^{K\text{ or }L}$, J_{KL} = 8.0, $J_{HK,IK\text{ or }HL,IL}$ = 1.6 cps) and −1.36 ppm (H$^{L\text{ or }K}$, J_{KL} = 8.0, $J_{HL,IL\text{ or }HK,IK}$ = 1.4 cps) (2.1 H total); mass spectrum (150°) *m/e* 39 (11.3, $C_3H_3^+$), 66 (100.0, $C_5H_6^+$), 82 (36.1 $C_5H_6O^+$), 91 (12.8, $C_7H_7^+$), 115 (16.0, M$^+$ − CH_5O), 117 (24.1, M$^+$ − CH_3O), 129 (16.5, M$^+$ − H_3O), 130 (51.2, M$^+$ − H_2O), 148 (4.3, M$^+$).

Aluminum Hydride Reduction of Dienone 1.—A slurry of aluminum hydride in ether was prepared according to the procedure of Jorgenson.[3i,19] To a stirred mixture of 0.38 g (10 mmol) of lithium aluminum hydride in 50 ml of dry ether there was added 0.4 g (3 mmol) of aluminum chloride in small portions. To this stirred slurry of aluminum hydride and lithium chloride, the ketone **1** (0.50 g, 3.4 mmol) was added dropwise as a solution in 10 ml of ether. After stirring for 0.5 hr at *ca.* 25°, the reaction mixture was hydrolyzed by the cautious addition of 5 ml of water, followed by 15 ml of 5 *N* hydrochloric acid. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent and sublimation of the residue at 100° (0.5 mm) afforded 0.38 g (76%) of *endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-*syn*-3-ol (**2**), mp 62–72°. One recrystallization from hexane gave 0.28 g of alcohol, mp and mmp 63–65°. The infrared and nmr spectra of this product were identical with those of an authentic sample. Analysis by glc also showed only one component. The estimated limit of gc detection for the dihydro ketone **3** and dihydro alcohol **4** was *ca.* 2%.

Aluminum Deuteride Reduction of Dienone 1.—A slurry of aluminum deuteride was prepared by the addition of 1.8 g (13.5 mmol) of aluminum chloride to a stirred, cold (−30°) mixture of 1.5 g (40 mmol) of lithium aluminum deuteride in 500 ml of dry ether. The stirred mixture was warmed to *ca.* 25° and 15.0 g (103 mmol) of ketone **1** in 90 ml of ether was added dropwise over a period of 0.5 hr. After stirring at *ca.* 25° for 18 hr, the hydride solution was decomposed by the dropwise addition of 10 ml of water, followed by 100 ml of dilute sulfuric acid. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation left a thick yellow oil which, after sublimation at 100° (0.5 mm), afforded 9.0 g (60%) of a white waxy solid. Recrystallization from hexane gave 3.8 g of crystalline solid, mp 56–58°. The infrared and nmr spectra of this sample were nearly identical with those of the deuterated dienol **6** described below. Gc analysis indicated less than 5% impurities.

Lithium Tri-*t*-butoxyaluminum Hydride Reduction of Dienone 1. Preparation of *endo*-Tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (3). A slurry of lithium tri-*t*-butoxyaluminum hydride[20] was prepared by the dropwise addition of 3.50 g (43.3 mmol) of *t*-butyl alcohol to a stirred mixture of 0.60 g (15.8 mmol) of lithium aluminum hydride in 125 ml of dry ether. To this mixture was added a solution of the dienone **1** (1.00 g, 6.85 mmol) in 3 ml of ether. After stirring at room temperature for 16 hr, the mixture was hydrolyzed by the dropwise addition of 5 ml of water, followed by 25 ml of 5 *N* hydrochloric acid. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave 0.70 g (70%) of a colorless oil, which by gc analysis had the composition shown in Table I.

Repetition of the above experiment with 1.90 g (29 mmol) of *t*-butyl alcohol, 0.30 g (8 mmol) of lithium aluminum hydride, and 0.50 g (3.4 mmol) of ketone **1** in 100 ml of ether, followed by the usual work-up and sublimation at 100° (0.5 mm), gave 0.20 g (40%) of the ketone **3**: mp 100–103°; $\nu_{max}^{CCl_4}$ 3070 (w, =C—H), 2970 (s), 2950 (s), and 2875 (m) (C—H), 1740 (s, C=O) cm^{-1}; $\nu_{max}^{CS_2}$ 730 (s, *cis* H's) cm^{-1}; $\lambda_{max}^{n\text{-hexane}}$ 273 mμ (sh, ε 15.8), 284 (sh, 21.0), 295.5 (26.4), 305.5 (27.4, n → π*), 317 (21.1), 329 (sh, 9.8); λ_{max}^{MeOH} ~290 mμ (sh, ε 29.6); nmr spectrum ($CDCl_3$) a multiplet at −6.4 to −5.9 with a maximum at −6.18 (1.9 H, =C—H), a multiplet at −3.3 to −2.55 with a maximum at −2.93 (4.0 H, ⩾C—H), and a multiplet at −2.55 to −1.1 with maxima at −2.05 and −1.47 ppm (6.1 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_{12}O$: nuclidic mass, 148.0888. Found: nuclidic mass, 148.0874.

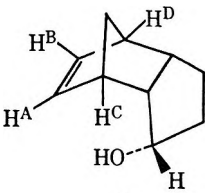
Sodium Borohydride Reduction of Dienone 1. Preparation of *endo,syn*-Tricyclo[5.2.1.0^{2,6}]dec-8-en-3-ol (4).—To a solution of 0.75 g (20 mmol) of sodium borohydride in 20 ml of methanol at

(18) R. W. Alder and M. C. Whiting, *J. Chem. Soc.*, 4595 (1963).

(19) See also, A. E. Finholt, A. C. Bond, and H. I. Schlesinger, *J. Amer. Chem. Soc.*, **69**, 1999 (1947).

(20) H. C. Brown and R. F. McFarlin, *ibid.*, **80**, 5372 (1958).

0°, there was added dropwise a solution of 2.5 g (17 mmol) of ketone **1** in 5 ml of methanol. The solution was stirred at 0° for 0.5 hr and at *ca.* 25° for 2 hr. The methanol solution was evaporated under vacuum to *ca.* one-half its original volume and hydrolyzed by stirring with 10 ml of 5 *N* hydrochloric acid for 15 min. The reaction mixture was diluted with 100 ml of water and extracted with two 50-ml portions of ether. The combined extracts were washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was sublimed at 100° (0.5 mm) to give 1.8 g (72%) of a waxy solid. The sublimate was resublimed and recrystallized from hexane to give 1.05 g of alcohol **4**: mp 134.5–137.5°; $\nu_{max}^{CCl_4}$ 3640 (w) and ~3350–3250 (w) (O—H), 3070 (w, =C—H), 2970 (s), 2940 (s), and 2875 (m) (C—H) cm^{-1}; $\nu_{max}^{CS_2}$ 737 (s, *cis* H's) cm^{-1}; nmr spectrum ($CDCl_3$) an unsymmetrical doublet of doublets centered at −6.30 ($H^{A \text{ or } B}$, J_{AB} = 5.5, $J_{AC \text{ or } BD}$ = 2.6 cps) overlapping with another



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unsymmetrical doublet of doublets at −6.12 ($H^{B \text{ or } A}$, J_{AB} = 5.8, $J_{BD \text{ or } AC}$ = 2.8 cps) (2.0 H total), an approximate quartet ($J \sim 7$ cps) centered at −4.3 superimposed on a multiplet at −4.5 to −4.0 (1.0 H, >CHOH–), a multiplet at −3.1 to −2.5 with a maximum at −2.81 (4.0 H, –C—**H**), and a multiplet at −2.1 to −1.1, with a maximum at −1.42, overlapping with a singlet at −1.93 ppm (~1.1 H, O—**H**) (7.1 H total, $-CH_2-$); mass spectrum *m/e* 132.0947 ($M^+ - H_2O$, calcd for $C_{10}H_{12}^+$ 132.0939), 150 (M^+).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39; nuclidic mass, 150.1047. Found: C, 79.78; H, 9.38; nuclidic mass, 150.1053.

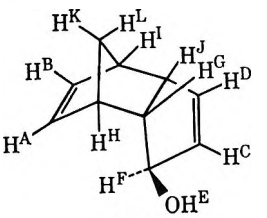
Repetition of this reaction under essentially the same conditions and analysis of the crude reaction mixture by gc (10 ft × 0.25 in. 20% XE-60 silicone nitrile on 60–80 mesh Gas-Chrom Z, 175°, He flow rate 75 ml/min) showed only a single product **4**, t_R 18.2 min.

Lithium Aluminum Hydride Reduction of Dienone 1. A. 0.087 *M* Hydride.—The solid ketone **1** (150 mg, 1.0 mmol) was added in one portion to a stirred slurry of 50 mg (1.3 mmol) of lithium aluminum hydride in 15 ml of dry ether (0.087 *M*). The reaction mixture was stirred at *ca.* 25° for 1 hr and hydrolyzed by the successive addition of 0.1 ml of water, 0.2 ml of 15% sodium hydroxide, and 0.3 ml of water. The hydrolyzed solution was stirred for 1 hr, the ether layer was decanted, and the granular precipitate was washed with fresh ether. The combined ether solutions were dried ($MgSO_4$) and concentrated to *ca.* 3 ml; 50 mg of *o*-dichlorobenzene was added as an internal standard for gc analysis. The results of this analysis are given in Table I.

B. 0.017 *M* Hydride.—To a stirred slurry of 10 mg (0.26 mmol) of lithium aluminum hydride in 15 ml of dry ether (0.017 *M*), 150 mg (1.0 mmol) of ketone **1** was added in one portion. The reaction mixture was stirred at *ca.* 25° for 1 hr and hydrolyzed by adding 0.05 ml of water, 0.1 ml of 15% sodium hydroxide, and 0.2 ml of water. Further work-up and analysis as in part A gave the results shown in Table I.

A similar reaction was carried out by adding a solution of the ketone **1** (0.50 g, 3.4 mmol, free of the precurson dienol **5**) in several milliliters of dry ether to a stirred slurry of lithium aluminum hydride (0.133 g, 3.5 mmol) in 200 ml of dry ether (0.017 *M*) at 22° and stirring for 1 hr. Work-up as described above with evaporation to dryness gave 0.42 g (83%) of a white solid whose nmr spectrum indicated a composition of 93% **2** and 7% **5**, based on integration of the –CHOH– peaks at −4.59 and −3.96 ppm, respectively. The infrared spectrum was also consistent with this composition and indicated the presence of a small amount of the dihydro ketone **3**, as evidenced by the appearance of medium–weak bands at *ca.* 1740 and 1168 cm^{-1}.

An authentic sample of the *anti*-hydroxyldienol **5**, bp 73–74° (0.8–0.5 mm), was prepared according to the selenium dioxide oxidation procedure of Woodward and Katz.[3g] Spectral data: $\nu_{max}^{CCl_4}$ 3620 (w, free O—H), 3330 (m, br, bonded O—H), 3060 (m, =C—H), 2970 (s), 2940 (s), 2900 (m) and 2875 (m) (C—H), 1625 (w, cyclopentenyl C=C), 1580 (w, norbornenyl C=C) cm^{-1}; $\nu_{max}^{CS_2}$ 730 (s, *cis* H's) cm^{-1}; nmr spectrum (CCl_4) a multiplet at −6.0 to −5.8 with a maximum at −5.85 (2.0 H,



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two of four olefinic protons) overlapping with a multiplet at −5.8 to −5.4 with a maximum at −5.61 (2.1 H, remaining two olefinic protons), a singlet at −4.38 (1.0 H, H^E), a multiplet at −4.05 to −3.9 with a maximum at −3.96 (1.0 H, H^F), a multiplet at −3.5 to −3.1 (1.0 H, $H^{G \text{ or } J}$), a multiplet at −3.1 to −2.9 centered at −3.00 (1.0 H, $H^{H \text{ or } I}$), a multiplet at −2.9 to −2.6 with a maximum at −2.75 (1.0 H, $H^{I \text{ or } H}$), an eight line multiplet centered at −2.49 (0.9 H, $H^{J \text{ or } G}$, J_{GJ} = 7.8, $J_{IJ \text{ or } GH}$ = 4.6, $J_{DJ \text{ or } FG}$ = 2.1 cps), and two overlapping unsymmetrical doublets of triplets centered at −1.66 ($H^{K \text{ or } L}$, J_{KL} = 8.0, $J_{HK,IK \text{ or } HL,IL}$ = 1.7 cps), and −1.34 ppm ($H^{L \text{ or } K}$, J_{KL} = 8.0, $J_{HL,IL \text{ or } HK,IK}$ = 1.4 cps), (2.0 H total); mass spectrum *m/e* 66 ($C_5H_6^+$), 82 ($C_5H_6O^+$), 130 ($M^+ - H_2O$), 148 (M^+).

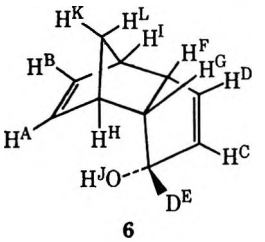
C. Inverse Addition, 0.079 *M* Hydride.—A solution of lithium aluminum hydride was prepared by stirring a slurry of 0.15 g (4.0 mmol) of lithium aluminum hydride and 50 ml of dry ether (0.079 *M*) for 2 hr at *ca.* 25°. This mixture was then filtered into a dry addition funnel, and the hydride solution was added dropwise to a stirred, cold (0–5°) solution of 0.50 g (3.4 mmol) of ketone **1** in 50 ml of dry ether (0.068 *M*). The addition was carried out over a period of 1 hr and the reaction mixture was then stirred at *ca.* 25° for 0.5 hr. Hydrolysis was accomplished by adding 1 ml of water, 1 ml of 15% sodium hydroxide, and 3 ml water. The granular solids were filtered and washed with fresh ether, and the combined ether solutions were dried ($MgSO_4$). Concentration and gc analysis showed the results given in Table I. Evaporation of all the ether left 0.48 g (96%) of a colorless oil.

Lithium Aluminum Deuteride Reduction of Dienone 1. A. Hydrolysis with Water.—A solution of the ketone **1** (0.3 g, 2 mmol) in 1 ml of dry ether was added to a stirred slurry of lithium aluminum deuteride (0.2 g, 4.8 mmol) in 20 ml of ether over a period of 0.5 min. After stirring at *ca.* 25° for 0.5 hr, 1 ml of water was added cautiously, followed by 5 ml of 5 *N* hydrochloric acid. The ether layer was separated, washed with water, and dried. The dihydro alcohol **7** was isolated by preparative gc (Apiezon L column described above, 225°, He flow rate 40 ml/min, t_R 9.9 min): mp 131–133°; nmr spectrum ($CDCl_3$) multiplets centered at −6.2 (1.5 H, =C—**H**), −4.3 (0.4 H, –CHOH–), −2.8 (4.0 H, >C—**H**), and −1.5 ppm (6.2 H, $-CH_2-$ and O**H**); mass spectrum *m/e* 152, M^+, $C_{10}H_{12}D_2O^+$.

B. Hydrolysis with Deuterium Oxide.—This reaction was carried out as described in part A except that 1 ml of deuterium oxide was substituted for the 1 ml of water used for the hydrolysis. The dihydro alcohol **8** was isolated by preparative gc as above: mp 132–133°; nmr spectrum multiplets at −6.2 (1.5 H, =C—H), −4.3 (0.2 H, –CHOH–), −2.8 (4.0 H, >C—**H**), and −1.5 ppm (5.2 H, $-CH_2-$ and O**H**); mass spectrum *m/e* 153, M^+, $C_{10}H_{11}D_3O^+$.

C. Preparation of *endo*-Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-*d*-*syn*-3-ol (6).—A solution of the dienone **1** (25.6 g, 0.175 mol) in 200 ml of dry ether was added over a period of 1 hr to a stirred suspension of lithium aluminum deuteride (3.1 g, 0.074 mol) in 1 l. of dry ether at 26–28°. After stirring for another 20 min, 3.1 ml of water were added with external cooling, followed by 3.1 ml of 15% aqueous sodium hydroxide and 9.3 ml of water. The mixture was filtered and the ether was removed from the filtrate under vacuum to give 26.5 g of white solid. Recrystallization from hexane gave 19.0 g (73%) of white crystalline dienol **6**, mp 75–85°. A 2.0-g portion was recrystallized twice from pentane and sublimed three times at 60° (0.15 mm) to give 1.08 g (39%) of the analytical sample of **6**: mp 86.5–87.5°; $\nu_{max}^{CCl_4}$ 3615 (m, free O—H), 3500 (m, br, bonded O—H), 3060 (m, =C—H), 2975 (s), 2940 (s), 2910 (m) and 2880 (m) (C—H), 2225 (w), 2185 (w), 2155 (w), and 2135 (w) (C—D), 1625 (w, cyclopentenyl C=C), 1585 (w, norbornenyl C=C) cm^{-1}; $\nu_{max}^{CS_2}$ 732 (s, *cis* H's)

cm^{-1}; nmr spectrum (CCl_4) an unsymmetrical doublet of doublets centered at −6.12 (1.1 H, $H^{A \text{ or } B}$, J_{AB} = 5.7, $J_{AH \text{ or } BI}$ = 2.2 cps), an unsymmetrical doublet of doublets centered at



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−5.68 ($H^{B \text{ or } A}$, J_{AB} = 5.7, $J_{BI \text{ or } AH}$ = 3.0 cps) overlapping with a singlet at −5.51 (H^{C}, H^{D}) (2.8 H total), an unsymmetrical doublet of doublets centered at −3.24 (1.0 H, H^{F}, J_{FG} = 7.9, J_{FI} = 4.0 cps), a multiplet at −3.1 to −2.5 with a maximum at −2.91 (3.1 H, H^{G}, H^{H}, H^{I}), a singlet at −2.15 (0.9 H, H^{J}), and two overlapping unsymmetrical doublets of triplets centered at −1.55 ($H^{K \text{ or } L}$, J_{KL} = 8.0, $J_{HK,IK \text{ or } HL,IL}$ = 1.7 cps) and −1.36 ppm ($H^{L \text{ or } K}$, J_{KL} = 8.1, $J_{HL,IL \text{ or } HK,IK}$ = 1.4 cps) (2.1 H total), no absorption detected in the −5.0 to −4.0 ppm region for H^{E}; mass spectrum (200°) *m/e* 66 (100.0, base peak, $C_5H_6^+$), 83 (56.1, $C_5H_6DO^+$), 91 (0.72, $C_7H_7^+$), 92 (0.68, $C_7H_6D^+$), 117 (1.6, $M^+ - CH_2DO$), 130 (1.3, $M^+ - HDO$), 131 (2.5, $M^+ - H_2O$), 149 (very weak, M^+) 150 (0.22, $M^+ + H$).

Anal. Calcd for $C_{10}H_{11}DO$: C, 80.50; H (D), 8.78. Found: C, 80.5; H (D), 8.31.

Stability of Dienol 2 to Lithium Aluminum Hydride.—The dienol 2 (50 mg) was added to a slurry of lithium aluminum hydride (100 mg) in 5 ml of dry ether and allowed to stand at *ca.* 25° for 18 hr. After hydrolysis with water and dilute hydrochloric acid, separation of the aqueous layer, washing with water, and concentration of the ether solution, gc analysis showed only starting material.

Chromic Acid Oxidation of Dihydro Alcohol 4.—To a cold (10–20°), stirred solution of 0.5 g (3.4 mmol) of alcohol 4 in 10 ml of redistilled acetone the Jones reagent[9] (2.7 *M* CrO_3 in H_2SO_4–H_2O) was added dropwise until an orange-brown coloration persisted. The acetone solution was then decanted from the chromium salts which were triturated with fresh acetone. The combined acetone solutions were concentrated under vacuum and the residue was taken up in 50 ml of ether. The organic layer was washed with two 20-ml portions of water and dried ($MgSO_4$). Evaporation of the ether and sublimation of the residue afforded 0.3 g (60%) of a waxy, white solid, mp 89–93°. Gc analysis of this material showed one compound with a retention time corresponding to that of the dihydro ketone 3. The infrared and nmr spectra of this material were identical with those of the authentic material.

Lithium Tri-*t*-butoxyaluminum Hydride Reduction of Dihydro Ketone 3.—A slurry of lithium tri-*t*-butoxyaluminum hydride was prepared by adding 2.3 g (31 mmol) of *t*-butyl alcohol to a solution of 0.38 g (10 mmol) of lithium aluminum hydride in 70 ml of dry ether. This mixture was stirred for 0.5 hr and 0.55 g (3.8 mmol) of ketone 3 in 5 ml of ether was added. The reaction mixture was stirred at *ca.* 25° for 5 hr and hydrolyzed by the addition of 10 ml of water, followed by 20 ml of 5 *N* hydrochloric acid. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent and sublimation of the residue at 100° (0.5 mm) afforded 0.4 g (73%) of a white solid, mp 125–134°, mmp 128–134°, whose infrared spectrum was identical with that of the dihydro alcohol 4 described above. Analysis by gc showed only one product having a retention time identical with that of 4.

Registry No.—1, 5530-96-1; 2, 24708-29-0; 3, 22981-84-6; 4, 22981-83-5; 5, 24529-79-1; 6, 25296-31-5.

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Reaction of Cupric Alkoxide and Carbon Monoxide

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The reaction of cupric alkoxide with carbon monoxide was investigated. Cupric dimethoxide [$Cu(OCH_3)_2$], cupric dialkoxide of allyl alcohol [$Cu(OC_3H_5)_2$], cupric chloride methoxide [$Cu(OCH_3)Cl$], and cupric acetylacetonate methoxide [$Cu(acac)(OCH_3)$] were easily carbonylated to produce dialkyl carbonates. Carbonylation of cupric alkoxide in the presence of a secondary amine gave the corresponding carbamate. In the reaction, copper(II) was reduced to copper(I) and the extent of reduction was in good agreement with the yields of carbonylated products. The suggested reaction path involves the intermediate formation of carbomethoxycupric species by the insertion of carbon monoxide into the copper–oxygen bond of cupric alkoxide.

In our previous study,[1] the carbonylation of a ternary mixture of cupric acetate, methanol, and piperidine produced the corresponding carbamate. This finding suggested an intermediate carbomethoxycupric species which was formulated as being a product of the insertion of carbon monoxide into the copper–oxygen bond of cupric methoxide. In the present study, the reaction of cupric alkoxide with carbon monoxide was examined.

Studies of the carbonylation have hitherto been focused upon the insertion of carbon monoxide between carbon and metal of the groups VI to VIII. The carbonyl insertion into metal–oxygen and metal–nitrogen bonds has been little studied.[2] The present study opens up a new field of carbonylation which involves copper(II) as the metal component and alkoxyl group as the ligand component.

Carbonate Formation from Cupric Methoxide and Carbon Monoxide.—Cupric dimethoxide was readily carbonylated to produce dimethyl carbonate in high yields (Table I). Pyridine was a preferable reaction solvent, in which the carbonylation proceeded even at room temperature. Reactions in other solvents required higher reaction temperatures. Other cupric methoxide compounds such as $Cu(OCH_3)Cl$ and $Cu(acac)(OCH_3)$ were also effectively carbonylated to produce dimethyl carbonate. In the carbonylation of cupric dialkoxide of allyl alcohol, the olefinic group was not involved in the reaction and the product was diallyl carbonate. This finding provides an interesting contrast to the carbonylation of allyl alcohol in the presence of cobalt and rhodium carbonyl in which the olefinic

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TABLE I
CARBONYLATION OF CUPRIC METHOXIDES

Cupric methoxide	Amount, mmol	CO, kg/cm²	Solvent	Amount, mmol	Temp, °C	Time, hr	Yield of $(CH_3O)_2CO$, %
$Cu(OCH_3)_2$	7.9	80	Py[a]	79	0	20	16
	8.6	80	Py	86	Room temp	48	62
	3.9	75	Py	39	35	5	78
	7.5	10	Py	150	35	20	78
	8.2	80	Py	82	70	20	84
	4.9	80	Py	49	110	23	28
	6.4	60	DMSO	64	70	20	44
	5.5	80	DMSO	110	110	39	82
	6.0	60	NEt_3	60	70	20	6
	5.8	80	NEt_3	116	110	39	48
	6.8	60	THF	68	70	20	20
	5.7	80	THF	114	110	39	78
$Cu(OCH_3)Cl$	7.9	90	THF	79	115	19	89
$Cu(acac)(OCH_3)$	7.9	80	Py	79	100	13	51
$Cu(OC_3H_5)_2$[b]	7.9	85	Py	79	70	29	44

[a] Py = pyridine. [b] Cupric dialkoxide of allyl alcohol.

TABLE II
CARBONYLATION OF CUPRIC DIMETHOXIDE IN THE PRESENCE OF PIPERIDINE[a]

$Cu(OCH_3)_2$, mmol	 , mmol	Pyridine (solvent), mmol	Temp, °C	Time, hr	Yield of  , %[b]
4.3	4.3	43	0	20	54
13.6	13.6	136	Room temp	43	46
6.4	6.4	64	60	20	96
4.6	4.6	46	110	23	72

[a] Carbonylation was carried out under a CO pressure of 80 kg/cm². [b] Based on $Cu(OCH_3)_2$.

group is also involved to form a lactone.[3] Cupric acetylacetonate was not carbonylated under the conditions of the present study. No reaction was observed in the attempted carbonylation of the alkoxides of cobalt(II) and iron(III) in pyridine at 120–150° under carbon monoxide pressure of 80 kg/cm². Thus, the carbonylation of metal alkoxide appears to be restricted to cupric alkoxide.

Carbamate Formation from Cupric Methoxide, Secondary Amine and Carbon Monoxide.—Interestingly enough, the reaction of cupric dimethoxide and carbon monoxide carried out in the presence of secondary amine gave the corresponding carbamate (eq 1).

$$Cu(OCH_3)_2 + R_2NH \xrightarrow{CO} R_2NCOCH_3 \quad (1)$$

The results of the carbonylation of cupric dimethoxide in the presence of piperidine are given in Table II. Similarly, cupric chloride methoxide was also carbonylated to produce carbamate.

Reduction of Cu^{II} to Cu^{I} in Carbonylation.—Examination of the change of valence of copper in carbonylation is essential for the reaction stoichiometry and is informative to the reaction mechanism. Cu^{II} and Cu^{I} were analyzed separately by iodometry and thiocyanate method (see Experimental Section). The extent of reduction of Cu^{II} to Cu^{I} in the carbonylations of $Cu(OCH_3)_2$ and $Cu(OCH_3)Cl$ with or without diethylamine is shown in Table III. The distillation residues of the mixtures of these reactions were all soluble in dilute hydrochloric acid. This observation indicates the absence of metallic copper in the reaction

TABLE III
CARBONYLATION OF CUPRIC METHOXIDES. ANALYSIS OF VALENCE OF COPPER

Cupric methoxide	Yield, % $(CH_3O)_2CO$	Yield, % $Et_2NCO_2CH_3$	Cu^{I},[a] %
Carbonylation in the Absence of Piperidine			
$Cu(OCH_3)_2$[b]	51		54
$Cu(OCH_3)Cl$[c]	89		83
Carbonylation in the Presence of Diethylamine			
$Cu(OCH_3)_2$[d]	7	54	58
$Cu(OCH_3)Cl$[e]	3	73	79

[a] The yield of Cu^{I} was calculated based on the initial amount of cupric methoxide. [b] Carbonylation in pyridine at 35° for 15 hr under 90 kg/cm² of CO. [c] The reaction conditions are given in Table I. Carbonylation in THF at 115° for 19 hr under 90 kg/cm² of CO. [d] A mixture of $Cu(OCH_3)_2$ (8.3 mmol), Et_2NH (8.3 mmol), and pyridine (83 mmol), was subjected to carbonylation with CO (90 kg/cm²) at 35° for 15 hr. [e] A mixture of $Cu(OCH_3)Cl$ (11.2 mmol), Et_2NH (11.2 mmol), and tetrahydrofuran (112 mmol) was subjected to carbonylation with CO (90 kg/cm²) at 115° for 19 hr.

system. In the absence of diethylamine, the per cent reduction of Cu^{II} to Cu^{I} was in good agreement with the yield of dimethyl carbonate. This finding substantiates the over-all stoichiometry in eq 2.

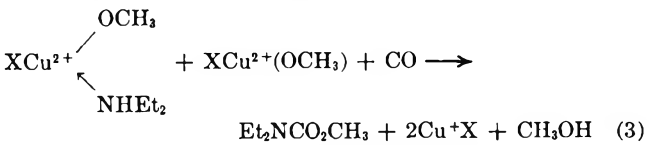
$$2XCu^{2+}(OCH_3) + CO \longrightarrow (CH_3O)_2CO + 2Cu^{+}X \quad (2)$$
$$(X = -OCH_3 \text{ and } Cl)$$

Cuprous methoxide is reasonably assumed to be the reduced species of cupric dimethoxide. The absence of metallic copper in the reaction mixture shows that cuprous methoxide is not active for carbonylation in the presence of pyridine at 35°.

The carbonylation in the presence of diethylamine produced methyl N,N-diethylcarbamate as the major

(3) J. Falbe, *Chem. Ber.*, **98**, 886 (1965).

product and dimethyl carbonate as the minor product. In this case, the per cent reduction of Cu^{II} approximately agreed with the combined yield of the two carbonylated products. The production of carbamate may be explained by the carbonylation of cupric methoxide together with the coordinated amine ligand (eq 3) or with the aminocopper compounds (eq 4). The



$$XCu^{2+}(OCH_3) + XCu^{2+}(OCH_3) + CO \longrightarrow Et_2NCO_2CH_3 + 2Cu^{+}X + CH_3OH \quad (3)$$

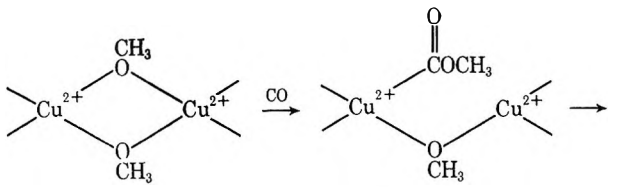
$$\underset{\text{II}}{XCu^{2+}(NEt_2)} + XCu^{2+}(OCH_3) + CO \longrightarrow Et_2NCO_2CH_3 + 2Cu^{+}X \quad (4)$$

diethylaminocopper compound (II) is formed by the substitution of methoxyl group by diethylamino group as follows. Methanol was actually formed in an

$$XCu^{2+}(OCH_3) + Et_2NH \longrightarrow XCu^{2+}(NEt_2) + CH_3OH \quad (5)$$

amount corresponding to the yield of carbamate. The stoichiometry of the carbonylation in the presence of dimethylamine is accounted for by the combination of two equations, eq 2 and 3 or eq 2 and 4.

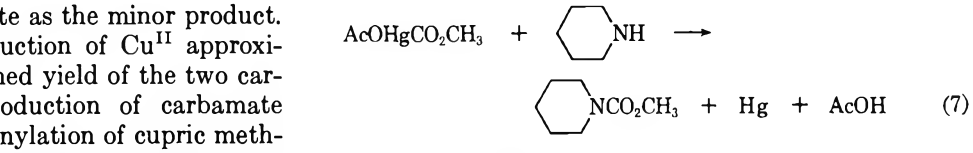
Reaction Mechanism.—The results are explained by the insertion of carbon monoxide into the copper–oxygen bond of cupric methoxide to generate carbomethoxycupric species which then undergoes coupling with an adjacent methoxyl group. The reaction will proceed in aggregate form. The aggregation has been



$$2\ \text{>}Cu^{+} + CH_3OCOCH_3 \quad (6)$$

demonstrated in the three species of cupric methoxide of the present study.[4-6] $Cu(OCH_3)_2$ and $Cu(OCH_3)Cl$ are known to be highly polymeric,[4] and $Cu(OCH_3)Cl$ is in dimeric form in pyridine.[5] $Cu(acac)(OCH_3)$ also has a dimeric structure with the methoxyl oxygen bridge and an outer bidentate ligand of acetylacetonate.[6] Therefore, the coupling between the carbomethoxyl and methoxyl ligands producing the cuprous species is quite possible and is illustrated by eq 6. The reaction pattern of eq 6 satisfies the stoichiometry of eq 2. The coupling of two carbomethoxyl groups to produce dimethyl oxalate was not observed.

The carbamate formation in the carbonylation of a mixture of cupric methoxide and secondary amine is also explained by assuming an unstable intermediate of carbomethoxycupric species. Coupling of dicarbomethoxyl group with amide group or with the coordinated amine ligand leads to carbamate. This reaction resembles the reactions of carbomethoxymercuric compounds with secondary amine to produce carbamate (eq 7).[7-9]



The $Cu(OCH_3)_2$–CO and $Cu(acac)(OCH_3)$–CO systems have been used as initiators of free-radical polymerization.[10] The active species are the reduced cuprous compounds of $Cu(OCH_3)$ and Cu(acac), which undergo homolytic fission to produce methoxyl and acetylacetonyl radicals, respectively.

Experimental Section

Reagents.—$Cu(OCH_3)_2$ and $Cu(OCH_3)Cl$ were prepared from $CuCl_2$ and $LiOCH_3$,[4] and $Cu(acac)OCH_3$ was synthesized from $Cu(acac)_2$ and methanol in the presence of KOH.[6] $Cu(OCH_2CH{=}CH_2)_2$ was prepared from $CH_2{=}CHCH_2OLi$ and $CuCl_2$ according to the procedure of the synthesis of $Cu(OCH_3)_2$. $Co(OCH_3)_2$ and $Fe(OCH_3)_3$ were prepared from the corresponding metallic chlorides and $LiOCH_3$.[11] Carbon monoxide was a commercial reagent. Pyridine was dried by refluxing over sodium hydroxide and calcium hydride, and fractionally distilled. Tetrahydrofuran was distilled twice from sodium wire. Dimethyl sulfoxide was distilled under reduced pressure and stored over molecular sieves. Triethylamine, diethylamine and piperidine were distilled over sodium hydroxide.

General Procedure of Carbonylation.—Cupric alkoxide, the amine if used, and the solvent were placed in a 50-ml stainless steel tube under nitrogen atmosphere, to which carbon monoxide gas was added under high pressure at room temperature. The tube was closed and was heated at a desired temperature. After reaction, the tube was cooled to −78° and carbon monoxide was released. The reaction mixture was distilled at room temperature up to 200° under 1 mm of Hg. The distillate was collected and analyzed by glpc. Carbonates and carbamates were identified by comparison of ir and nmr spectra and glpc retention times with those of authentic samples. The authentic sample of dimethyl carbonate was a commercial reagent, and that of diallyl carbonate was prepared from phosgen and allyl alcohol in the presence of triethylamine. Authentic carbamates were synthesized from methyl chloroformate and the corresponding amine.

The Analysis of Valence of Copper.—The residue of reduced pressure distillation of the reaction mixture was analyzed for copper. Cu^{II} was determined by the ordinary iodometry.[12] Thus, acetic acid and potassium iodide was added to the aqueous suspension of the sample, and the liberated iodine was titrated with a standard 0.1 *N* $Na_2S_2O_3$ solution to the starch end point. The total copper was determined by the thiocyanate method[13] for Cu^{I} after Cu^{II} had been reduced to Cu^{I} by Na_2SO_3. Thus, a part of the distillation residue (about 0.1 g) was dissolved in a mixture of 20 ml of 5% Na_2SO_3 aqueous solution and 40 ml of 0.1 *N* HCl aqueous solution. Then, 1% KSCN aqueous solution was added slowly with magnetic stirring until no more precipitate was formed. The precipitate of CuSCN thus obtained was collected by filtration, dissolved in aqueous 6 *N* HCl, and titrated under nitrogen atmosphere with a standard 0.1 *N* KIO_3 aqueous solution to the chloroform end point (red to yellow). These two analytical procedures were verified by reference experiments using a definite amount of cupric chloride.

Registry No.—Cupric dimethoxide, 1184-54-9; cupric dialkoxide of allyl aclohol, 25125-02-4; cupric chloride methoxide, 25248-62-8; cupric acetylacetonate methoxide, 15225-86-2; carbon monoxide, 630-08-0.

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Synthetic Reactions by Complex Catalysts. XVII. Copper-Catalyzed Reaction of Azide with Thiol

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Copper(I) salts effectively catalyze the reaction of azide (I) with thiol (II), producing sulfenylamide (III), primary amine (IV), and disulfide (V). The products depend primarily upon the nature of thiol. In the cases of alkanethiol and aralkanethiol, III, IV, and V are produced and III is the main product, while, in the case of aromatic thiol, IV and V are the products. Mechanistic studies have shown that III is first formed which further reacts with thiol to produce IV and V.

This paper describes a new reaction of azide with thiol by the aid of a copper compound catalyst. The exploration of this reaction was suggested by our previous findings of the specific catalyst activity of copper compounds for the insertion reactions of isocyanide[1] and carbene[2] into the N–H bond of amine, the O–H bond of alcohol, and the S–H bond of thiol. Isocyanide and carbene are characterized by the presence of lone pair electrons in carbon atom. The decomposition of azide with the evolution of nitrogen produces an unstable species of nitrene which also bears lone pair electrons in nitrogen and may be taken as an analog of carbene.

The present study has disclosed that copper(I) salts effectively catalyze the reaction of azide (I) with thiol (II). The products are sulfenylamide (III), primary amine (IV) and disulfide (V). Mechanistic studies

$$\underset{\text{I}}{RN_3} + \underset{\text{II}}{R'SH} \xrightarrow{\substack{Cu^I \\ \text{salt}}} \underset{\text{III}}{RNHSR'} + \underset{\text{IV}}{RNH_2} + \underset{\text{V}}{R'SSR'} \quad (1)$$

Ia, R = CH_2CO_2Bu-*t*
b, R = CO_2Bu-*t*

IIa, R′ = *t*-Bu
b, R′ = $PhCH_2$
c, R′ = Ph

IIIa, R = CH_2CO_2Bu-*t*; R′ = *t*-Bu
b, R = CO_2Bu-*t*; R′ = $PhCH_2$
c, R = CO_2Bu-*t*; R′ = *t*-Bu
d, R = CH_2CO_2Bu-*t*; R′ = Ph
e, R = CO_2Bu-*t*; R′ = Ph

IVa, R = CH_2CO_2Bu-*t*
b, R = CO_2Bu-*t*

Va, R′ = *t*-Bu
b, R′ = $PhCH_2$
c, R′ = Ph

have revealed that III is first formed which further reacts with thiol to produce IV and V. The primary product of III may be regarded as being a product of the insertion of nitrene (RN:) into the S–H bond of thiol. The results of the present study are interestingly compared with Takebayashi's study in which the decomposition of phenyl azide proceeded very rapidly in benzenethiol to produce aniline and diphenyl disulfide in high yields.[3] A mechanism of radical reaction of an intermediate nitrene was proposed for the phenyl azide–benzenethiol reaction. In addition, the thermal and photolytic decompositions of azide in hydrogen-containing solvents often produce primary amine (IV in eq 1), for which a radical mechanism of hydrogen abstraction of nitrene has been assumed.[3,4] In the present study, the copper-catalyzed reaction of azide with thiol, however, was suggested to be a nonradical process.

Results and Discussion

In the present study, the azide reagents are *t*-butyl azidoacetate (Ia) and azidoformate (Ib), and the thiol reagents are 2-methyl-2-propanethiol (IIa), α-toluenethiol (IIb), and benzenethiol (IIc). The reaction in the presence of cuprous chloride or oxide is illustrated in Table I. Without copper catalyst, two azides, Ia and Ib, did not react with IIa even at 80°. They were recovered unchanged almost quantitatively. In the presence of copper catalyst, however, the azide–thiol reactions proceeded smoothly at room temperature. The products depend primarily upon the nature of thiol. In the cases of alkanethiol and aralkanethiol, III, IV and V are produced and III is the main product. In the case of aromatic thiol, IV and V are the products.

TABLE I

REACTION OF AZIDE WITH THIOL[a]

$$\underset{\text{I}}{RN_3} \xrightarrow{\text{R'SH, II}} \underset{\text{III}}{RNHSR'} \xrightarrow{\text{R'SH}} \underset{\text{IV}}{RNH_2} + \underset{\text{V}}{R'SSR'}$$

N_3R, 10 mmol	R′SH, 45~69 mmol	Catalyst, 1 mmol	Product, % III[b]	IV[b]	V[b]
$N_3CH_2CO_2Bu$-*t* (Ia)	*t*-BuSH (IIa)	Cu_2O	64	30	31
$N_3CH_2CO_2Bu$-*t* (Ia)	*t*-BuSH (IIa)		0	0	0
N_3CO_2Bu-*t* (Ib)	$PhCH_2SH$ (IIb)	CuCl	60	30	35
N_3CO_2Bu-*t* (Ib)	*t*-BuSH (IIa)	CuCl	77	20	16
N_3CO_2Bu-*t* (Ib)	*t*-BuSH (IIa)		0	0	0
$N_3CH_2CO_2Bu$-*t* (Ia)	PhSH (IIc)	Cu_2O	0	99	102[c]
N_3CO_2Bu-*t* (Ib)	PhSH (IIc)	CuCl	0	99	107[c]

[a] Reactions were carried out at room temperature for 4~10 hr under nitrogen atmosphere. [b] Product yields are based upon the amount of azide. [c] The production of diphenyl disulfide over 100% may be ascribed to the oxidation of thiol by oxygen in the reaction system.

In the reaction of Ia and IIa, two experimental findings support the mechanism in which IIIa is first formed; IIIa further reacts with the second molecule of IIa to produce IVa and Va.

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(2) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and T. Shimizu, *Tetrahedron Lett.*, 1273 (1967); *J. Org. Chem.*, **33**, 544 (1968).

(3) M. Takebayashi and T. Shingaki, *Kogyo Kagaku Zasshi*, **64**, 469 (1961).

(4) (a) O. C. Dermer and M. T. Edmison, *J. Amer. Chem. Soc.*, **77**, 70 (1955); (b) J. F. Heacock and M. T. Edmison, *ibid.*, **82**, 3462 (1960); (c) J. E. Leffler and Y. Tsuno, *J. Org. Chem.*, **28**, 902 (1963); (d) W. Lwowski and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **87**, 1947 (1965); (e) L. Horner and G. Bauer, *Tetrahedron Lett.*, 3573 (1966); (f) W. Lwowski, *Agnew. Chem.*, **79**, 922 (1967).

TABLE II

REACTION[a] OF *t*-BuSNHCH$_2$CO$_2$Bu-*t* (IIIa) WITH *t*-BuSH (IIa)

t-BuSNHCH$_2$CO$_2$Bu-*t* + *t*-BuSH ⟶ NH$_2$CH$_2$CO$_2$Bu-*t* + *t*-BuSSBu-*t*

IIIa IIa IVa Va

Catalyst	Time, hr	IIIa, %	IVa, %	Va, %
No catalyst	22	100	0	0
CuCl (1 mmol)	6	40	60	61.5
CuCl (1 mmol) + *p*-BQ[b] (4 mol%)	6	38	62	61

[a] Reaction conditions: IIIa (1 mmol) and IIa (4.4 mmol) at 80° under nitrogen atmosphere. [b] *p*-BQ = *p*-benzoquinone.

$$N_3CH_2CO_2Bu\text{-}t + t\text{-BuSH} \xrightarrow{Cu^+ \text{ catalyst}} t\text{-BuSNHCH}_2CO_2Bu\text{-}t \quad (2)$$

Ia IIa IIIa

$$IIIa + IIa \xrightarrow{Cu^+ \text{ catalyst}} NH_2CH_2CO_2Bu\text{-}t + t\text{-BuSSBu-}t$$

IVa Va

In the first experiment, IIIa was subjected to the reaction with IIa. The IIa–IIIa reaction in the presence of cuprous chloride proceeded to produce IVa and Va (Table II). No other product was detected in the reaction mixture. It is important to note that the IIa–IIIa reaction also requires a copper catalyst. Without catalyst, IIIa was recovered quantitatively from the heat-treated mixture of IIa and IIIa. Furthermore, the copper-catalyzed reaction of IIIa with IIa was not affected by the addition of *p*-benzoquinone as a radical scavenger.

In the second series of experiments, the change of the amounts of three products during the course of reaction of Ia with excess IIa was examined (Figure 1). The amount of IIIa increased in the first 2 hr, then it remained unchanged in the subsequent 2 hr, and finally it began to decrease when Ia was consumed. The productions of IVa and Va continued to increase during the whole period of reaction. At a reaction time of 4 hr, Ia was consumed almost completely and the combined yield of IIIa and IVa became about 100% on the basis of Ia. After 4 hr, the decrease of IIIa corresponded to the increase of IVa. These findings support the mechanism of consecutive reactions; *i.e.*, IVa and Va are produced from the primary product of IIIa. In addition, the time-conversion curve of the Ia–IIa reaction with cuprous oxide catalyst was not affected by the addition of 4 mol % of *p*-benzoquinone.

The copper-catalyzed reaction of azide with aromatic thiol is also important especially from the mechanistic point of view. The Ia–IIc and Ib–IIc reactions took place to produce the corresponding primary amine (IV) and disulfide (V) (Table I). The corresponding benzenesulfenylamides (III) were not detected in the reaction mixtures. In addition, the reaction of azide with aromatic thiol occurred without any added catalyst. In the presence of copper compound, however, the reaction proceeds at much faster rates. The time-conversion curves of the Ia–IIc reaction under varying conditions are shown in Figure 2. The extent of reaction was monitored by the glpc analysis of IVa. Heating of a mixture of Ia and IIc at 80° under nitrogen atmosphere without any added catalyst caused the reaction between the two components to produce IVa

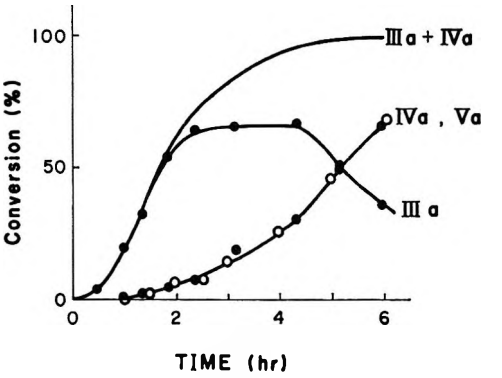


Figure 1.—Time conversion of the reaction of N$_3$CH$_2$COOBu-*t* (Ia) with *t*-BuSH (IIa) by Cu$_2$O catalyst at 80°: IIIa, *t*-BuSNHCH$_2$CO$_2$Bu-*t* (●); IVa, NH$_2$CH$_2$CO$_2$Bu-*t* (●); Va, *t*-BuSSBu-*t* (○).

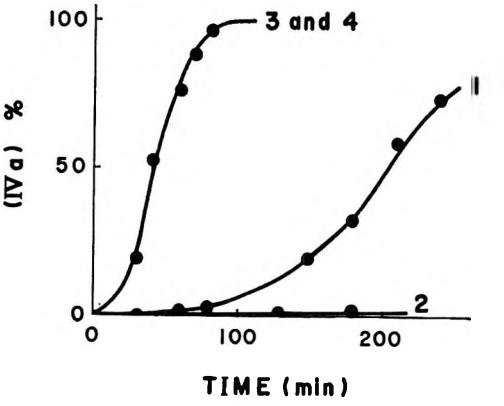


Figure 2.—Time conversion of the reactions of *t*-butyl azidoacetate (Ia) with benzenethiol (IIc) [reaction conditions: *t*-butyl azidoacetate (7 mmol), benzenethiol (39 mmol); at 80° under N$_2$]: 1, no catalyst; 2, *p*-benzoquinone (11.8 mol%); 3, Cu$_2$O (1 mmol); 4, Cu$_2$O (1 mmol)–*p*-benzoquinone (20.0 mol %).

and Vc (curve 1). This agrees with a report of Takebayashi.[3] Addition of *p*-benzoquinone suppressed the reaction (curve 2). As to the inhibition by *p*-benzoquinone, the reaction of *p*-benzoquinone with thiol is known.[5] Therefore, *p*-benzoquinone might have been consumed by the reaction with thiol. In the experiment of Figure 2, however, the amount of *p*-benzoquinone is as high as 11.8 mol % of thiol; the suppression of the reaction may be ascribed to the scavenging by the remaining *p*-benzoquinone. Reference experiments have shown that smaller amounts of *p*-benzoquinone, *e.g.*, 5 mol %, do not inhibit the azide–thiol reaction.

Addition of a small amount of cuprous oxide caused the Ia–IIc reaction at a much higher rate (curve 3). Here, it is important that the time-conversion curve of the copper-catalyzed reaction is not affected even by 20 mol % of *p*-benzoquinone. These findings may be taken to suggest a nonradical mechanism of the copper-catalyzed reaction.

For the Ia–IIc reaction, a mechanism involving the sulfenylamide as an intermediate product (IIId) is also suggested. Unlike the reaction with aliphatic thiol, the sulfenylamide (IIId) was not detected in the reaction mixtures both in noncatalyzed and copper-

(5) M. Schubert, *J. Amer. Chem. Soc.*, **69**, 712 (1947).

$$\underset{\text{Ia}}{N_3CH_2CO_2Bu\text{-}t} + \underset{\text{IIc}}{PhSH} \xrightarrow{Cu^+ \text{ catalyst}} \underset{\text{IIId}}{[t\text{-}BuO_2C\text{-}CH_2NHPh]} \xrightarrow{\text{IIc}} \underset{\text{IVa}}{NH_2CH_2CO_2Bu\text{-}t} + \underset{\text{Vc}}{PhSSPh} \quad (3)$$

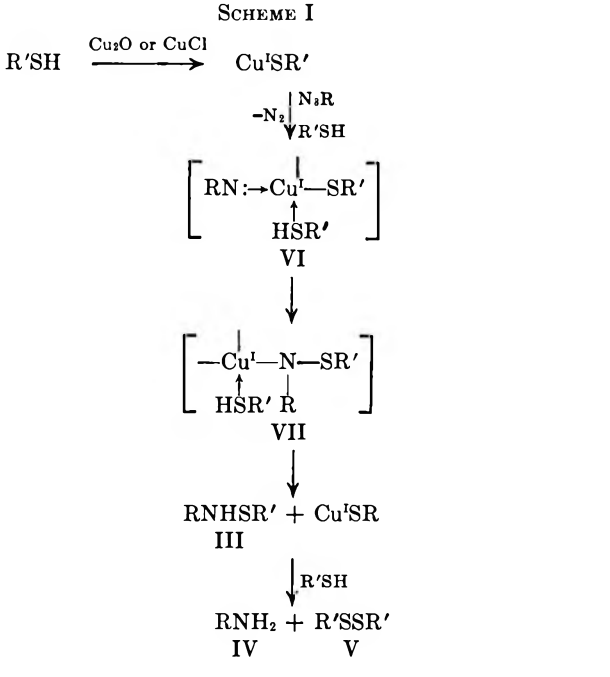
catalyzed reactions. A reference experiment, however, showed that the reaction of N,N-diethylbenzenesulfenylamide with benzenethiol proceeded quickly even at 0° to afford diethylamine and diphenyl disulfide (eq 4). This reaction did not require any added catalyst.

$$Et_2N\text{-}SPh + PhSH \longrightarrow Et_2NH + PhSSPh \quad (4)$$

The reaction of sulfenylamide and thiol has been reported also by Mukaiyama, *et al.*[6]

As the real species of catalyst, cuprous mercaptide may be postulated, because the reaction mixtures with cuprous oxide and with cuprous chloride as the catalyst always contained the corresponding cuprous mercaptide. The insertion of nitrene to the copper(I)–sulfur bond constitutes an essential step for the formation of the sulfenylamide intermediate. A tentative mechanistic scheme is given as follows (Scheme I). Nitrene from azide is coordinated with cuprous mercaptide, and the insertion probably takes place in the ligand sphere of a mixed ligand complex (VI). After the insertion, the hydrogen transfer from thiol to cuprous sulfenylamide in VII produces III and cuprous mercaptide.

SCHEME I



Experimental Section

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidoacetate (Ia).—To a stirred mixture of IIa (44 mmol) and cuprous oxide (1 mmol), Ia (10 mmol) was added dropwise during 30 min at room temperature under nitrogen atmosphere. Stirring was then continued for additional 10 hr at 80°. After the insoluble part was removed by filtration, the filtrate was distilled *in vacuo* to give a distillate (1.9 g) boiling at 90~94° (5 mm). The distillate was then analyzed by glpc. The products were N-*t*-butoxycarbonylmethyl-2-methyl-2-propanesulfenylamide (IIIa; 64%), *t*-butyl ester of glycine (IVa; 30%), and di-*t*-butyl disulfide (Va; 31%). IIIa was identified by ir and nmr spectra and elemental analysis: ir of IIIa (neat) 3360 (s), 1740 (vs) and 1250–1100 cm^{-1} (vs); nmr ($CDCl_3$) τ 6.38 (2 H, s, $-CH_2-$), 8.51 (9 H, s, $-OC_4H_9\text{-}t$), 8.79 (9 H, s, $-S-C_4H_9\text{-}t$).

Anal. Calcd for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.38. Found: C, 54.26; H, 9.93; N, 6.10.

IVa was identified by ir and nmr spectra: ir of IVa (neat) (3360 (s), 1730 (vs), 1370 (s), 1240 (s) and 1150 cm^{-1} (s); nmr ($CDCl_3$) τ 6.70 (2 H, s, $-CH_2-$), 7.98 (2 H, broad, $-NH_2$), and 8.55 (9 H, s, $-OC_4H_9\text{-}t$).

Reaction of α-Toluenethiol (IIb) with *t*-Butyl Azidoformate (Ib).—The reaction was carried out by a similar procedure. The products were N-*t*-butoxycarbonyl-α-toluenesulfenylamide (IIIb; 60%), *t*-butyl urethan (IVb; 30%), and dibenzyl disulfide (Vb; 35%). IIIb was identified by ir and nmr spectra and elemental analysis: ir of IIIb (Nujol) 3440 (w), 1720 (vs), 1360 (vs), 760 (vs), and 690 cm^{-1} (s); nmr ($CDCl_3$) τ 2.72 (5 H, s, $-C_6H_5$), 6.40 (2 H, s, $-CH_2-$) and 8.55 (9 H, s, $-OC_4H_9\text{-}t$).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.56; H, 6.94; N, 5.67.

IVb and Vb were identified by comparison of ir and nmr spectra with those of the corresponding authentic samples.

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidformate (Ib).—To a stirred mixture of IIa (55 mmol) and cuprous chloride (1 mmol), Ib (10 mmol) was added dropwise during 30 min at room temperature under nitrogen atmosphere. Stirring was then continued for additional 10 hr at room temperature. Then the insoluble part was removed from the reaction mixture by filtration and the filtrate was concentrated and analyzed by glpc. The products were N-*t*-butoxycarbonyl-2-methyl-2-propanesulfenylamide (IIIc; 77%), *t*-butylurethan (IVb; 20%), and di-*t*-butyl disulfide (Va; 16%). IVb and Va were identified by comparison of the glpc retention times and ir spectra with those of the corresponding authentic samples. IIIc was isolated by preparative glpc, white crystalline, mp 95–96°, whose structure was determined by ir and nmr spectra and elemental analysis: ir of IIIc (KBr, tablet) 3320 (s), 1715 (vs), 1450 (s), 1360 (s), 1245 (s), 940 (vw) and 840 cm^{-1} (s); nmr ($CDCl_3$) τ 4.5 (1 H, broad, $-NH-$), 8.50 (9 H, s, $-OC_4H_9\text{-}t$), 8.75 (9 H, s, $-S-C_4H_9\text{-}t$).

Anal. Calcd for $C_9H_{19}NO_2S$: C, 52.65; H, 9.33; N, 6.82. Found: C, 52.38; H, 9.62; N, 6.74.

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidoacetate (Ia) (Figure 1).—A mixture of IIa (44 mmol), Ia (8 mmol), and cuprous oxide (1 mmol) was heated at 80° under nitrogen atmosphere. The amounts of IIIa, IVa and Va at several times of reaction were determined by glpc.

Reaction of Benzenethiol (IIc) with *t*-Butyl Azidoacetate (Ia) (Figure 2).—Curve 1 reaction: a mixture of IIc (39 mmol) and Ia (7 mmol) was heated at 80° under nitrogen atmosphere without any added catalyst. Curve 2 reaction: *p*-benzoquinone (11.8 mol %) was added at the beginning of curve 1 reaction. Curve 3 reaction: a mixture of IIc (39 mmol), Ia (7 mmol), and cuprous oxide (1 mmol) was heated at 80°. Curve 4 reaction: *p*-benzoquinone (20.0 mol %) was added at the beginning of curve 3 reaction.

Reaction of N,N-Diethylbenzenesulfenylamide[7] with Benzenethiol.—N,N-Diethylbenzenesulfenylamide (4.9 mmol) was added dropwise to benzenethiol (40 mmol) cooled with ice bath under nitrogen atmosphere without any added catalyst. The reaction immediately occurred, and ceased in 5 min. Then the insoluble part was separated from the reaction mixture by filtration. Diphenyl disulfide (94%) was obtained from the insoluble part. The filtrate was analyzed by glpc. The product was diethylamine (85%). Any other product was not detected from the reaction mixture. Diethylamine was identified by comparison of the glpc retention time and ir spectra with those of the authentic sample.

Registry No.—Ia, 6367-36-8; Ib, 1070-19-5; IIa, 75-66-1; IIb, 100-53-8; IIc, 108-98-5; IIIa, 25297-00-1; IIIb, 25297-01-2; IIIc, 25297-02-3; IVa, 6456-74-2; Va, 110-06-5.

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Organic Syntheses by Means of Metal Complexes. V.[1] Reactions of Olefins, Carbon Tetrachloride, and Carbon Monoxide Catalyzed by Metal Carbonyls[2]

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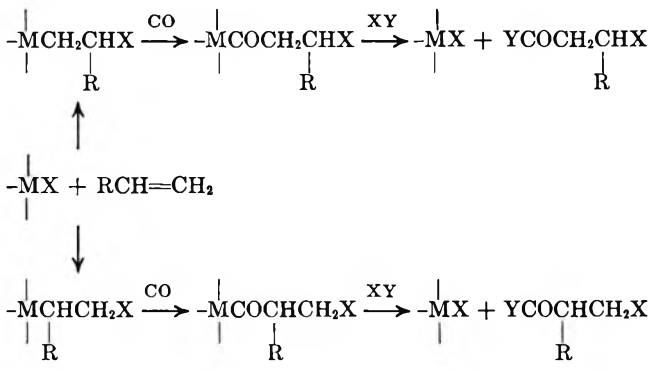
Dicobalt octacarbonyl, cyclopentadienyliron dicarbonyl dimer, and cyclopentadienylmolybdenum tricarbonyl dimer are effective catalysts for the addition reaction of carbon tetrachloride and carbon monoxide to olefins to form 2-alkyl-4,4,4-trichlorobutyryl chloride. These dinuclear metal carbonyls are also active catalysts for the addition of carbon tetrachloride to olefins to form 1,1,1,3-tetrachloroalkane. The mechanism of these dinuclear metal carbonyl catalyzed reactions is discussed.

Metal carbonyls catalyze various reactions of olefins, among which carbonylations are the most important. In carbonylations, it is generally believed that an insertion of olefins into a metal σ bond to form an alkyl complex is followed by carbon monoxide insertion to form an acyl complex. Finally the acyl complex affords carbonyl compounds. This mechanism can be expressed by Scheme I.

SCHEME I



In this mechanism, formation of σ-bonded complex is essential as a starting point. Dinuclear metal carbonyls such as $Co_2(CO)_8$ (I) react with some simple molecules with splitting of the metal–metal bond to form σ-bonded complexes. For example, in the I-catalyzed oxo reaction or hydrosilation,[3] hydrogen or a silane reacts with I to form the following σ-bonded complexes (reactions 1 and 2), which then undergo olefin insertion.

$$\xrightarrow{H_2} 2HCo(CO)_4 \quad (1)$$

$$Co_2(CO)_8 \xrightarrow{H\text{–}SiR_3} HCo(CO)_4 + R_3SiCo(CO)_4 \quad (2)$$

I

$$\xrightarrow{CCl_4} CCl_3Co(CO)_4 + ClCo(CO)_4 \quad (3)$$

The reaction of CCl_4 with I to form $Co_3(CO)_9CCl$ is known,[4,5] and the intermediate formation of the species $CCl_3Co(CO)_4$ and $ClCo(CO)_4$ has been assumed (reaction 3). Once the σ-bonded complex is formed from CCl_4, olefin insertion into the σ bond to form an alkyl complex is expected. Based on this assumption, we attempted to apply this reaction of dinuclear metal carbonyls to a new catalytic carbonylation reaction of olefins.

The addition reaction of CCl_4 to olefins catalyzed by mononuclear metal carbonyls, such as $Fe(CO)_5$, $Mo(CO)_6$, or $Cr(CO)_6$, has been reported. Thus $Fe(CO)_5$-catalyzed addition of CCl_4 to ethylene gave a mixture of telomer homologs, $CCl_3(CH_2CH_2)_nCl$ (n = 1, 2, 3, 4, and higher), in 70% conversion.[6] From the above consideration, it is expected that dinuclear metal carbonyls should be better catalysts for the CCl_4 addition reactions. The dinuclear metal carbonyls are indeed very active catalysts for the addition reaction of CCl_4 and CO to olefins, as the catalyst I, $[C_5H_5Fe(CO)_2]_2$ (II), and $[C_5H_5Mo(CO)_3]_2$ (III) were found most effective.

The reaction of ethylene, carbon monoxide, and CCl_4 in methanol to give $CCl_3(CH_2CH_2)_nCO_2CH_3$ (n = 1–3) in 40% conversion using di-*t*-butyl peroxide as a catalyst at 1000 atm has been reported.[7] Different from the reactions catalyzed by butyl peroxide and $Fe(CO)_5$, the reactions catalyzed by the dinuclear metal carbonyls are clean and selective without giving a mixture of homologs. The catalytic activity of metal carbonyls coordinated with a cyclopentadienyl group has scarcely been reported, although it was recently reported that II is an active catalyst for the oxo reaction.[8] Further usefulness of the cyclopentadienyl-coordinated metal carbonyls was found in the present studies.

Results and Discussion

The reaction of CCl_4 with olefins in the presence of a catalytic amount of I was first investigated. Addition

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(5) G. Bor, L. Marko, and B. Marko, *Chem. Ber.*, **95**, 333 (1962).

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TABLE I

REACTION OF CARBON TETRACHLORIDE WITH OLEFINS IN THE PRESENCE OF $[Co(CO)_4]_2$ (I)[a]

Olefins	Reaction: Temp, °C	Reaction: Time, hr	Products (g)
Ethylene[b] (100 atm)	160	17	$CCl_3CH_2CH_2Cl$ (1.0) $CCl_3(CH_2)_4Cl$ (3.5)
Propylene (12 g)	150	15	$CCl_3CH_2CH(CH_3)Cl$ (4.2)
1-Buene (12 g)	160	16	$CCl_3CH_2CH(C_2H_6)Cl$ (8.0)
1-Butene (6 g)	160	1	$CCl_3CH_2CH(C_2H_5)Cl$ (4.3)
1-Hexene (7 g)	180	16	$CCl_3CH_2CH(n\text{-}C_4H_9)Cl$ (8.0)
1-Hexene (14 g)	20	48	$CCl_3CH_2CH(n\text{-}C_4H_9)Cl$ (1.5)
1-Octene (14 g)	160	15	$CCl_3CH_2CH(n\text{-}C_6H_{13})Cl$ (6.5)
cis-2-Butene (6 g)	160	16	$CCl_3CH(CH_3)CH(CH_3)Cl$ (3.0)
trans-2-Butene (6 g)	160	16	$CCl_3CH(CH_3)CH(CH_3)Cl$ (2.7)
2-Hexene (7 g)	160	16	$CCl_3CH(C_3H_7)CH(CH_3)Cl$ $CCl_3CH(CH_3)CH(C_3H_7)Cl$ (3.6)
Cyclohexene (16 g)	150	15	No sole product

[a] The reactions were carried out with 40 ml of CCl_4 and 1 g of the catalyst in a glass vessel placed in an autoclave (300 ml). [b] CCl_4 (20 ml) was used in a 100-ml autoclave.

of CCl_4 to various olefins was observed at about 160° and 1,1,1,3-tetrachloroalkanes were obtained. The results are shown in Table I. Ethylene is somewhat unusual and a mixture of 1:1 and 1:2 adducts was obtained showing that a successive ethylene insertion is possible. On the other hand, only 1:1 adduct was obtained with other olefins. Conversion was lower with internal olefins than terminal olefins. For 1 olefins, there are two possible orientations of the olefin additions. Actually, however, only products formed by addition of CCl_3 to the terminal carbon were obtained.

$$RCH{=}CH_2 + CCl_4 \longrightarrow \underset{\displaystyle Cl}{\underset{|}{R}}CHCH_2CCl_3$$

For example, only 1,1,1,3-tetrachloropentane was obtained selectively from 1-butene. This is the same result as obtained in the radical-initiated addition reaction of CCl_4 to olefins. It is clearly different from other I-catalyzed reactions such as the oxo reaction, in which two products derived from different additions to double bond are obtained in various ratios. As in the oxo reaction, only catalytic amounts of I are necessary. After the reaction was complete, $CoCl_2$ was recovered from the reaction mixture. The reaction can be applied to simple olefins, but not to butadiene. Acrylonitrile, methyl acrylate, and styrene polymerized with this catalyst.

The reaction under CO pressure was then investigated with the expectation that the CO insertion would follow olefin insertion to give carbonylated products. With 1 olefin, CCl_4, and CO, the reaction proceeded smoothly to give 2-alkyl-4,4,4-trichlorobutyryl chloride. The formation of butyryl chlorides is competitive with simple addition of CCl_4 to olefins to form 1,1,1,3-tetrachloroalkanes.

$$RCH{=}CH_2 + CCl_4 + CO \longrightarrow Cl_3CCH_2\underset{\displaystyle R}{\underset{|}{C}}HCOCl + Cl_3CH_2C\underset{\displaystyle R}{\underset{|}{C}}HCl$$

A higher CO pressure and a lower reaction temperature tended to increase the ratio of the carbonylation to the simple addition. It should be noted that a simple CO insertion without olefin insertion to form trichloroacetyl chloride was not observed.

For this carbonylation reaction, mononuclear metal carbonyls, such as $Fe(CO)_5$ or $Mo(CO)_6$, were almost inactive. I is active, but higher activity was observed with dinuclear metal carbonyls derived from iron and molybdenum carbonyls. Mononuclear molybdenum and iron carbonyls can be converted into the dinuclear ones by coordination of a cyclopentadienyl group as a ligand.[9]

$$2Mo(CO)_6 + \text{dicyclopentadiene} \longrightarrow [C_5H_5Mo(CO)_3]_2 + 6CO + H_2$$

With these dimeric carbonyls, high yields of 2-alkyl-4,4,4-trichlorobutyryl chlorides were obtained, the reaction proceeding even at 50° with the iron catalyst. Results are shown in Table II. Another typical mononuclear carbonyl is $Ni(CO)_4$ from which $[C_5H_5Ni(CO)]_2$ can be derived; this, however, was found to be completely inactive. The catalytic action of I is somewhat different from that of the iron and molybdenum catalysts. For example, ethylene does not give the carbonylated product with I, but high yields of the carbonylated products were obtained with the other catalysts. Also, hydroquinone showed some inhibitory action with I and a little with III. There was no effect with II. The reaction carried out in ethanol produced corresponding esters in nearly the same yields as in the absence of the solvent. Thus, this carbonylation reaction is useful for the synthesis of 2-alkyl-4,4,4-trichlorocarboxylic acids from which various compounds can be derived by diplacement or elimination of the chlorines.

We propose the following mechanism for this reaction. The first step is the formation of the trichloromethyl complex by reaction of the dinuclear carbonyls with CCl_4 (reaction 4). The insertion of olefin into the metal–trichloromethyl bond forms the 1-alkyl-3,3,3-trichloropropyl complex (reaction 5). Reaction of the propyl complex with another molecule of CCl_4 gives the 1,1,1,3-tetrachloroalkane with regeneration of the trichloromethyl complex (reaction 6). CO insertion into the propyl complex gives the acyl complex (reaction 7), which then reacts with CCl_4 to form 2-alkyl-4,4,4-trichlorobutyryl chloride with regeneration of the trichloromethyl complex (reaction 8).

(9) R. B. King "Organometallic Syntheses," Vol. 1, Academic Press New York, N .Y., 1965, pp 109, 114.

TABLE II

REACTION OF OLEFINS, CCl_4 AND CO CATALYZED BY $[Co(CO)_4]_2$ (I), $[C_5H_5Fe(CO)_2]_2$ (II), AND $[C_5H_5Mo(CO)_3]_2$ (III)[a]

Olefins	Catalyst, 1 g	CO pressure, atm	Reaction Temp, °C	Reaction Time, hr	Products[b] (g)
Ethylene (30 atm)	II	170	119	15	$CCl_3CH_2CH_2COCl$ (3.3)
Ethylene (30 atm)	III	170	120	15	$CCl_3CH_2CH_2COCl$ (15.4)
Ethylene (30 atm)	I	170	135	15	$CCl_3CH_2CH_2Cl$ (0.3) $CCl_3(CH_2)_4Cl$ (0.8)
Propylene (12 g)	II	200	53	14	$CCl_3CH_2CH(CH_3)COCl$ (12) $CCl_3CH_2CH(CH_3)Cl$ (3.0)
Propylene (12 g)	II	200	118	15	$CCl_3CH_2CH(CH_3)COCl$ (12) $CCl_3CH_2CH(CH_3)Cl$ (8.0)
Propylene[c] (12 g)	II	200	68	15	$CCl_3CH_2CH(CH_3)COOC_2H_5$ (11.2) $CCl_3CH_2CH(CH_3)Cl$ (2.7)
Propylene[d] (12 g)	II	200	67	15	$CCl_3CH_2CH(CH_3)COCl$ (13) $CCl_3CH_2CH(CH_3)Cl$ (3.0)
Propylene (12 g)	III	200	50	15	None
Propylene (12 g)	III	60	93	15	$CCl_3CH_2CH(CH_3)COCl$ (8.8) $CCl_3CH_2CH(CH_3)Cl$ (15)
Propylene (12 g)	III	200	95	3	$CCl_3CH_2CH(CH_3)COCl$ (10) $CCl_3CH_2CH(CH_3)Cl$ (9.0)
Propylene[e] (12 g)	III	150	103	4	$CCl_3CH_2CH(CH_3)COCl$ (1.1) $CCl_3CH_2CH(CH_3)Cl$ (1.8)
Propylene (10 g)	I	200	83	15	$CCl_3CH_2CH(CH_3)COCl$ (5.0) $CCl_3CH_2CH(CH_3)Cl$ (2.3)
Propylene[c] (10 g)	I	200	125	15	$CCl_3CH_2CH(CH_3)COOC_2H_5$ (9.0) $CCl_3CH_2CH(CH_3)Cl$ (6.4)
Propylene (10 g)	I	50	128	15	$CCl_3CH_2CH(CH_3)COCl$ (1.1) $CCl_3CH_2CH(CH_3)Cl$ (2.0)
Propylene[f] (10 g)	I	200	120	15	$CCl_3CH_2CH(CH_3)COCl$ (trace) $CCl_3CH_2CH(CH_3)Cl$ (trace
1-Butene (12 g)	II	200	90	15	$CCl_3CH_2CH(C_2H_5)COCl$ (9.8) $CCl_3CH_2CH(C_2H_5)Cl$ (4.5)
1-Butene (12 g)	III	200	93	15	$CCl_3CH_2CH(C_2H_5)COCl$ (6.5) $CCl_3CH_2CH(C_2H_5)Cl$ (3.8)
1-Butene (12 g)	I	200	160	15	$CCl_3CH_2CH(C_2H_5)COCl$ (7.5) $CCl_3CH_2CH(C_2H_5)Cl$ (7.0)
1-Hexene (4 g)	III	200	91	15	$CCl_3CH_2CH(n\text{-}C_4H_9)COCl$ (3.8) $CCl_3CH_2CH(n\text{-}C_4H_9)Cl$ (2.5)
1-Hexene (7 g)	I	180	160	15	$CCl_3CH_2CH(n\text{-}C_4H_9)COCl$ (4.4) $CCl_3CH_2CH(n\text{-}C_4H_9)Cl$ (8.5)
1-Octene (7 g)	II	200	118	15	$CCl_3CH_2CH(n\text{-}C_6H_{13})COCl$ (7.6) $CCl_3CH_2CH(n\text{-}C_6H_{13})Cl$ (3.5)
1-Octene (7 g)	I	200	130	15	$CCl_3CH_2CH(n\text{-}C_6H_{13})COCl$ (6.5) $CCl_3CH_2CH(n\text{-}C_6H_{13})Cl$ (6.0)
trans-2-Butene (9 g)	III	200	120	15	$CCl_3CH(CH_3)CH(CH_3)COCl$ (1.6) $CCl_3CH(CH_3)CH(CH_3)Cl$ (1.8)
trans-2-Butene (6 g)	I	170	160	15	$CCl_3CH(CH_3)CH(CH_3)Cl$ (2.0)
cis-2-Butene (12 g)	I	200	120	15	$CCl_3CH(CH_3)CH(CH_3)COCl$ (1.7) $CCl_3CH(CH_3)CH(CH_3)Cl$ (4.0)
Isobutene (9 g)	I	160	160	15	$CCl_3CH_2C(CH_3)_2Cl$ (2.0)
1,3-Butadiene (12 g)	II	200	74	6	None
1,3-Butadiene (12 g)	III	200	120	15	None
1,3-Butadiene (12 g)	I	200	120	15	$CCl_3CH_2CH{=}CHCH_2COCl$ (0.6)

[a] The reactions were carried out with 40 ml of CCl_4 in a glass vessel. [b] Amount of the acid chlorides was calculated from the weight of isolated acid amide. [c] The mixture of 20 ml of CCl_4 and 20 ml of ethanol was used. [d] Hydroquinone (1.0 g) was added. [e] Hydroquinone (0.86 g) was added. [f] Hydroquinone (1.27 g) was added.

TABLE III

PROPERTIES AND ANALYSES OF 1,1,1,3-TETRACHLOROALKANES

$CCl_3CH(R^1)CHClR^2$				Calcd, %				Found, %				
R^1	R^2	Registry no.	Bp, °C (mm)	C	H	Cl	Calcd mol wt	C	H	Cl	Found mol wt	Nmr spectrum
CH_3	H	a	88–89 (53)	24.52	3.09	72.39	196	24.81	3.08	72.10	202.7	8.31 (d, 3), 6.79 (heptet, 2), 5.58 (m, 1)
C_2H_5	H	b	80–83 (18)	28.60	3.84	67.55	210	28.65	3.80	67.25	213	8.86 (t, 3), 8.03 (m, 2), 6.79 (octet, 2), 5.77 (m, 1)
CH_3	CH_3	c	75 (15)	28.60	3.84	67.55		28.93	3.88	67.00		8.46 (t, 6), 6.85 (octet, 1), 5.10 (octet, 1)
n-C_4H_9	H	d	119–120 (27)	35.33	5.08	59.59	238	35.59	5.11	59.30	243	9.05 (t, 3), 8.54 (m, 4), 8.14 (2), 6.81 (octet, 2), 5.72 (1)
n-C_6H_{13}	H	e	73–75 (1)	40.64	6.06	53.31	266	41.19	6.12	531.0	279.9	9.08 (t, 3), 8.62 (m, 8), 8.14 (m, 2), 6.79 (octet, 2), 5.75 (m, 1)

TABLE IV

PROPERTIES AND ANALYSES OF AMIDES AND ESTERS DERIVED FROM 2-ALKYL-4,4,4-TRICHLOROBUTYRYL CHLORIDES

CCl_3CH_2CHCOX (R^2, R^1)

X	R^1	R^2	Registry no.	Mp or bp (mm), °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Calcd mol wt	Found, % C	Found, % H	Found, % N	Found, % Cl	Found mol wt	Nmr spectrum
NH_2	H	H	a	88–89	25.22	3.18	7.35	55.85	190.5	25.34	3.25	7.20	56.00	185	7.20, 7.03
OC_2H_5	H	H	b	110–115 (28)	32.83	4.13		48.46	219.5	33.21	4.18		48.10	216.3	
NH_2	CH_3	H	c	103–104	29.37	3.94	6.85	52.02	204.4	29.52	3.97	6.71	52.23	205.7	
OC_2H_5	CH_3	H	d	95–97 (12)	36.00	4.75		45.55	234	36.11	4.74		45.52	230	8.76 (t, 3), 8.71 (d, 3), 7.6–6.4 (m, 3), 5.93 (2)
NH_2	C_2H_5	H	e	97–98	32.98	4.61	6.41	48.68		33.02	4.66	6.31	48.65		8.96 (t, 3), 8.36 (2), 7.63–6.26 (m, 3)
OC_2H_5	C_2H_5	H	f	120–130 (25)	38.81	5.29		42.97	247.6	38.65	5.18		43.45	247.3	
NH_2	CH_3	CH_3	g	56–57	32.98	4.61	6.41	48.68	219	33.14	4.66	6.55	48.54	219	8.84–8.50 (double d, 6), 7.75–6.64 (m, 2)
NH_2	n-C_4H_9	H	h	82–83	38.97	5.72	5.68	43.14		38.81	5.72	5.52	43.27		9.07 (t, 3), 8.57 (m, 6), 7.28 (2), 6.55 (quartet, 1)
OC_2H_5	n-C_4H_9	H	i	150–160 (25)	43.57	6.22		38.59	275.6	43.77	6.18		38.50	281.8	
NH_2	n-C_6H_{13}	H	j	87–88	43.73	6.61	5.10	38.79	275	43.59	6.42	4.93	38.64	279	
OC_2H_5	n-C_6H_{13}	H	k	127–130 (5)	47.47	6.97		35.01	303.6	47.51	6.92		35.00	297	
$CCl_3CH_2CH{=}CHCH_2CONH_2$			l	94–97	33.29	3.72	6.47	49.13	216.5	33.77	3.95	5.89	48.89	202	6.89 (d, 2), 6.56 (d, 2), 4.11 (quintet, 2)

$$[M(CO)_n(C_5H_5)_2]_2 + CCl_4 \longrightarrow ClM(CO)_nC_5H_5 + CCl_3M(CO)_nC_5H_5 \quad (4)$$

$$CCl_3M(CO)_nC_5H_5 + RCH{=}CH_2 \longrightarrow CCl_3CH_2\underset{\displaystyle R}{\underset{|}{C}}HM(CO)_nC_5H_5 \quad (5)$$

$$CCl_3CH_2\underset{\displaystyle R}{\underset{|}{C}}HM(CO)_nC_5H_5 + CCl_4 \longrightarrow RCHClCH_2CCl_3 + CCl_3M(CO)_nC_5H_5 \quad (6)$$

$$CCl_3CH_2\underset{\displaystyle R}{\underset{|}{C}}HM(CO)_nC_5H_5 + CO \longrightarrow CCl_3CH_2\underset{\displaystyle R}{\underset{|}{C}}HCOM(CO)_nC_5H_5 \quad (7)$$

$$CCl_3CH_2\underset{\displaystyle R}{\underset{|}{C}}HCOM(CO)_nC_5H_5 + CCl_4 \longrightarrow RCH\underset{\displaystyle COCl}{\underset{|}{C}}HCH_2CCl_3 + CCl_3M(CO)_nC_5H_5 \quad (8)$$

There is a close similarity, such as selective formation of only one product, between the metal carbonyl catalyzed addition of CCl_4 and radical-initiated reactions,[7] and hence there is a possibility that a trichloromethyl radical, rather than the trichloromethyl complex shown above, is an active species. However, little or no inhibition by hydroquinone in the metal carbonyl catalyzed addition reactions weakens this possibility. Certainly metal-coordinated species, namely, σ-metal complexes or coordinated radicals, play an important role.

Bamford and others have published a series of papers dealing with the metal carbonyl initiated radical polymerization of vinyl monomers in the presence of CCl_4; they proposed that the polymerizations are initiated by a radical formed by the reaction of CCl_4 with metal carbonyls.[10] In their polymerization, only monomeric metal carbonyls are reported to be active; dinuclear carbonyls such as I are not active. Under the present reaction conditions, however, styrene, acrylonitrile, and methyl acrylate polymerized with I.

Experimental Section

The nmr spectra were determined on a Varian high-resolution spectrometer Model HR-100 in CCl_4 and are expressed in τ values. The molecular weights were determined in benzene using the Mechrolab vapor pressure osmometer. II and III were synthesized by the known method.[9] The addition and carbonylation reactions were carried out in a stainless steel autoclave with shaking. Only typical examples are shown below.

Reaction of Ethylene and CCl_4 Catalyzed by I.—CCl_4 (20 ml) and I (1 g) were mixed in a glass vessel equipped with a gas inlet capillary, which was placed in a 100-ml autoclave. The ethylene was introduced (100 atm). The reaction was carried out at 160° for 17 hr. Crude reaction product was isolated by distillation at 60–120° (25 mm). Redistillation gave 1,1,1,3-tetrachloropropane (1.0 g) and 1,1,1,5-tetrachloropentane (3.5 g).

Reaction of Propylene with CCl_4 and CO Catalyzed by II.—The catalyst (1 g) and CCl_4 (40 ml) were mixed in the glass vessel, which was placed in a 300-ml autoclave. Propylene (20 ml) was introduced, followed by CO (200 atm), and the reaction was carried out at 53° for 14 hr. Ir spectrum of the crude reaction mixture showed the presence of acyl chloride at 1780 cm^{-1}. The reaction mixture was treated with concentrated NH_3 and extracted with CH_2Cl_2. Distillation of the extract gave 1,1,1,3-

(10) C. H. Bamford, G. C. Eastmond, and D. Writtle, *J. Organometal. Chem.*, **17**, 33 (1969), and the references cited therein.

tetrachlorobutane (3 g) at 86–88° (50 mm) and the residue solidified. The solid was recrystallized from a CCl_4–*n*-hexane mixture to give 4,4,4-trichloro-2-methylbutyramide (11 g). The amide (9 g) was dissolved in ethanolic HCl (40%, 50 ml) and refluxed for 3 hr. The solution was neutralized with ammonia and ethanol was evaporated. NH_4Cl was removed by filtration and the filtrate was subjected to distillation to give ethyl 4,4,4-trichloro-2-methylbutyrate at 95–97° (12 mm, 7.5 g).

Following derivatives of succinic acids were obtained by the hydrolysis of the trichloro esters formed from various olefins in concentrated H_2SO_4 and their melting points are shown (reported melting points): CH_3–, 111–112° (111°); C_2H_5–, 97° (98°); *n*-C_4H_9–, 80° (81°); *n*-C_6H_{13}–, 83° (83–84°).

Properties of the other reaction products and their derivatives are shown in Tables III and IV.

Registry No.—Carbon tetrachloride, 56-23-5; carbon monoxide, 630-08-0; I, 10210-68-1; II, 12087-10-4; III, 12091-64-4; Table III—a, 13275-19-9; b, 19967-19-2; c, 20518-70-1; d, 13375-88-7; e, 1070-27-5; Table IV—a, 25236-71-9; b, 20101-80-8; c, 25236-73-1; d, 25236-74-2; e, 25236-75-3; f, 25236-76-4; g, 25236-77-5; h, 25236-78-6; i, 25236-79-7; j, 25236-80-0; k, 25236-81-1; l, 25236-82-2; ethylene, 74-85-1; propylene, 115-07-1; 1-butene, 106-98-9; 1-hexene, 592-41-6; 1-octene, 111-66-0; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 2-hexene, 592-43-8; isobutene, 115-11-7; 1,3-butadiene, 106-99-0.

Zinc Reduction of γ Diketones

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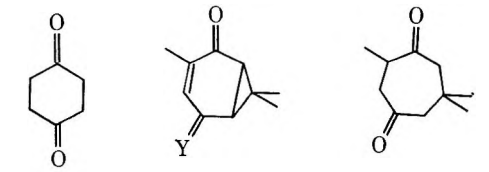
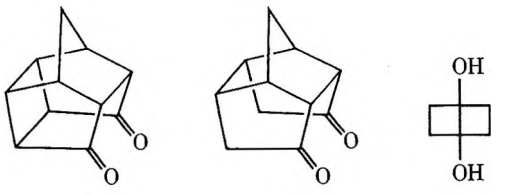
The reduction of cyclic γ diketones with amalgamated zinc and hydrochloric acid has been studied. While the eight- and seven-ring systems yield 1,2-glycols, cyclohexane-1,4-dione fragments into acyclic hexane-2,5-dione. Reduction of the latter produces 2-hexanol. The ease of reduction of 1,2-diacylethylenes, -cyclopropanes, and -cyclobutane is compared. A seven-membered-ring analog of the quinone–hydroquinone reduction–oxidation system is described.

In continuation of a study of the Clemmensen reduction of diketones,[1] an investigation of the reaction of some cyclic γ diketones with amalgamated zinc in hydrochloric acid was undertaken. Diketones **1**, **3**, and **5** were chosen as six-, seven-, and eight-membered cyclic 1,4-dione representatives. The latter two substances were prepared by reduction of ketones **2a**[2] and **4**,[3] respectively, with zinc in acetic acid.

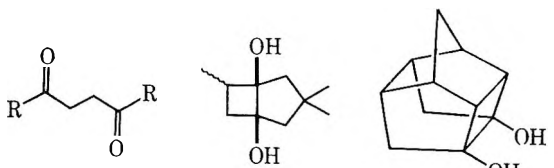


1 **2a**, Y = O; **b**, Y = H, OH **3**



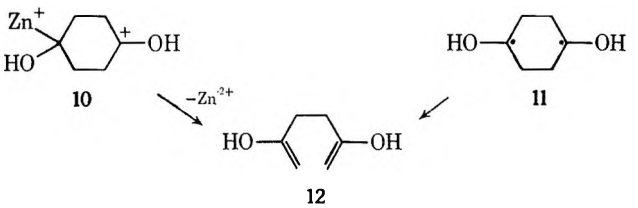
4 **5** **6**

The Clemmensen products were expected to be pinacols, although the high strain of potential pinacolic product **6** from **1** suggested that the reduction of the six-membered cyclic diketone might take a different course from that of its homologs. The Clemmensen reduction of cyclohexane-1,4-dione (**1**) yielded acetonylacetone (**7a**), while the reduction of 2,6,6-trimethylcycloheptane-1,4-dione (**3**) gave the pinacol isomer pair **8** and that of **5** led to pinacol **9**. Periodate oxidation of the diols reverted them to their diketonic precursors.



7a, R = Me; **b**, R = *t*-Bu **8** **9**

The fragmentation of **1** is reminiscent of the conversion of 1,4-dibromocyclohexane or 1,4-diiodocyclohexane into diallyl on zinc reduction[4] and can be envisaged to involve the breakup of the reduction intermediate(s) (**10**, **11**, or organozinc equivalents) into the dienol (**12**) of **7a**.[5]



10 **11** **12**

The formation of products besides **7a** on reduction of **1** at elevated temperature led to a study of the Clemmensen reduction of acetonylacetone (**7a**). The sole isolable product of a reaction at room temperature was 2-hexanol, while the latter and a mixture of stereoisomeric 2,5-dimethyltetrahydrofurans (**13a**) were obtained from a reaction at slightly elevated temperature and proved to be the products of overreduction of cyclohexane-1,4-dione (**1**).[6] In view of the possibility of the

(1) E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965).

(2) E. J. Corey and H. J. Burke, *J. Amer. Chem. Soc.*, **78**, 174 (1956).

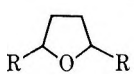
(3) R. C. Cookson, E. Crundwell, and J. Hudec, *Chem. Ind. (London)*, 1003 (1958).

(4) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

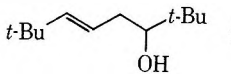
(5) (a) For a general discussion of heterolyses of this type, *cf.* C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1 (1967). (b) For examples of homolyses of this type, *cf.* S. G. Cohen and R. Zand, *J. Amer. Chem. Soc.*, **84**, 586 (1962); W. R. Roth and M. Martin, *Tetrahedron Lett.*, 3865 (1967).

(6) An independent study of the Clemmensen reduction of acetonylacetone and cyclohexane-1,4-dione under somewhat different conditions by J. G. St. C. Buchanan and B. R. Davis, *J. Chem. Soc. C*, 1340 (1967), has yielded related results. The authors are indebted to Dr. Davis for furnishing them information on this work prior to publication.

product of fragmentation of acetonylacetone (**7a**), *i.e.*, acetone, having been missed on work-up, another acyclic diketone, **7b**,[7] was exposed to the Clemmensen reaction. The reduction products consisted of a mixture of 2,5-di-*t*-butyltetrahydrofuran (**13b**) stereoisomers, *trans*-2,2,7,7-tetramethyl-5-octen-3-ol (**14**), and 2,2,-7,7-tetramethyl-3-octanol (**15**). The acyclic γ diketones thus had undergone their own mode of reduction, yielding neither pinacols nor scission products.



13a, R = Me
b, R = *t*-Bu



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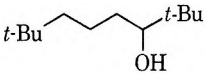

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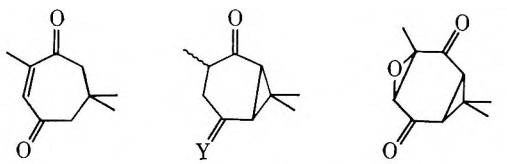
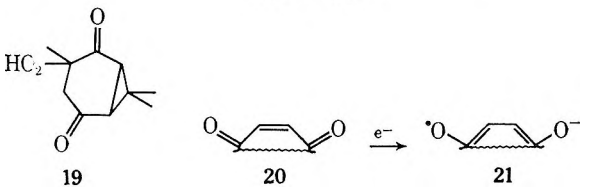
Alongside the above investigation a qualitative study of the ease of reduction of 1,2-diacylethylene, 1,2-diacylcyclopropane, and 1,2-diacylcyclobutane derivatives by zinc in acetic acid was undertaken. Several of the following substances were prepared for this endeavor. Selenium dioxide oxidation of diketone **3** yielded 2,6,6-trimethyl-2-cycloheptene-1,4-dione (**16**). Hydrogenation of enolone **2b**[2] gave ketol **17b**, whose Jones oxidation afforded diketone **17a**. An alternate attempt of transformation of **2b** into **17a**, by base-catalyzed isomerization, went awry. Exposure of either **2b** or **17a** to hydroxide without precaution of exclusion of air led to diketoepoxide **18**. The initial enolate apparently trapped oxygen from the air and the intermediate hydroperoxide, *e.g.*, **19**, suffered oxygen–oxygen bond cleavage by intramolecular displacement by the second enolate.

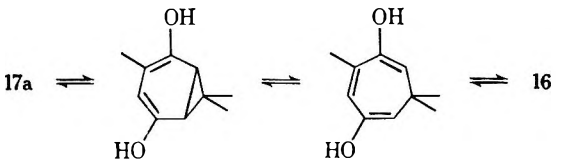


16 **17a**, Y = O; b, Y = H, OH **18**



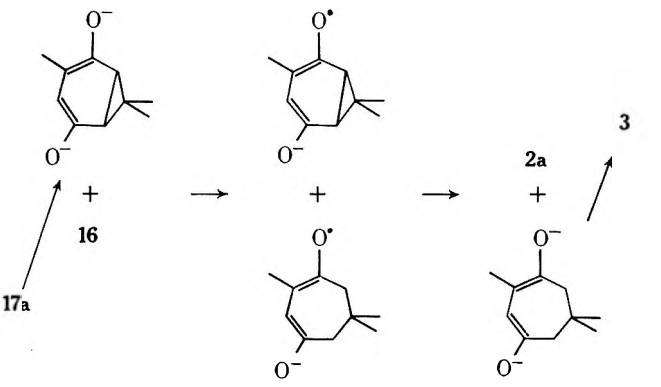
19 **20** **21**

Zinc reduction of **16**, **17a**, and **18** in acetic acid yielded **3**. While, however, the reduction of enedione **16** was extraordinarily facile, the reductions of the diacylcyclopropanes **17a** and **18** and the transformation of diacylcyclobutane **4** into **5** under the same reaction conditions (*vide supra*) required extended time or/and elevated temperature. Thus the ability of an enedione to form a highly delocalized anion radical (or its conjugate acid) on electron acceptance (**20** → **21**) facilitates the reduction. This conclusion indicated that the easy conversion of **2a** into **3** on reduction with zinc in acetic acid (*vide supra*) had occurred in an indirect manner. While the double-bond system of **2a** had to be the site of initial reduction, diketone **17a** could not have been a reduction intermediate. If, however, it be assumed that after the initial one- or two-electron transfer stage a norcaradiene–cycloheptatriene rearrangement takes place, **16** would have become the reduction intermediate (*vide infra*) and, being an enedione, could have been expected to undergo further reduction rapidly.



To gain more insight into the rearrangement of the ring systems, a base-catalyzed isomerization of **17a** into **16** was attempted. Surprisingly, however, exposure of **17a** to potassium hydroxide in methanol at 0° under nitrogen produced the diketones **2a** and **3** in equimolar quantity. Thus the desired transformation had occurred but had been followed by an unprecedented oxidation–reduction process involving **16** and **17a** dienol, reminiscent of quinone–hydroquinone interactions.[8] The likely reduction–oxidation sequence is portrayed in Scheme I.

SCHEME I



Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. Proton magnetic resonance spectra of deuteriochloroform solutions containing tetramethylsilane as internal standard were taken on a Varian Associates A-60 spectrometer.

Clemmensen Reductions.—A mixture of 95 mg of cyclohexane-1,4-dione (**1**) and 10 g of amalgamated zinc in 55 ml of 6.5 *N* hydrochloric acid was stirred at room temperature for 2 hr. The solution was decanted off the remaining zinc; the latter was washed with water; and the combined aqueous solutions were saturated with sodium chloride and extracted with methylene chloride. The extract was treated with solid sodium bicarbonate and thereafter dried over anhydrous magnesium sulfate. Filtration and solvent evaporation yielded 68 mg of a liquid whose gas phase chromatographic analysis (Carbowax column at 205°) revealed it to consist of over 95% of one component and less than 2% of starting material. Preparative gpc collection (SE30 column at 150°) gave acetonylacetone (**7a**) identical with an authentic sample by ir and pmr analyses and gpc retention time. Clemmensen reduction of **1** at elevated temperature led to products of similar reductions of **7a** (*vide infra*).

A mixture of 125 mg of 2,6,6-trimethylcycloheptane-1,4-dione (**3**) and 10 g of amalgamated zinc in 55 ml of 6.5 *N* hydrochloric acid was stirred at room temperature for 2 hr. Work-up as above gave 97 mg of liquid diol **8** (no carbonyl absorption in the ir spectrum).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.27; H, 10.62.

(7) R. Ramasseul and A. Rassat, *Bull. Soc. Chim. Fr.*, 2214 (1963).

(8) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, pp 845–878.

Fractional sublimation of **8** yielded two isomers: mp 34–35°, pmr δ 1.06 (d, 3, J = 7 Hz, cyclobutyl Me), 1.08 (s, 3, Me), 1.11 (s, 3, Me); mp 96–98°, pmr δ 1.09 (d, 3, J = 7 Hz, cyclobutyl Me), 1.08 (s, 3, Me), 1.13 (s, 3, Me). Periodate oxidation of either isomer of **8** in a manner analogous to the oxidation of **9** (*vide infra*) afforded **3**, identical with an authentic sample by ir, pmr, and gpc comparison, in over 95% yield.

A mixture of 500 mg of dione **5** and 10 g of amalgamated zinc in 31 ml of concentrated hydrochloric acid, 23 ml of water, and 4 ml of methanol was heated at 80° for 10 min. Work-up as above gave 500 mg of a white solid whose sublimation at 40° (0.05 Torr) led to diol **9**: mp 202° dec; ir (KBr) OH 2.90 (m) μ, no C=O.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.44; H, 8.13.

A mixture of 50 mg of diol **9** and 3 ml of a 5% sodium periodate solution in 2 ml of water and 1 ml of methanol was stirred at room temperature for 30 min and then extracted with methylene chloride. The extract was washed with sodium bicarbonate solution, dried, and evaporated, leaving 35 mg of dione **5**, mp and mmp 255° dec, ir spectrum identical with that of authentic **5**.

A mixture of 670 mg of acetonylacetone (**7a**) and 10 mg of amalgamated zinc in 55 ml of 6.5 N hydrochloric acid was stirred at room temperature for 13 hr. (An extra 15 ml of concentrated hydrochloric acid was added in intervals during this period.) Work-up as above gave 470 mg of a liquid whose gpc analysis showed it to contain no starting material and greater than 97% a single compound. Chromatography of the product on silica gel and elution with 7:3 petroleum ether (bp 30–60°)–ether yielded 450 mg of 2-hexanol identical with an authentic sample by ir and pmr analyses and gpc retention time.

A mixture of 2.0 g of acetonylacetone (**7a**), 20 g of amalgamated zinc, and 60 ml of concentrated hydrochloric acid in 46 ml of water was refluxed for 15 min. Work-up as above gave 1.1 g of a liquid whose gpc analysis indicated the presence of *ca.* 60% 2-hexanol, 35% starting dione, and 5% another substance. Isolation of the latter by preparative gpc and comparison of the material with authentic 2,5-dimethyltetrahydrofuran (**13a**) stereoisomers[9] (ir, pmr, gpc) showed it to be **13a**.

A mixture of 180 mg of 2,2,7,7-tetramethyloctane-3,6-dione (**7b**), 15 g of amalgamated zinc, and 60 ml of 6.5 N hydrochloric acid in 15 ml of methanol was stirred at room temperature for 5.5 hr. Work-up as above gave 154 mg of liquid whose gpc analysis showed the absence of starting compound and the presence of four components in 11, 65, 14, and 12% yields. Their isolation by preparative gpc gave respectively 2,5-di-*t*-butylfuran [ir and pmr spectra identical with those cited in the literature];[7] liquid 2,5-di-*t*-butyltetrahydrofuran (**13b**) stereoisomers [pmr δ 0.88 (s, 9, *t*-butyl H's), 0.89 (s, 9, *t*-butyl H's of other isomer), 1.62 (m, 4, methylenes), 3.45 (m, 2, methines); *m/e* 184 (M), 183 (M − 1, base peak)]; *trans*-2,2,7,7-tetramethyl-5-octen-3-ol (**14**) [mp 53–55°; pmr δ 0.92 (s, 9, methyls), 1.01 (s, 9, methyls), 2.1 (m, 2, methylene), 3.20 (q, 1, J = 10.0, 2.5 Hz, oxymethine), 5.43 (q, 1, J = 7.5, 6.0 Hz, olefinic H), 5.52 (s, 1, olefinic H), double resonance (the 2.1 signal coupled with the 3.20 and 5.43 signals)].

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.26; H, 13.02.

The fourth substance was 2,2,7,7-tetramethyl-3-octanol (**15**): mp 80–81°; pmr δ 0.90 (s, 18, methyls), 1.1–1.5 (m, 6, methylenes), 3.2 (m, 1, methine).

Anal. Calcd for $C_{12}H_{26}O$: C, 77.35; H, 14.06. Found: C, 77.06; H, 13.75.

Diketones 16, 17a, and 18.—A mixture of 75 mg of dione **3** and 200 mg of selenium dioxide in 24 ml of methanol was refluxed for 44 hr.[10] It was then decanted from precipitated selenium, diluted with water, and extracted with methylene chloride. The extract was washed with water, dried, and evaporated. Chromatography of the residue on 2 g of silica gel topped by a layer of precipitated silver yielded a 25-mg fraction whose gpc analysis showed the presence of one component and a 50-mg fraction containing more than 90% (by gpc) starting material. Distillation of the product gave yellow, liquid 2,6,6-trimethyl-2-cycloheptene-1,4-dione (**16**): pmr δ 1.12 (s, 6, saturated methyls), 2.01 (d, 3, J = 2.0 Hz, olefinic Me), 2.62 (s, 2, methylene), 2.69 (s, 2, methylene), 6.42 (d, 1, J = 2.0 Hz, olefinic H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.94; H, 8.56.

A mixture of 166 mg of enolone **2b**[2] [pmr δ 1.06 (s, 3, Me), 1.22 (s, 3, Me), 1.77 (d, 3, J = 2.0 Hz, olefinic Me), 4.35 (d, 1, J = 3.0 Hz, oxymethine), 6.51 (q, 1, J = 3.0, 2.0 Hz, olefinic H)] and 60 mg of 10% palladium–charcoal in 40 ml of ethanol was hydrogenated at atmospheric pressure and room temperature. After an uptake of one hydrogen equivalent the mixture was filtered and the filtrate evaporated. Chromatography of the residue, 135 mg, on silica gel and elution with 1:1 petroleum ether–ether gave 45 mg of a liquid whose distillation led to ketol **17b**: ir (neat), OH 2.90 (m), C=O 5.92 (s) μ; pmr δ 1.04 (d, 3, J = 6.5 Hz, Me), 1.11 (s, 3, cyclopropyl Me), 1.19 (s, 3, cyclopropyl Me), 2.49 (septet, 1, J = 6.5 Hz, α-ketomethine), 3.48 (m, 1, oxymethine).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.56.

Jones reagent,[11] 1.5 ml, was added over a 30-min period to a solution of 250 mg of ketol **17b** in 40 ml of acetone at −50°. After an additional 15 min 2 ml of methanol was added and the mixture allowed to come to room temperature slowly. Methylene chloride, 50 ml, and solid sodium bicarbonate were added, and the mixture was shaken and filtered. The filtrate was dried and evaporated and the residue chromatographed on silica gel. Elution with 4:1 petroleum ether–ether gave 197 mg of an oil [ir (neat) C=O 5.92 (s) μ] whose distillation yielded diketone **17a**: mp 49–50°; pmr δ 1.10 (d, 3, J = 6.5 Hz, Me), 1.28 (s, 6, cyclopropyl methyls), 2.1–2.7 (m, 3, α-ketomethylene, α-ketomethine).[12]

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.56; H, 8.68.

A solution of 100 mg of enolone **2b** in 25 ml of 0.07 N sodium hydroxide solution was stirred at room temperature for 5 hr. Upon neutralization with hydrochloric acid it was extracted with methylene chloride. The extract was dried and evaporated. Chromatography of the residue, 74 mg, on silica gel and elution with 10:1 petroleum ether–ether yielded 27 mg of a colorless oil whose distillation gave liquid epoxy diketone **18**: ir (neat) C=O 5.87 (s) μ; pmr δ 1.10 (s, 3, cyclopropyl Me), 1.31 (s, 3, cyclopropyl Me), 1.51 (s, 3, epoxy Me), 1.98 (s, 2, cyclopropyl Hs), 3.37 (s, 1, epoxy H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.71.

A solution of 25 mg of **17a** and 30 mg of potassium hydroxide in 21 ml of methanol was kept at 0–5° for 1.5 hr. Work-up as above gave 18 mg of **18**.

Reductions by Zinc in Acetic Acid.—A mixture of 0.40 g of dione **4**[3] and 1 g of zinc dust in 20 ml of glacial acetic acid was stirred at room temperature for 5 hr. It then was poured into ice water and extracted with methylene chloride. The extract was washed with dilute sodium hydroxide solution, dried, and evaporated. Sublimation of the solid residue, 0.40 g, gave diketone **5**: mp 255° dec; ir (CCl_4) C=O 5.72 (s) μ; pmr δ 1.8–2.0 (m, 2, methylene), 2.1–2.3 (broad s, 4, methines), 2.6–2.8 (broad s, 4, α-ketomethylenes), 2.7–2.9 (m, 2, α-ketomethines).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.84; H, 6.79.

A mixture of 2.00 g of diketone **2a**[2] [pmr δ 1.32 (s, 6, cyclopropyl methyls), 1.96 (d, 3, J = 2.0 Hz, olefinic Me), 2.31 (s, 2, cyclopropyl H's), 6.49 (d, 1, J = 2.0 Hz, olefinic H)] and 4 g of zinc dust in 30 ml of glacial acetic acid was stirred at room temperature for 10 min. Work-up as above gave 1.75 g of gpc pure product whose distillation yielded liquid diketone **3**: ir (neat) C=O 5.85 (s) μ; pmr δ 0.99 (s, 3, Me), 1.08 (s, 3, Me), 1.12 (d, 3, J = 7.0 Hz, Me), 2.2–2.9 (m, 7, methylenes, methine).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.57; H, 9.50.

A mixture of 9.5 mg of **16** and 0.5 g of zinc dust in 15 ml of glacial acetic acid was stirred at room temperature for 5 min. Work-up as above gave 8 mg of a liquid identified by gpc and ir as diketone **3**.

A mixture of 60 mg of **17a** and 1 g of zinc dust in 20 ml of glacial acetic acid was refluxed for 12 hr. During this time 3 g of zinc dust and 10 ml of glacial acetic acid were added. Work-up as above gave 35 mg of a liquid identified by gpc, ir, and pmr as diketone **3**.

(9) D. Gagnaire and P. Monzeglio, *Bull. Soc. Chim. Fr.*, 474 (1965).

(10) *Cf.* C. S. Barnes and D. H. R. Barton, *J. Chem. Soc.*, 1419 (1953).

(11) K. Bowden, E. R. H. Jones, I. M. Heilbron, and B. C. L. Weedon, *ibid.*, 39 (1946).

(12) Jones oxidation of **17b** at room temperature led to enedione **2a**.

A mixture of 6 mg of **18** and 0.5 g of zinc dust in 20 ml of glacial acetic acid was refluxed for 1.5 hr. During this time 1.5 g of more zinc dust was added in portions. Work-up as above gave 5 mg of a liquid identified by gpc and ir as diketone **3**.

Disproportionation of Diketone 17a.—A solution of 25 mg of **17a** and 30 mg of potassium hydroxide in 28 ml of methanol was kept at 0° under nitrogen for 1 hr. It was neutralized with 6.5 *N* hydrochloric acid, diluted with 30 ml of water, and extracted with methylene chloride. The extract was dried and evaporated. Chromatography of the residue, 23 mg, on silica gel and elution with 6:1 petroleum ether–ether yielded 8 mg of a solid identified by gpc and ir as diketone **2a**, while elution with 3:1 petroleum ether–ether gave 7 mg of a liquid identified as dione **3** by gpc and ir.

Registry No.—**1**, 637-88-7; **3**, 25237-81-4; **5**, 25282-60-4; **8**, 25237-82-5; **9**, 25237-83-6; **14**, 25237-84-7; **15**, 25237-85-8; **16**, 25282-56-8; **17a**, 25237-86-9; **17b**, 25237-87-0; **18**, 25237-88-1.

Acknowledgment.—The authors are indebted to the Eli Lilly and Co. for support of this work.

Permanganate Oxidations. V. Kinetics and Mechanisms of the Oxidation of Mandelate Anions[1,2]

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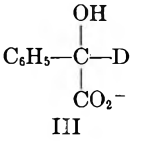
The kinetics of the permanganate oxidation of mandelic acid were examined over the pH range of 7.3 to 13.65 *via* spectrophotometric stopped-flow techniques. The reaction appears to proceed through three different paths. Presumably oxidative decarboxylation, to give benzaldehyde and carbon dioxide, and a reaction independent of hydroxide ion concentration occur between pH 7.3 and 12.7. Above pH 12.7, where phenylglyoxylic acid is formed, the reaction shows a first-order dependence on hydroxyl ion concentration and the rate expression is $v = k$[mandelate anion][OH^-][MnO_4^-]. The mandelate anion exhibits a kinetic isotope effect of 3.15 and 5.45 at pH 13.3 and 13.6, respectively. A positive salt effect is observed at pH 13.3. Correlation of the second-order rate constants with σ^n and σ^0 substituent constants gives ρ values of 1.0 and 0.97, respectively. The $\Delta H^{\pm}$ and $\Delta S^{\pm}$ for four different mandelate anions varied from 6.6 to 7.7 kcal/mol and −33.3 to −38.2 eu. The kinetic data, at pH greater than 12.7, is consistent with either a hydride transfer from the mandelate dianion to permanganate or a hydrogen atom abstraction from the mandelate dianion by permanganate in the rate-determining step.

Although the kinetics and mechanisms of the permanganate oxidation of malic acid,[3] tartaric acid,[4,5] citric acid,[6] mandelic acid,[7] and lactic acid[8,9] have been investigated in neutral and acid media, no mechanistic studies have been reported concerning the permanganate oxidation of hydroxy acids in alkaline media. Permanganate oxidizes the mandelate anion (I) to phenylglyoxylic acid (II) under basic conditions (eq 1).[10] In contrast, when mandelic acid is oxidized

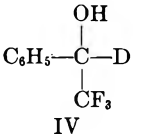
$$\underset{\text{I}}{C_6H_5CHOHCO_2^-} + 2MnO_4^- + 2OH^- \longrightarrow \underset{\text{II}}{C_6H_5C(=O)CO_2^-} + 2MnO_4^{2-} + 2H_2O \quad (1)$$

in acid solution, oxidative decarboxylation occurs to give benzaldehyde and carbon dioxide.[7] In order to obtain a more detailed mechanistic picture of the permanganate oxidation of the mandelate anion (I), we have examined the kinetics of the reaction from pH 7.3 to 13.65 *via* spectrophotometric stopped-flow techniques.

The permanganate oxidation of α-deuteriomandelate anion (III) is also of interest because of its close structural similarity to IV which gives a remarkably



III



IV

large k_H/k_D of 16.1 in alkaline permanganate oxidations.[11–13]

Experimental Section

Reagents.—Distilled water was purified by passing through two type R-2 ion-exchange columns.[14] Standard volumetric (Acculute) sodium hydroxide (CO_2 free) concentrate was diluted to the specified volume for the desired pH. Potassium permanganate stock solutions were also prepared from standard volumetric solutions (Acculute). The stock solution was stored under nitrogen, and the absorbancy index was checked before each set of kinetic runs. Reagent grade sodium chloride (Mallinckrodt), potassium nitrate (Mallinckrodt), and potassium sulfate (Mallinckrodt) were used without further purification to adjust ionic strength. All solutions were prepared immediately before use, and the pH was measured potentiometrically.

Mandelic Acid (Matheson Coleman and Bell) was recrystallized from benzene before use, mp 118–119° (lit.[15] mp 119.5–120.5°).

Substituted Mandelic Acids.—Mandelic acid derivatives were prepared *via* the imido ester (eq 2),[16] the cyanohydrin (eq 3),[17]

(1) Part IV: F. Freeman and A. Yeramyan, *J. Org. Chem.*, **35**, 2061 (1970).

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(5) G. V. Bakore and R. Shanker, *Curr. Sci.*, **28**, 279 (1959).

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(7) G. V. Bakore, R. Shanker, and U. Goyal, *ibid.*, **1**, 331 (1963).

(8) S. Senent-Perez, L. Ramos, and H. Sanz-Garcia, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **53**, 573, 583 (1957); *Chem. Abstr.*, **54**, 1992 (1960).

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(10) C. D. Hurd and R. W. McNamee, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1941, p 244.

(11) R. Stewart and R. Van der Linden, *Tetrahedron Lett.*, **2**, 28 (1960).

(12) R. Stewart and R. Van der Linden, *Discuss. Farday Soc.*, 211 (1960).

(13) J. L. Kurz, *J. Amer. Chem. Soc.*, **86**, 2229 (1964).

(14) Illinois Water Treatment Co., Rockford, Ill.

(15) C. R. Zanesco, *Helv. Chem. Acta*, **49**, 1002 (1966).

(16) G. Barger and A. J. Ewins, *J. Chem. Soc.*, **95**, 552 (1908).

(17) S. S. Jenkins, *J. Amer. Chem. Soc.*, **53**, 2341 (1931).

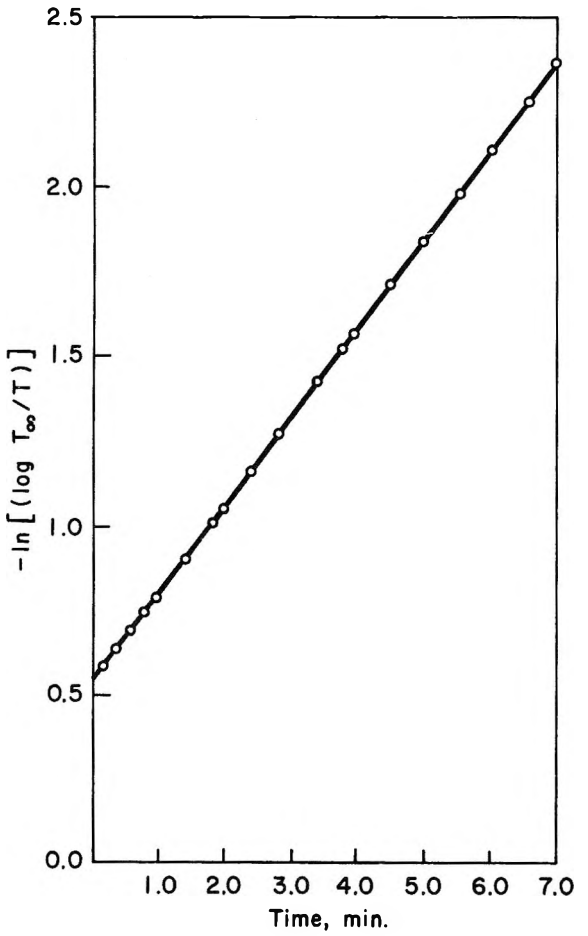


Figure 1.—A typical pseudo-first-order kinetic plot. The conditions are [mandelate anion] = 4.0×10^{-2} *M*, [OH^-] = 0.20 *M*, [MnO_4^-] = 4.0×10^{-4} *M*, μ = 0.5 *M*, λ = 510 mμ, temp 25.0°.

$$\text{RCHO} \xrightarrow[3.\ \text{EtOH, HCl}]{1.\ \text{NaHSO}_3\ 2.\ \text{HCN}} \text{RCHOHC(OEt)=NH·HCl} \xrightarrow[2.\ \text{KOH, }\Delta\text{, H}^+]{1.\ \text{H}_2\text{O, }\Delta} \text{RCHOHCOOH} \quad (2)$$

$$\text{RCHO} + \text{HCN} \longrightarrow \text{RCHOHCN} \xrightarrow{\text{HCl, }\Delta} \text{RCHOHCOOH} \quad (3)$$

$$4\text{-Br-C}_6\text{H}_5\text{COCH}_3 + \text{Br}_2 \longrightarrow 4\text{-Br-C}_6\text{H}_5\text{COCHBr}_2 \xrightarrow[2.\ \text{H}^+]{1.\ \text{OH}^-} 4\text{-Br-C}_6\text{H}_5\text{CHOHCOOH} \quad (4)$$

and the dibromo ketone (eq 4).[18] The deuterated acids were prepared according to the exchange procedure of Kemp and Waters.[19] Examination of the pmr spectra showed the complete disappearance (98–99%) (to within the limitations of the technique) of the α-proton signal. Table I summarizes the synthetic data.[16-23]

Apparatus and Kinetic Method.—The rate of disappearance of permanganate was followed spectrophotometrically, at 510 and 522 mμ, in a stopped-flow reactor.[24] The Beckman DU spectrometer was coupled to a Bristol strip chart recorder (0.2 sec for full-scale deflection and chart speeds to 120 in./min) or a Sargent Model SRLG recorder *via* an energy recording adapter.

The kinetics were studied under pseudo-first-order conditions, and the rate constants were obtained from the slopes of plots of $-\ln[\log(T_\infty/T)]$ against time where T_∞ is the per cent transmission at a point just before colloidal manganese dioxide begins to form (Figure 1). An IBM 1620 computer was used for all calculations,[25] and all rate constants given in the tables are the average of two or more determinations.

TABLE I

METHODS OF PREPARATION OF MANDELIC ACID DERIVATIVES

Substituent	Method of preparation[a]	Mp, °C Obsd	Mp, °C Lit.
2-Cl	Imido ester[b]	84–85	85.0–85.5[e]
4-Cl	Cyanohydrin[c]	120.5–121	120.5–121[c]
4-Br	Dibromo ketone[d]	118.5–120	117–119[d]
4-F[a,e]		135–136.5	138.5[d]
4-CH_3	Cyanohydrin[c]	144.5–145.5	145–145.5[f]
4-OCH_3	Imido ester[b]	105.5–107.5	108[g]
3,4-OCH_2O–	Imido ester[b]	158–158.5	162[h]
α-C_6H_5	Benzylic acid rearrangement[i]	149–150	149–150[i]
α-D	Exchange[j]	118.5–120	
4-Cl-α-D	Exchange[j]	115–117	

[a] Benzene was used as recrystallizing solvent. [b] Reference 16. [c] Reference 17. [d] Reference 18. [e] Reference 20. [f] Reference 21. [g] Reference 22. [h] Reference 10. [i] Reference 23. [j] Reference 19.

Results

Order of Reaction.—The rate law was determined by measuring the effect of varying the concentrations of the reactants on the rate constants. The effects of mandelate anion (I) and permanganate concentrations are summarized in Table II. A first-order dependence on the concentration of mandelate anion (I) is observed over a tenfold range of concentration at constant hydroxide and constant permanganate ion concentrations. A plot of the pseudo-first-order rate constant (k_ψ) *vs.* the concentration of I gives a straight line passing through the origin (Figure 2) which also indicates a first-order dependence on the concentration of I. The first-order dependence on permanganate concentration is demonstrated by the constancy of the

TABLE II

RATE DATA FOR THE OXIDATION OF MANDELATE ANION AT pH 13.3[a]

[Mandelate anion] × 10^2 *M*	[MnO_4^-] × 10^4 *M*	k_ψ[b] × 10^2 sec^{-1}	k_2[c] × 10^1 M^{-1} sec^{-1}
2.0	4.0	0.65	3.25
4.0	4.0	1.28	3.20
8.0	4.0	2.57	3.20
10.0	4.0	3.05	3.05
12.0	4.0	3.55	2.96
20.0	4.0	5.85	2.93
4.0[d]	4.0	1.28	3.20
4.0[d]	8.0	1.25	3.13
4.0[d]	12.0	1.28	3.20
4.0[e]	4.0	1.35	3.38
4.0[e]	6.0	1.25	3.13
4.0[e]	7.0	1.22	3.04

[a] λ = 510 mμ, μ = 0.5, [OH^-] = 0.20 *M*, 10-mm cell. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = k_ψ/[mandelate anion]. [d] 4-mm cell. [e] λ = 522 mμ.

(18) J. J. Klingenberg, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., p 110.
(19) T. J. Kemp and W. A. Waters, *J. Chem. Soc.*, 1192 (1964).
(20) Aldrich Chemical Co.
(21) J. L. Riebsomer, J. Irvine, and R. Andrews, *J. Amer. Chem. Soc.*, **60**, 1015 (1938).
(22) J. J. Klingenberg, J. P. Thole, and R. D. Lingg, *J. Chem. Eng. Data*, **11**, 94 (1966).
(23) S. I. Vogel, "A Textbook of Practical Organic Chemistry," Wiley, New York, N. Y., 1966, p 715.
(24) F. Freeman, A. Yeramyan, and F. Young, *J. Org. Chem.*, **34**, 2438 (1969).
(25) K. B. Wiberg, "Computer Programming for Chemists," W. A. Benjamin, New York, N. Y., 1965, p 168 ff.

pseudo-first-order rate constant (k_ψ) at 510 and 522 mμ over a 4 to 12 × 10^{-4} M permanganate concentration range.

The effect of hydroxide ion concentration on the rate of reaction (Figure 3) was determined giving the data in Table III. It is seen that the rate does not increase

TABLE III
EFFECT OF HYDROXIDE ION CONCENTRATION ON THE RATE OF OXIDATION OF MANDELATE ANION[a]

pH	[OH⁻], M	k_ψ[b] × 10^3 sec⁻¹	k_2[c] × 10^2 M^{-1} sec⁻¹	$k_2 - k_0$[d] × 10^2 M^{-1} sec⁻¹	k_3,[e] l.² mol⁻² sec⁻¹
7.31[f]	2.19 × 10^{-7}	3.67	9.18		
8.60[f]	3.98 × 10^{-6}	3.83	9.58		
9.64[f]	4.37 × 10^{-5}	4.83	12.1		
11.0[f]	10^{-3}	3.17	7.93		
12.7	0.05	4.33	10.8	6.5	1.30
13.0	0.10	7.00	17.5	13.2	1.32
13.3	0.20	12.8	32.0	27.7	1.38
13.4	0.25	15.7	39.3	34.8	1.39
13.6	0.40	23.5	58.8	54.3	1.36
13.65	0.45	26.0	65.0	60.7	1.35

[a] [$C_6H_5CHOHCOO^-Na^+$] = 4.0 × 10^{-2} M, [MnO_4^-] = 4.0 × 10^{-4} M, μ = 0.5 M, λ = 510 mμ, temp 25.0°, 10-mm cell. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = k_ψ/[$C_6H_5CHOHCOO^-Na^+$]. [d] Intercept of a plot of k_2 *vs.* [OH^-] gives k_0. [e] Third-order rate constant, $(k_2 - k_0)/[OH^-]$. [f] Influenced by disproportionation of manganate [Mn^{VI}] and/or hypomanganate [Mn^V].[26]

appreciably from pH 7.3 to 12.7 which is consistent with a zero-order dependence on hydroxide ion concentration for this pH range. Indeed, a plot of the second-order rate constant ($k_2 = k_\psi/[I]$) *vs.* hydroxide ion concentration between pH 12.7 and 13.65 gives a straight line that does not go through the origin. This is also consistent with both zero-order and first-order terms describing the effect of hydroxyl ion concentration on the rate of oxidation. The rate law then appears to be

$$\frac{-d[MnO_4^-]}{dt} = k_0[\text{mandelate anion}][MnO_4^-] + k[\text{mandelate anion}][OH^-][MnO_4^-] \quad (5)$$

where k_0 = 4.37 × 10^{-2} l. mol⁻¹ sec⁻¹ and k = 1.36 l.² mol⁻² sec⁻¹. However, the intercept (k_0) is smaller than the average k_2 value (9.92 × 10^{-2} l. mol sec⁻¹) observed over the pH range of 7.3–12.7. If one assumes that oxidative decarboxylation (eq 6) is also operative in

$$C_6H_5CHOHCO_2H \xrightarrow{MnO_4^-} C_6H_5CHO + CO_2 \quad (6)$$

slightly basic solution,[7] then it would appear that the observed rate constant is composed of k_0, k, and a rate constant for eq 6.[26] The rate would then appear to be

$$\frac{-d[MnO_4^-]}{dt} = k_n[\text{mandelic acid}][MnO_4^-] + k_0[\text{mandelate anion}][MnO_4^-] + k[\text{mandelate anion}][OH^-][MnO_4^-] \quad (7)$$

(26) (a) It is difficult to attempt to elucidate the full significance of the rate constants over the unbuffered pH range of 7.3–12.7 owing to the number of possible reactions that can occur in the permanganate oxidation of I. Further complications are caused in spectrophotometric studies by the precipitation of colloidal manganese dioxide and the disproportionation of manganate [Mn^{VI}] and hypomanganate [Mn^V]. Anomalous kinetic behavior has been observed, *via* titrimetric techniques, around pH 11 for the permanganate oxidation of formate anion[26b,c] and piperonal.[26d] (b) K. B. Wiberg and R. Stewart, *J. Amer. Chem. Soc.*, **78**, 1214 (1955). (c) R. P. Bell and D. P. Onwood, *J. Chem. Soc. B*, 150 (1967). (d) K. B. Wiberg and R. Stewart, *J. Amer. Chem. Soc.*, **77**, 1768 (1955).

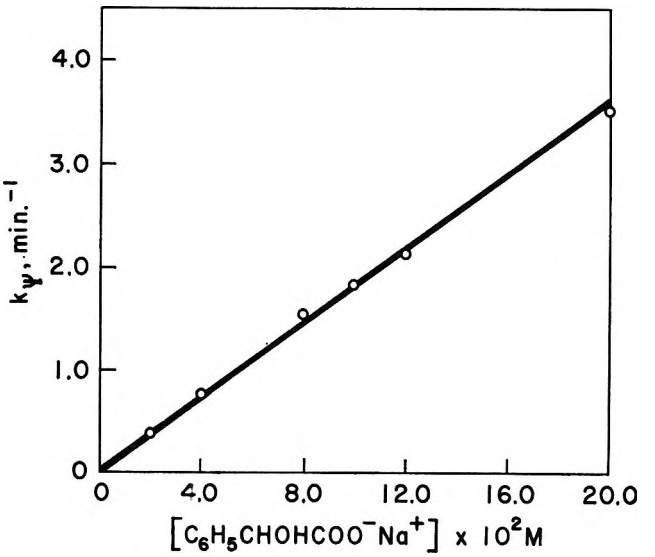


Figure 2.—Effect of mandelate anion concentration on the pseudo-first-order rate constants for the permanganate oxidation at 25.0°.

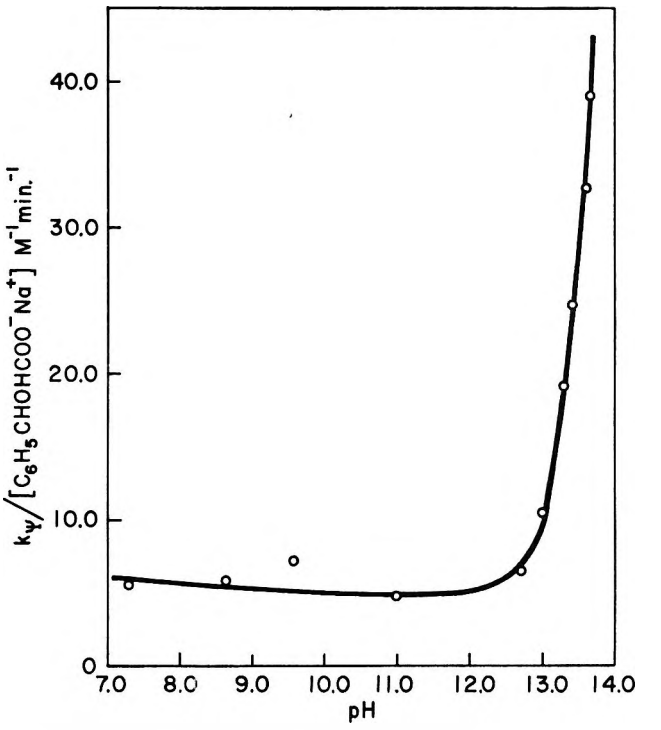


Figure 3.—Effect of pH on the rate of the permanganate oxidation of mandelate anion.

where k_n is presumably the constant for oxidative decarboxylation, k_0 is the rate constant for the uncatalyzed reaction, and k is the rate constant for the base-catalyzed reaction.

A plot of $k_2 - k_0$ against [OH^-] gives a straight line passing through the origin (Figure 4) which further supports the first-order dependence on hydroxide ion concentration above pH 12.7. The rate law above pH 12.7 then appears to be

$$\frac{-d[MnO_4^-]}{dt} = k[\text{mandelate anion}][OH^-][MnO_4^-] \quad (8)$$

Activation Parameters.—Table IV gives the thermodynamic data for the permanganate oxidation of I and its 4-bromo (V), 4-chloro (VI), and 4-methyl (VII) derivatives.

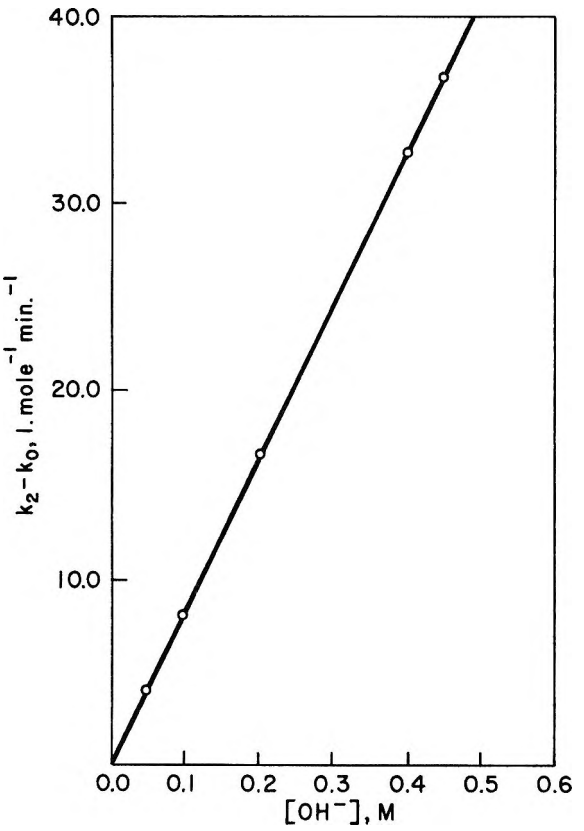


Figure 4.—Effect of hydroxide ion concentration on the rate of permanganate oxidation of mandelate anion. The conditions are [mandelate anion] = 4.0×10^{-2} M, [MnO_4^-] = 4.0×10^{-4} M, temp 25.0°.

TABLE IV
ACTIVATION PARAMETERS FOR THE PERMANGANATE OXIDATION OF MANDELATE ANIONS[a]

Mandelate anion derivative	$\Delta H^{\pm}$, kcal/mol	$-\Delta S^{\pm}$, eu
4-H	7.5	35.5
4-Br	7.7	33.3
4-Cl	6.6	37.2
4-CH_3	6.8	38.2

[a] [Anion] = 4.0×10^{-2} M, [MnO_4^-] = 4.0×10^{-4} M, [OH^-] = 0.20 M, μ = 0.5 M, λ = 510 mμ, temp 25.0°.

Effects of Ionic Strengths.—Table V shows that there is a positive salt effect in the permanganate oxidation of I with sodium chloride, potassium nitrate, and potassium sulfate.

TABLE V
RATE DEPENDENCE ON IONIC STRENGTH[a]

	$k_2^b \times 10^1$ l. mol^{-1} sec^{-1}		
μ	NaCl	KNO_3	K_2SO_4
0.25	2.13	1.98	1 98
0.50	3.22	3.25	2.80
0.75	4.35	4.60	3.68
1.00	5.60	5.10	4.70

[a] [$C_6H_5CHOHCOO^-Na^+$] = 4.0×10^{-2} M, [MnO_4^-] 4.0×10^{-4} M, [OH^-] = 0.20 M, λ = 510 mμ, temp 25.0°. [b] $k_2 = k_\psi/$[$C_6H_5CHOHCOO^-Na^+$].

Kinetic Isotope Effects.—The isotope effects for the permanganate oxidation of α-deuteriomandelate anion (III) and 4-chloro-α-deuteriomandelic anion (VIII) are given in Table VI.

TABLE VI
KINETIC ISOTOPE EFFECTS IN THE PERMANGANATE OXIDATION OF α-DEUTERIOMANDELATE ANIONS AT 25.0°

Mandelate anion	pH	k_H/k_D[a]
III	13.3	3.15
III	13.6	5.45
VIII	13.3	2.79

[a] $k_2 = k_\psi/$[mandelate anion].

Linear Free-Energy Relationships.—Correlation of log k_2 with σ *normal* values[27,28] gave a ρ value of 0.996 with a correlation coefficient (r) of 0.970 and a standard deviation (s) of 0.047. A slightly better correlation was obtained with σ° values[27,29] giving a ρ of 0.97 with r = 0.975 and s = 0.043. The data are summarized in Table VII.

TABLE VII
EFFECTS OF SUBSTITUENTS ON THE RATE OF PERMANGANATE OXIDATION OF MANDELATE ANIONS[a]

Substituent	$k_2^b \times 10^1$ M^{-1} sec^{-1}	Log k_2
4-CH_3	2.92	0.4654
4-H	3.22	0.5079
4-F	4.70	0.6721
4-Cl	6.52	0.8143
4-Br	6.82	0.8338
2-Cl[c]	2.80	0.4472
OCH_3[c]	3.85	0.5855
3,4-OCH_2O–[c]	13.5	1.130

[a] λ = 510 mμ, pH = 13.3, [OH^-] = 0.20 M, μ = 0.5 M, temp 25.0°. [b] $k_2 = k_\psi/$[mandelate anion]. [c] Not used in correlation.

Attempted Oxidation of Benzilic Acid.—At 25.0° benzilic acid (4.0×10^{-2} M) is essentially inert to permanganate (4.0×10^{-4} M) at a pH of 13.3.

Discussion

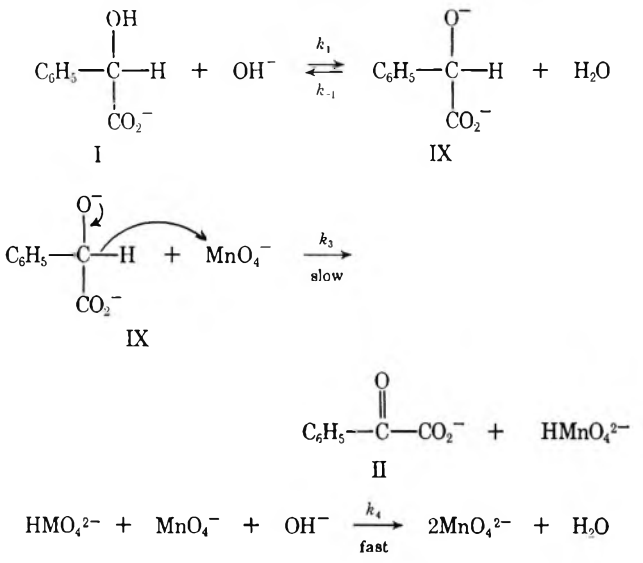
It is clear from the kinetic data described above that at least three mechanisms are operative in the permanganate oxidation of I over the pH range of 7.3 to 13.65. The reactions from pH 7.3 to 12.7 are independent of hydroxyl ion concentration and the reaction pathway above pH 12.7 is dependent on the first power of hydroxide ion concentration. Since the hydroxy group of I is only partly ionized under the reaction conditions, the kinetic data suggest a scheme in which the mandelate dianion (IX) is formed in an equilibrium step and is oxidized by permanganate in the rate-determining step. A reasonable mechanism conforming to the observed kinetics between pH 12.7 and 13.65 is shown in Scheme I. The rate equation derived from this mechanism is

$$v = k[\mathrm{IX}][MnO_4^-] = kK_{eq}\frac{[\mathrm{I}][OH^-][MnO_4^-]}{[H_2O]} = \frac{kK_{eq}}{k_{eq'}}[\mathrm{I}][OH^-][MnO_4^-] \quad (9)$$

where K_{eq} is the equilibrium constant for the formation of IX. Thus, it can be seen that the mechanism

(27) H. van Belkkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim Pays-Bas*, **78**, 815 (1959).
(28) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(29) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

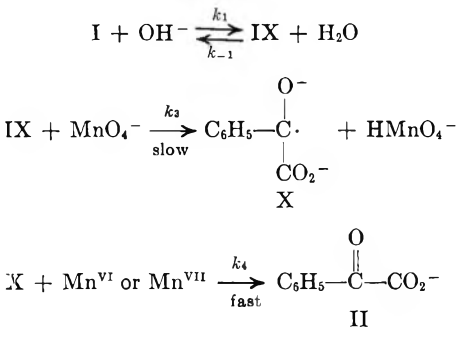
SCHEME I



postulated in Scheme I can account for the observed rate law (eq 8).[30]

Although Scheme I depicts a reasonable mechanistic pathway for the permanganate oxidation of I, the anion-radical mechanism shown in Scheme II also merits consideration.

SCHEME II



The observed kinetic isotope effects of 3.15 and 5.45 for the oxidation of I at pH 13.3 and 13.6, respectively, and the k_H/k_D value of 2.79 for VIII at pH 13.3 clearly demonstrates that the rate-limiting step must involve the cleavage of the carbon–hydrogen bond. These observations may be accounted for by either a two-electron oxidation (Scheme I) or a one-electron oxidation (Scheme II). It might appear that the observed isotope effects are more consistent with a two-electron oxidation (Scheme I) since it is known that very large kinetic isotope effects are generally obtained for reactions involving a hydrogen atom abstraction from the α position of alcohols and alkoxides anions.[31] For example, the permanganate oxidation of IV,[11,12] XI,[12] and XII[13,32] have k_H/k_D values of 16.1, 19.1, and 14,

$(CF_3)_2CHO^-$ XI CF_3CHOHO^- XII $(HCO_2^-)Co^{III}(NH_3)_5$ XIII

respectively. The suggestion by Stewart that these oxidations may involve hydrogen atom abstraction rather than hydride anion has appeared recently.[33,34] Furthermore, the k_H/k_D for the hydrogen abstraction in eq 10 is 17,[35] and the k_H/k_D for the one-electron per-

$$CH_3CH_2OH + H\cdot \longrightarrow CH_3\dot{C}HOH + H_2 \qquad (10)$$

manganate oxidation of XIII is 10.1.[36] However, this is not the complete picture since I is not completely ionized (to IX) at pH 13.3 and 13.6. Therefore, the observed k_H/k_D is probably not the maximum value for the oxidation of IX. Indeed, at pH 13.3 one is probably observing a secondary isotope effect of the *second kind*[37] for the ionization of I as well as a primary isotope effect for the oxidation of IX. At pH 13.6, the equilibrium lies farther toward IX and the k_H/k_D value of 5.45 is probably closer to the actual value for the permanganate oxidation of IX. Similar variations in the deuterium isotope effects, as a function of pH, have been reported for the permanganate oxidation of IV[12] and fluoral hydrate.[32]

The observed rate of oxidation is expected to be sensitive to the effect of ring substitution on the preequilibrium ionization step. It should be noted that two opposing substituent effects are operative in the permanganate oxidation of IX. Electron-attracting groups should facilitate the ionization of I ($\rho = +$) and retard hydride transfer from IX to permanganate.

$$\log\left(\frac{k}{k_0}\right)_{obsd} = \log\left(\frac{K}{K_0}\right)_{eq} + \log\left(\frac{k}{k_0}\right)_{rate} = \sigma(\rho_{eq} + \rho_{rate})$$

The good correlations with σ^n and σ^0 substituent constants show that the ρ value of approximately 1.0 arises only from direct electrostatic and polar effects. Although free-radical reactions may be correlated by σ^n and σ^0 parameters,[38] the observed ρ ($\rho \cong 1.0$) probably results from ρ_{eq} being of opposite sign and larger size than ρ_{rate}.

A mechanism involving species of the same charge in the rate-determining step is consistent with the positive salt effects observed with sodium chloride, potassium nitrate, and postassium sulfate (Table V).

The thermodynamic parameters for the oxidation of mandelate anions (Table IV), which are characterized by low enthalpies of activation ($\Delta H^{\pm}$ = 6.6 to 7.7 kcal/mol) and large negative entropies of activation ($\Delta S^{\pm}$ = −33.3 to −38.2 eu), are consistent with other permanganate reactions involving anions and dianions.[13,32,39,40] It has been postulated that the observed activation parameters also include the enthalpy and entropy of activation of the preequilibrium step.[40,41]

(30) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1963, p 216.

(31) R. Stewart, "Oxidation Mechanisms: Applications to Organic Chemistry," W. A. Benjamin, New York, N. Y., 1964, pp 16, 63.

(32) R. Stewart and M. Mocek, *Can. J. Chem.*, **41**, 1160 (1963).

(33) Reference 31, p 67.

(34) In an attempt to differentiate between a hydrogen atom abstraction mechanism and a hydride transfer mechanism in the permanganate oxidation of fluoral hydrate, Kurz[12] estimated the acidity of the activated complex (from transition state theory) and concluded that the reaction proceeded *via* a hydride anion transfer. However, the validity of this conclusion depends on the accuracy of the estimated acidities.

(35) C. Lifshitz and G. Stein, *J. Chem. Soc.*, 3706 (1962).

(36) V. Halpern and J. P. Candlin, *J. Amer. Chem. Soc.*, **85**, 2518 (1963).

(37) E. A. Halevi in "Progress in Physical Organic Chemistry," Vol. I., S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience, New York, N. Y., 1963, p 109 ff.

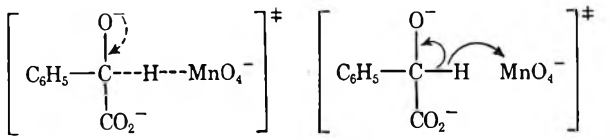
(38) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 35.

(39) F. Freeman, J. B. Brant, N. B. Hester, A. A. Kamego, M. L. Kasner, T. G. McLaughlin and E. W. Paull, *J. Org. Chem.*, **35**, 982 (1970).

(40) R. Stewart *J. Amer. Chem. Soc.*, **79**, 3057 (1957).

(41) More reliable[26b] rate coefficients for the hydroxide independent terms in eq 7 would enable one to calculate their contributions to the salt effects, the substituent effects, and the activation parameters.

Although the kinetic data presented are consistent with both Scheme I and II, the activated complex in Scheme I could be represented by XIV and the activated complex for Scheme II could be represented by XV. In view of the close analogy between Scheme I and II, the available data for the permanganate oxidation of alkoxide ions and the anions of aldehyde hydrates, it is not possible to differentiate between the hydride transfer mechanism and the hydrogen atom mechanism.



XIV XV

Registry No.—I, 769-61-9; I, 4-Br, 25296-24-6; I, 4-Cl, 25296-25-7; I, 4-CH_3, 25356-01-8.

Acknowledgment.—We would like to thank Professor S. S. Kuwahara of this department and Mr. A. A. Kamego[42] for obtaining the pmr spectra.

(42) Department of Chemistry, University of California, Santa Barbara, Calif.

A Novel Single-Step Sulfone Synthesis

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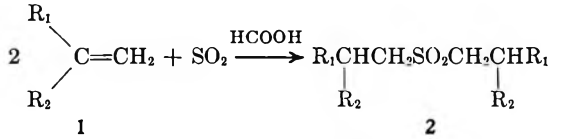
Received January 26, 1970

A recently reported synthesis of sulfones from olefins and sulfur dioxide in the presence of formic acid–tertiary amine "adducts" has been investigated. The reaction appears to be limited to monosubstituted olefins bearing an electron-withdrawing group. The sulfones are usually accompanied by the corresponding disulfides, which can be the major products under certain conditions. Disubstituted terminal olefins do yield disulfides. The solvent "adducts" were found to be azeotropes; in fact formic acid *per se* is not required, only formate ion. Mechanistically the intermediacy of sulfoxylic acid (H_2SO_2, formed by reduction of sulfur dioxide) in the generation of a sulfinic acid from the olefin is confirmed. The sulfone is formed by addition of the sulfinic acid to a second mole of olefin. Deuterium tracer work indicates that exchange of the protons α to the sulfinyl group occurs in the intermediate sulfinic acid. The deuterium tracer work also militates against a termolecular reaction of olefin, sulfur dioxide, and formate ion leading in one step to sulfinic acid and thus supports stepwise generation of sulfoxylic and sulfinic acids. There are several feasible mechanistic pathways for disulfide formation. The most likely route consists of reaction of elemental sulfur (formed by formate reduction of sulfur dioxide) and a mercaptan (probably arising *via* disproportionation of the corresponding sulfinic acid).

A recent patent reported that reaction of certain terminal olefins with sulfur dioxide in the presence of "adducts" of formic acid and trimethyl- or triethylamine affords sulfones in 13–63% yield with evolution of carbon dioxide.[1a] The report states that "adducts"[1b]



1 2

a, R_1 = H; R_2 = $CONH_2$
b, R_1 = H; R_2 = COOH
c, R_1 = H; R_2 = CN
d, R_1 = H; R_2 = $COOCH_3$
e, R_1 = CH_3; R_2 = $COOCH_3$
f, R_1 = CH_3; R_2 = $CONH_2$

of formic acid and a variety of other tertiary amines are not as effective. Formic acid and formamides were also utilized.

In view of the intriguing nature of this transformation, the lack of evidence for mechanistic speculations and our interest in the chemistry of formic acid,[2] we have examined the scope and mechanism of the reaction.

The Reaction.—"Adducts" of formic acid and tertiary amines have been used as reducing media in other processes.[3] They have also seen use in other applications.[4] Examination of the "adducts" of formic acid with trimethyl- and tributylamine by vpc, ir, and pmr revealed that no new covalent compounds were present. The only compounds present were formic acid and the tertiary amine. The molar ratio of the two components varied from amine to amine. Moreover, for a given amine the composition varied with distillation pressure. These data are interpreted as indicating that the "adducts" are really azeotropes. This is substantiated by the fact that synthetic mixtures of the two components are as effective in the reaction as the distilled materials.

Using acrylamide (**1a**) as starting material and the formic acid–trimethylamine azeotrope (3.0:1.0), the optimum temperature under our reaction conditions was found to be 100° at which a 61% yield of bis(2-carboxamidoethyl) sulfone (**2a**) was obtained. Variation of the formic acid–trimethylamine ratio appeared to have little effect on yield. The tertiary amines were not unique as cosolvents with the formic acid. Pyridine, secondary and primary amines, formamides, and ammonium and sodium formates were also satisfactory. These results suggested that the active species in the solvent was formate ion. This view was supported by the lack of reaction with neat formic acid, neat fromamide, and acetic acid–trimethylamine (3.0:1.0). Indeed solutions of sodium or ammonium formate in acetic acid were suitable (55% yield under conditions

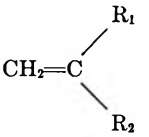
(1) (a) Farbenfabriken Bayer A.-G., German Patent 1,222,048 (1966); *Chem. Abstr.*, **65**, 13545e (1966). (b) A referee states that in German "adduct" means "loose addition product without forming covalent bonds" and in this context is correct (*vide infra*).

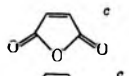
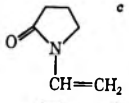
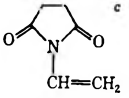
(2) H. W. Gibson, *Chem. Rev.*, **69**, 673 (1969).

(3) (a) M. Sekiya and K. Ito, *Chem. Pharm. Bull.*, **12**, 677 (1964); (b) M. Sekiya, Y. Harada, and K. Tanaka, *ibid.*, **15**, 833 (1967). See ref 2 for discussion of these and other uses of formic acid media as reducing agents.

(4) M. Sekiya, M. Tomic, and N. J. Leonard, *J. Org. Chem.*, **33**, 318 (1968). See also ref 2.

Table I
Scope of the Reaction with Olefin I

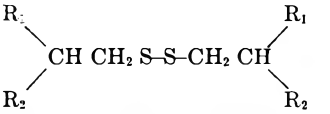


R_1	R_2	Conditions (Table VII)	Product	% yield
H	$CONH_2$	A	**2a**[d]	61
H	$CONH_2$	B[a]	**3a**[e]	44
H	COOH	A[a]	**2b**[f]	44
H	COOH	A	**2b**	6
			3b[g]	20
H	$COOCH_3$	A	**2d**[h]	52
			3c[i]	5
H	CN	A	**2c**[j]	12
H	$SO_2CH=CH_2$	A[a]	**4**[k]	80
CH_3	$COOCH_3$	C	**3d**[l]	34
H	$(CH_2)_7CH_3$	C[b]	Sulfur	81
H	C_6H_5	A[b]	Sulfur	
H	$COCH_2CH_3$	D[b]		
H	$CONH_2$	A[a]	**2a**	19
H	C_6H_5			
CH_3	$COOCH_3$	A[a]		
H	$(CH_2)_5CH_3$			
$ClCH=CCl_2$[c]		A[b]	Sulfur	53
trans-HOOCCH=CHCOOH[c]		A[a,b]		
$CH_3CH=CHCHO$[c]		C		
		A	Sulfur, succinic acid	5
		A[a]	Sulfur	31
		A[a]	Sulfur	78

[a] 3-hr addition. [b] Two-phase reaction. [c] Olefin structure in entirety. [d] Mp 228.5–229.5° (H_2O); lit.[1] mp 228°. *Anal.* Calcd for $C_6H_{12}N_2SO_4$: C, 34.60; H, 5.81; N, 13.46; S, 15.40. Found C, 34.68; H, 5.84; N, 13.44; S, 15.32. [e] Mp 176.0–178.0° (H_2O). *Anal.* Calcd for $C_6H_{12}N_2S_2O_2$: C, 34.59; H, 5.81; N, 13.45; S, 30.79. Found: C, 34.62; H, 5.80; N, 13.39; S, 30.85. [f] Mp 223.0–223.5° (H_2O); lit. mp 222–224° [N. Gunderman and C. Burba, *Chem. Ber.*, **94**, 2157 (1961)]; 223–225° [R. Dahnborn, *Acta Chem. Scand.*, **5**, 690 (1951)]; 220°.[1a] [g] Mp 156.0–157.5° (H_2O); lit. mp 154–155° [R. Dahnborn, *Acta Chem. Scand.*, **5**, 690 (1951); C. Buess, *J. Amer. Chem. Soc.*, **77**, 6613 (1955)]. *Anal.* Calcd for $C_6H_{10}S_2O_4$: C, 34.27; H, 4.79; S, 30.50. Found: C, 34.37; H, 4.76; S, 30.40. [h] Mp 111.8–112.5° (H_2O); lit. mp 115° [J. MacGregor and C. Pugh, *J. Chem. Soc.*, 736 (1950)]. *Anal.* Calcd for $C_8H_{14}SO_6$: C, 40.33; H, 5.92; S, 13.46. Found: C, 40.42; H, 5.88; S, 13.60. [i] Yellow liquid, analyzed after bicarbonate washing and drying; lit. yellow oil, no bp given; S, 27.9 [R. Pierson, A. Costanza, and W. Weinstein, *J. Polym. Sci.*, **17** 221 (1955)]. *Anal.* Calcd for $C_8H_{14}S_2O_4$: C, 40.32; H, 5.92; S, 26.91. Found: C, 40.46; H, 5.89; S, 26.78. [j] Mp 87.5–88.0° (H_2O); lit. mp 86°,[1a] 84° [J. Alexander and H. McCombie, *J. Chem. Soc.*, 1913 (1931)]. *Anal.* Calcd for $C_6H_8N_2SO_2$: C, 41.84; H, 4.68; N, 16.27; S 18.62. Found C, 41.86; H, 4.61; N, 16.12; S, 18.55. [k] Mp >330°, dec 300° (dil HNO_3); lit. mp >370°, dec 330° [W. Parham, H. Wynberg, and F. Ramp, *J. Amer. Chem. Soc.*, **75**, 2065 (1953)]. [l] Pale yellow liquid, bp 103–105° (0.08 mm). *Anal.* Calcd for $C_{10}H_9S_2O_4$: C, 45.09; H, 6.81; S, 24.08. Found: C, 44.91; H, 6.71; S, 24.16.

equivalent to those mentioned above). Because of the relative acidities of acetic and formic acid (pK_a of 4.75 *vs.* 3.75[5]) very little formic acid would be present in these solutions. Thus, while formic acid *per se* is not required, the formate ion is required.

In the case of acrylamide (**1a**) the solvent:substrate ratio was of consequence using formic acid–trimethylamine (3.0:1.0). In a run utilizing twice the normal amount of solvent, a new product was isolated in about the same yield as the sulfone **2a** under normal conditions. On the basis of spectral and elemental analyses this material proved to be disulfide **3a**. The formation of disulfides was not reported in the patent literature, although in some cases unidentified compounds were isolated.[1a] When acetic acid–ammonium formate was employed, no crossover to disulfide was observed at higher dilution, and the sulfone isolated was of higher purity than that obtained with formic acid–trimethylamine. Other olefins did not exhibit this crossover effect. It appears to be peculiar to the acrylamide reaction in formic acid–trimethylamide.

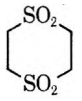


3a, R_1 = H; R_2 = $CONH_2$
b, R_1 = H; R_2 = COOH
c, R_1 = H; R_2 = $COOCH_3$
d, R_1 = CH_3; R_2 = $COOCH_3$
e, R_1 = CH_3; R_2 = $CONH_2$

The generality of the reaction was tested using a variety of olefins. These are summarized in Table I.

(5) "Handbook of Chemistry and Physics," 41st ed, Chemical Rubber Co., Cleveland, Ohio, 1960, p 1744.

Of the olefins tested only acrylonitrile, acrylic acid, methyl acrylate, and acrylamide yielded sulfones **2**. Divinyl sulfone yielded **4**. Except for acrylonitrile and



4

divinyl sulfone, disulfides **3** accompanied the sulfone products. Methyl methacrylate (**1e**) yielded only disulfide **3d**. In many cases where the olefins were unreactive, elemental sulfur was formed. Structural requirements of the olefin for sulfone formation appear to dictate that it be a monosubstituted ethylene bearing one of the following electron-withdrawing groups: CN, $CONH_2$, COOR, SO_2R. These structural requirements are similar to those stated previously[1a] with one important exception. It was reported that methacrylamide (**1f**) yielded (13%) sulfone **2f**. It was then concluded that 2,2-disubstituted terminal olefins are capable of undergoing the sulfone-forming reaction.[1a] However, our finding that methyl methacrylate (**1e**) yields not the corresponding sulfone **2e**, but rather disulfide **3d** casts doubt upon this conclusion. In the absence of any evidence for the assigned sulfone structure, it is possible that the compound previously isolated was disulfide **3e**. We did not prepare either of these compounds. It should be pointed out that C, H, and N elemental analyses will not distinguish between corresponding sulfones and disulfides (see Table I); a sulfur analysis is required. It, therefore, appears doubtful that disubstituted terminal olefins can serve as sulfone precursors in this process.

The physical properties and elemental analyses of the sulfones **2** and disulfides **3** are presented in Table I. Bis(2-carbomethoxypropyl) disulfide (**3d**) exhibited two peaks of 1.0:1.5 area ratio (in order of elution) on vpc. Separation of the components afforded two liquids with identical infrared spectra but for minor shifts and with pmr spectra identical except for small (~0.1 ppm) chemical shift differences. A distilled mixture of the liquids was subjected to elemental analysis which supported the contention that they were the *meso* and *dl* isomers of **3d**.

The pmr spectra were diagnostic for structure of the products resulting from reaction of the acrylic compounds. The sulfones showed somewhat distorted AX triplets at δ 3.1–3.2 and 3.7–3.8 assigned to methylene groups adjacent to the CN or COR and SO_2 groups, respectively. Sulfone **2b** had an eight-line A_2B_2 pattern. On the other hand, the disulfides all exhibited more complex splitting patterns due to the more nearly equal chemical shifts of the two sets of methylene protons. In disulfide **3a** a broad singlet was observed; with **3b** and **3c**, eight-line multiplets typical of A_2B_2 systems were recorded. No attempt was made to analyze these signals. Pmr spectral data are summarized in Table II.

The sulfones possessed typical peaks at about 1300 and 1150 cm^{-1} in the infrared (S–O stretch).

The mass spectra of sulfones **2a**, **2c**, and **2d** and disulfide **3a** were recorded. Sulfone **2a** appears to be noteworthy in that its spectrum (Table III) does not contain a peak corresponding to a parent ion (*m/e* 208),

TABLE II
PMR SPECTRA[a]

Compd	Chemical shift, δ
2a	3.18 (2 H, t, 7[b]), 3.80 (2 H, t, 7), ~7 (2 H, s)
2b[c]	3.21 (2 H, t, 6), 3.89 (2 H, t, 6)
2c	3.20 (2 H, t, 7), 3.74 (2 H, t, 7)
2d	3.08 (2 H, t, 7), 3.69 (2 H, t, 7), 3.91 (3 H, s)
3a	2.63 (broad s)
3b[c]	3.08 (8-line m)
3c	2.85 (4 H, 8-line m), 3.71 (3 H, s)
3d[d]	1.25 (3 H, d, 6), 2.82 (3 H, m), 3.68 (3 H, s)

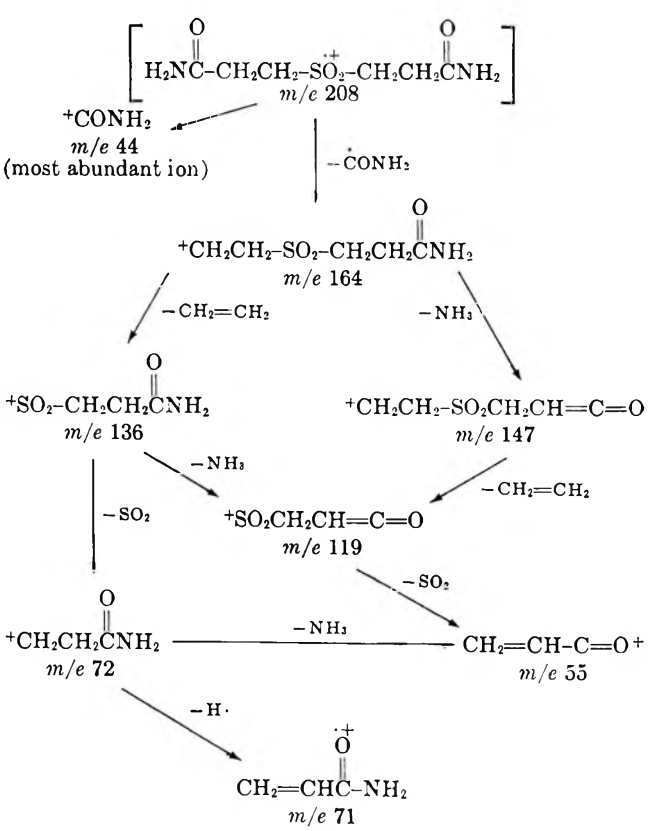
[a] Recorded in trifluoroacetic acid (25% w/w) unless otherwise indicated. [b] Coupling constants in hertz. [c] Recorded in pyridine (25% w/w). [d] Recorded in carbon tetrachloride (25% w/w).

TABLE III
MAJOR PEAKS IN MASS SPECTRUM OF **2a**

m/e	Rel abundance	*m/e*	Rel abundance
16	13	55	98
17	29	56	26
18	57	64	21
26	28	71	84
27	65	72	30
28	41	73	32
30	13	119	13
43	20	136	10
44	100	147	1.8
45	16	164	4.2

and it does not seem to fragment initially at the sulfone linkage. Instead, the molecule appears to undergo fragmentation piece by piece as evidenced by the series of lower mass peaks. Scheme I is a proposed rationalization of its fragmentation pattern.

SCHEME I



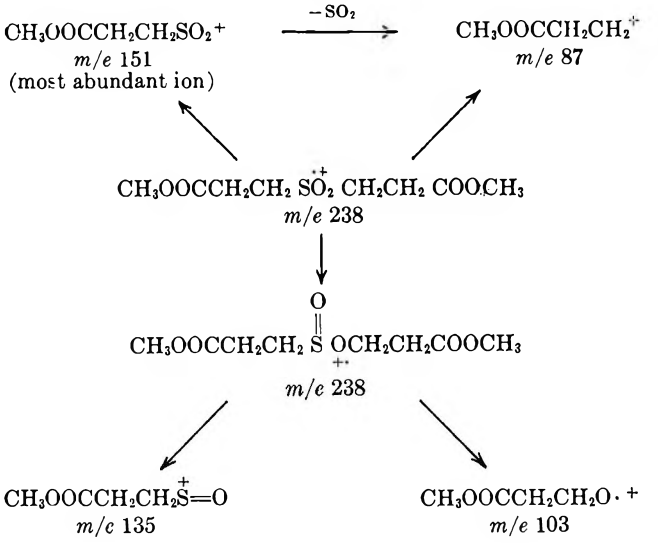
Sulfone **2c** likewise exhibits no parent ion at *m/e* 238 (Table IV). Rupture of the sulfone linkage is the main

Table IV
Major Peaks in Mass Spectrum of 2c

m/e	Rel abundance	m/e	Rel abundance
28	12	103	18
55	40	135	53
59	36	147	43
87	45	151	100
88	11		

cleavage. In addition, postionization rearrangement to the sulfinate ester, as has previously been observed in sulfones,[6] seems to occur in this system, on the basis of peaks at m/e 135 and 103. Scheme II is consistent with the observed spectrum for sulfone **2c**.

Scheme II



The mass spectrum of sulfone **2d** (Table V) does contain a molecular ion peak at m/e 172. Again, sulfone

Table V
Major Peaks in Mass Spectrum of 2d

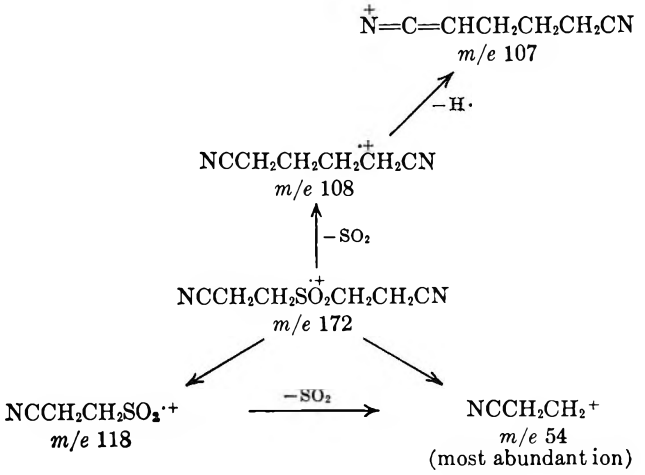
m/e	Rel abundance	m/e	Rel abundance
28	9	107	2.5
54	100	108	0.6
55	66	109	0.2
68	10	118	2.7
		172	2.2

cleavage predominates to give fragments m/e 118 and 54. Accurate mass measurements militate against m/e 118 arising from loss of 2 mol of hydrogen cyanide. This is corroborated by the lack of a peak at m/e 145 due to loss of 1 mol of hydrogen cyanide from the parent ion. Extrusion of sulfur dioxide is probably the origin of the m/e 108 peak, which is too large to be an isotope peak of m/e 107. The loss of a hydrogen atom is characteristic of alkyl nitriles and the formation of m/e 107 from m/e 108 is substantiated by a metastable cusp between m/e 108 and 109.[7] These fragmentations are depicted in Scheme III.

(6) S. Meyerson, H. Drews, and E. K. Fields, *Anal. Chem.*, **36**, 1294 (1964).

(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 112.

Scheme III



The mass spectrum of disulfide **3a** (Table VI) contains a parent ion peak (m/e 208). Disulfide (S–S)

Table VI
Major Peaks in Mass Spectrum of 3a

m/e	Rel abundance	m/e	Rel abundance
17	14	58	14
18	27	59	37
26	21	60	15
27	44	61	29
28	31	64	13
43	27	70	13
44	74	71	100
45	25	72	62
46	14	73	10
47	35	88	21
52	14	101	52
53	19	103	49
54	12	104	17
55	91	105	70
56	18	106	12
		208	8.4

cleavage with hydrogen transfer, possibly *via* a four-centered reaction, leads to m/e 105 and 103. A unique feature of the spectrum is the lack of major fragments greater than half the size of the parent ion. Peaks at m/e 71, 72, and 55 may have arisen by loss of hydrogen sulfide and ammonia from the m/e 105 species. Rationalization of the observed spectrum is given in Scheme IV.

The Mechanism.—The following mechanism was proposed[1a] to account for sulfone formation.

$$SO_2 + HCOOH \longrightarrow \underset{5}{HOSOH} + CO_2 \quad (1)$$

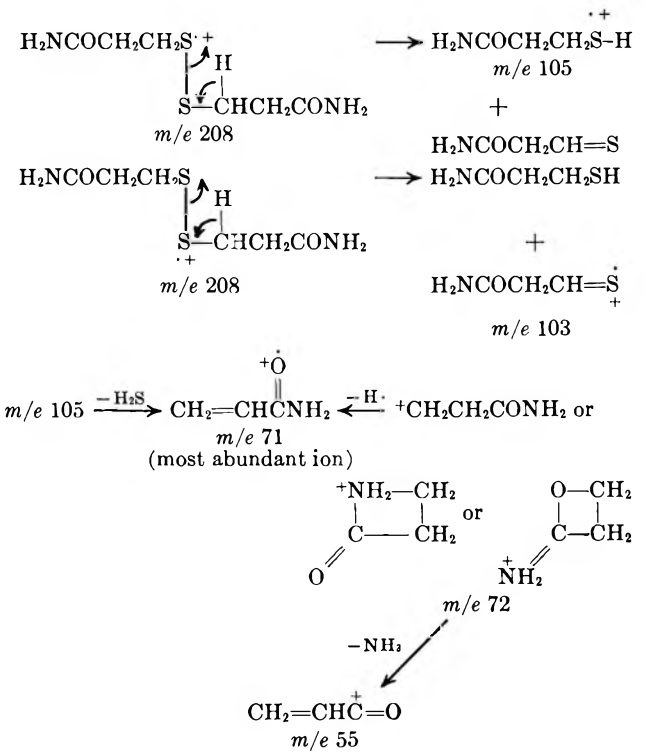
$$H_2SO_2 + 1 \longrightarrow \underset{\displaystyle R_2}{\overset{\displaystyle |}{R_1CHCH_2SO_2H}} \quad (2)$$

6a, $R_1 = H$; $R_2 = CONH_2$
b, $R_1 = CH_3$; $R_2 = COOCH_3$

$$6 + 1 \longrightarrow 2 \quad (3)$$

Our initial efforts in the mechanistic study of this multistage reaction were directed at the proposed addition of sulfinic acid **6** to olefin **1** (eq 3). Sulfinic acids are reported to react with alkyl halides and sulfates and

SCHEME IV



activated aromatic halides, yielding sulfones.[8] In addition, Russian workers have published an account of the preparation of sulfones from sodium arenesulfinates and acrylic acid derivatives in the presence of weak acids.[9] Thus, it appeared that the addition in question was feasible. Using sodium benzenesulfinate and acrylamide (**1a**) under our original reaction conditions (minus sulfur dioxide), a 90% yield of the expected sulfone **9** was isolated.

$$PhSO_2Na + \mathbf{1a} \longrightarrow \underset{\mathbf{9}}{PhSO_2CH_2CH_2CONH_2}$$

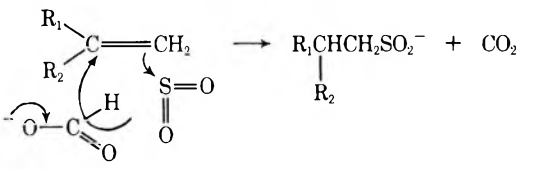
More significantly, it was of interest to determine whether the particular aliphatic sulfinic acid **6** proposed above as an intermediate would add to acrylamide (**1a**). Reductive cleavage of **9** led to a mixture of the desired **6a** (as its sodium salt) and sodium benzenesulfinate in a 2:1 ratio. Treatment of acrylamide (**1a**) with this mixture under normal reaction conditions led as expected to **9** along with the desired symmetrical sulfone **2a**, the product of addition of the sulfinic acid **6a** to acrylamide (**1a**). These experiments firmly demonstrate the feasibility of eq 3 as a route to sulfone **2** from sulfinic acid **6** and olefin **1**.

Next, to distinguish between occurrence of sulfoxylic acid (**5**) as a discrete intermediate as indicated in eq 1 or formation of sulfinic acid **6a** *via* some one-step reaction, tracer experiments using sodium formate-*d* were carried out.

Considering the first possibility, if sulfoxylic acid (**5**) is a discrete intermediate, it would be expected to exchange its protons with the reaction medium. Likewise, the sulfinic acid **6a** is quite acidic[10] and also would be expected to exchange its acidic proton with the solution. Thus, if formate-*d* were the "hydride" source in eq 1, the proportion of deuterium appearing in the methylene groups β to the sulfonyl group in sulfone **2a** would be a function of the amount of solvent employed.

However, if sulfinic acid **6a** is formed by a concerted termolecular process involving direct hydride transfer from formate ion to the tertiary carbon of the olefin, as depicted in Scheme V the protons β to the sulfonyl group in sulfone **2a** should contain 25% deuterium if formate-*d* is used, regardless of the amount of solvent.

SCHEME V



The possibility of exchange of any of the methylene protons in sulfone **2a**, either in the reaction or during work-up and analysis, was precluded by the following results. The sulfone **2a** was heated at 100° in the presence of sodium formate, acetic acid, and deuterium oxide. The sulfone was recovered and pmr analysis, using pivalic acid as an internal standard, revealed that no exchange took place at the methylene positions. Next, the sulfone **2a** was subjected to actual reaction conditions (except for the absence of sulfur dioxide) using sodium formate and acetic acid-d_4. Once again pmr analysis showed no exchange of methylene protons. To eliminate the possibility of exchange during pmr analysis, a sample was heated in trifluoroacetic acid-*d* (solvent for pmr analyses) for a few minutes and allowed to stand 24 hr prior to examination. No exchange of the methylene protons took place.

In a preparative experiment in which both sodium formate-*d* and acetic acid-d_4 were used, the pmr spectrum of the resultant sulfone showed broadened signals due to the protons α to the sulfonyl group and those β in a 1.15:1.00 ratio, respectively. If the mechanism of formation of sulfinic acid **6a** shown in Scheme V were correct and the methylene protons did not exchange, an $\alpha:\beta$ ratio of 1.45:1.00 would obtain; with exchange of the methylene protons α to the sulfinyl group an $\alpha:\beta$ ratio of 1.50:1.00 would result. It is apparent that the termolecular mechanism is not operative. If the mechanism in eq 1–3 is correct and the methylene protons α to the sulfinyl did not exchange, the $\alpha:\beta$ ratio would be 1.41:1.00. Assuming that the olefin exchanges only the amide NH protons, the results indicate that sulfinic acid **6a** undergoes exchange of protons. Since the protons α to the carbonyl group in sulfone **2a** do not exchange under reaction conditions, it is unlikely that those of the sulfinic acid **6a** do so. Thus, it appears that the protons α to the sulfinyl group exchange, either in the sulfinic acid or its anion. If complete exchange of these protons and those of the amide group is assumed, the area ratio of signals for protons α and β is statistically calculated to be 1.00:1.00, respectively.

The preparative reaction was carried out using sodium formate-*d* in the normal amount of acetic acid and in one-half that amount. In neither case was the ratio of protons α to β in **2a** 1.33:1.00. Thus, the termolecu-

(8) R. Otto, *Chem. Ber.*, **13**, 1272 (1880); H. Gilman, "Organic Chemistry, An Advanced Treatise," Vol. I, Wiley, New York, N. Y., 1958, p 874.

(9) V. Mikhailova, N. Borinsova, and D. Stankevich, *J. Org. Chem. USSR*, **2**, 1437 (1966).

(10) W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 69 (1951).

lar mechanism must be discarded, since it would not involve free deuterons in solution to cause exchange at α. One would expect from statistical calculations that as a result of exchange of α protons, the ratios of α to β in both of these reactions would be about 1.00:1.00. This is precisely what has been observed. These results lend support to eq 1 and 2 of the proposed mechanism.

To determine if acetic or formic acid were necessary, an attempt was made to prepare the sulfone **2a** in molten ammonium formate. No sulfone was formed. We take this as indicative of the fact that the ammonium ion cannot serve as the acid. In an attempt to substitute another hydride donor for formate ion, a run was carried out in methanol–sodium borohydride. Again no sulfone resulted. Together, these facts may imply that reduction of sulfur dioxide to sulfoxylic acid (**5**) requires protonation prior to reduction.

$$6 \xrightarrow{[H]} [R_1CHCH_2SOH] \xrightarrow{[H]} R_1CHCH_2SH$$
$$\qquad\qquad\quad R_2 \qquad\qquad\qquad R_2$$
$$\qquad\qquad\quad 7$$

8a, $R_1 = H$; $R_2 = CONH_2$
b, $R_1 = H$; $R_2 = COOH$

$$7 + 8 \longrightarrow 3 + H_2O$$

The formation of disulfide **3** in these reactions may be explained on the basis of intermediate sulfinic acid **6**. In reducing media sulfinic acids are known to produce disulfides, presumably *via* reduction to the sulfenic acid **7** and thence to mercaptan **8**.[11] Condensation of these two species would then yield disulfide **3**. Also mercaptan **8** and sulfinic acid **6** could condense to form a thiosulfinate **10**. The latter are known to undergo acid-catalyzed disproportionation to thiosulfonates **11** and disulfides **3**.[12] In addition, thiosulfonates (**11**) and mercaptans (**8**) are known to yield disulfides (**3**) along with sulfinic acids (**6**).[13]

$$6 + 8 \longrightarrow R_1CHCH_2\overset{\overset{O}{\|}}{S}—SCH_2CHR_1$$
$$\qquad\qquad\quad R_2 \qquad\qquad R_2$$
$$\qquad\qquad\quad 10$$

$$10 \longrightarrow R_1CHCH_2SO_2SCH_2CHR_1 + 3$$
$$\qquad\quad R_2 \qquad\qquad R_2$$
$$\qquad\quad 11$$

$$11 + 8 \longrightarrow 3 + 6$$

Mercaptan **8** could also arise from solfoxylic acid **5**. It is known that the latter disproportionates to sulfur dioxide, water, and hydrogen sulfide.[14] Addition of the latter to olefin **1** could then yield mercaptan **8**.

In the presence of base, aliphatic mercaptans are known to react with elemental sulfur to form disulfides **3** when the ratio of mercaptan to sulfur is greater than 2 mol/g-atom.[15] Hydrogen sulfide is the by-product and it could react with more olefin **1** to generate more mercaptan **8**.

$$8 + S^0 \longrightarrow 3 + H_2S$$
$$1 + H_2S \longrightarrow 8$$

In order to test the validity of these possibilities the following experiments were performed.

(1) Sodium benzenesulfinate was treated with acetic acid–ammonium formate. Though a small amount of odorous solid material was isolated it was not identified. It was probably diphenyl disulfide. The presence of thiophenol (the expected by-product) was noted by tlc. Thus, since aliphatic sulfinic acids are less stable than the aromatics,[10] the formation of disulfide **3** *via* sulfinic acid **6** seems possible.

(2) Reaction of 3-mercaptopropionic acid (**8b**) with sodium benzenesulfinate under normal reaction conditions led to the isolation of disulfide **3b** in low yield. This could arise from the presumed intermediate disulfide **12** by thiol exchange. Under the same conditions 3-mercaptopropionic acid (**8b**) alone did not yield disulfide **3b**. This result would support disulfide formation *via* thiosulfinates (**10**), especially since the aliphatic sulfinic acids would be expected to be more reactive (acidic) than the benzenesulfinic acids[10] used in this test.

$$C_6H_5SSCH_2CH_2COOH$$
$$12$$

(3) Reaction of 3-mercaptopropionic acid (**8b**) with elemental sulfur in acetic acid–ammonium formate led to an 86% yield of disulfide **3b**. Thus reaction of mercaptan with elemental sulfur seems the most likely route to disulfide.

It is possible that elemental sulfur arises from sulfoxylic acid (**5**). It has been reported that its disproportionation products in acidic solution include sulfur dioxide and sulfur.[16] By repetition of the cycle sulfur dioxide could be completely converted to sulfur. Indeed we have demonstrated that formate ion does bring about this reduction.

In an attempt to observe any previously undetected products, a pmr spectrum of a crude reaction mixture from acrylamide (**1a**) was examined. Some propionamide was observed along with sulfone **2a** and unreacted olefin **1a** in about an 8:46:46 ratio. The propionamide probably arises by reduction of acrylamide, which is an eneamide.[2] About 1 mol of formate ion/mol of sulfur dioxide added was consumed as previously reported.[1a] No other products could be detected, although the presence of the methyl resonance of acetic acid could obscure the –SH of any mercaptan (**8a**) present. In most of the reaction mixtures a foul mercaptan-like odor was noted.

It appears that all the findings can be reasonably rationalized on the basis of these proposals. Formation of disulfide **3a** by use of twice the normal amount of solvent formic acid–trimethylamine (3.0:1.0) is probably a reflection of the instability of sulfoxylic acid and sulfinic acid **6a**. Since their concentrations as well as that of the olefin were halved, the rate of sulfone formation decreased (by a factor of eight assuming bimolecular reactions) to the point where disproportionation of these species successfully competed. Acetic acid–ammonium formate is not so effective for the disproportionations, since under comparable conditions it

(11) J. Strating and H. Backer, *Recl. Trav. Chim. Pays-Bas*, **69**, 638 (1950).

(12) C. G. Venier, Ph.D. Thesis, Oregon State University, 1967; *Diss. Abstr. B*, **28**, 3873 (1967).

(13) T. F. Lavine, *J. Biol. Chem.*, **113**, 571, 583 (1936); L. Field, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(14) E. Marshak, *Khim. Nauka Prom.*, **2**, 524 (1957); *Chem. Abstr.*, **52**, 6040c (1958).

(15) B. D. Vineyard, *J. Org. Chem.*, **32**, 3833 (1967).

(16) H. Stamm and M. Goehring, *Angew. Chem.*, **58**, 52 (1945).

does not lead to disulfide. In view of the relative acidities of the two acids this is the expected trend.[12,17] The difference may, in part, be due to the reservoir of excess formate ion in the formic acid system, which could allow more efficient conversion of sulfur dioxide to sulfur and hence to disulfide as outlined above. In addition other sulfinic acids (6) apparently are not so sensitive to disproportionation since a similar solvent effect was not evident in other systems. Use of acetic acid is preferred for bringing about sulfone formation in general.

Based on the mechanism one might expect that unsymmetrical sulfones would result from reaction of two olefins, one which is capable of adding sulfoxylic acid and one which is not. Acrylamide and methyl methacrylate presumably undergo sulfinic acid formation as evidenced by isolation of the corresponding sulfone and disulfide, respectively (see Table I). Styrene and linear olefins (as exemplified by 1-decene) apparently do not give rise to a sulfinic acid since no disulfides or sulfones were detected. Crossed reactions were thus attempted between acrylamide:styrene and methyl methacrylate:1-octene; no unsymmetrical product was isolated in either instance. Apparently, ability to undergo addition of sulfoxylic acid is a necessary but not sufficient condition for addition of sulfinic acid.

The structural requirements for the olefin (1) appear to be a combination of electronic and steric effects (as is usually the case). First, it appears that powerful electron-withdrawing groups are required for both eq 2 and 3. This is known for condensations of sulfinate salts with olefins.[9] Probably both of these steps involve attack of the conjugate bases on the olefin with formation of a carbanion. Second, both steps exhibit a steric effect. Although fumaric acid satisfies the electronic requirements for sulfinic acid formation, this did not occur, *i.e.*, no disulfide, mercaptan, or sulfone were isolated; and, while methyl methacrylate (**1e**) forms the corresponding sulfinic acid (as shown by isolation of disulfide), reaction of the latter with olefin does not occur. In a crossed reaction of methyl methacrylate (**1e**) and acrylamide (**1a**), none of the unsymmetrical sulfone was isolated. This indicates that the presence of a methyl group on the olefin causes sufficient steric hindrance that no attack occurs, since sulfinic acid **6a** would be more reactive than sulfinic acid **6b** derived from methyl methacrylate owing to its lower steric bulk. That the latter is true is shown by the fact that the methyl methacrylate derived sulfinic acid **6b** did not react with acrylamide (**1a**).

The high yield of disulfone **4** is probably the result of the highly favorable entropy situation in the sulfinic acid derived from divinyl sulfone (**1**, $R_1 = H$; $R_2 = SO_2CH{=}CH_2$). Thus, reaction of the sulfinyl group with the adjacent double bond occurs before side reactions can take place.

Experimental Section

General.—Infrared spectra were recorded on a Beckman IR-5, solids in KBr, liquids neat. Pmr spectra were recorded on a Varian A-60A instrument. Chemicals shifts are relative to TMS (δ 0.00). The mass spectra were recorded on a Varian M-66 cycloidal focusing instrument. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Samples were routinely examined by thin layer chromatography on Eastman silica gel sheets using a benzene–methanol–acetic acid (82:9:9) solvent system and iodine as developer. Melting points were taken in capillaries on a Thomas–Hoover apparatus and are uncorrected. Boiling points are likewise uncorrected. The disulfide **3d** from methyl methacrylate was examined on a Perkin-Elmer 154B vapor fractometer using a 6 ft × 0.25 in. 5% Carbowax 20M on Chromosorb W column at 170° and a flow rate of 55 ml/min. Two peaks of retention times 13 and 24 min and of about 1.0:1.5 area ratio were observed.

Materials.—The formic acid used in this work was from Aldrich (97+%) and Matheson (98–100%). The sulfur dioxide was Matheson anhydrous grade, 99.98% pure. All the olefins were commercial samples and were used without further purification. Other materials were also employed as received.

Formic Acid–Tertiary Amine Azeotropes.—To 57.5 ml (1.48 mol) of formic acid was added 33.6 g (0.569 mol) of gaseous trimethylamine with cooling. Distillation through a 3-in. Bantamware Vigreux column gave a center cut of constant bp 115.5° (62 mm); pmr (neat) δ 2.90 (s, 4.4 H, $N(CH_3)_3$), 8.3 (s, 1.0 H, HCOOH), 13.1 (s, 1.0 H, HCOOH). Examination by vpc (6 ft × 0.25 in. Poropak S column at 160° and 60 ml/min flow) and infrared indicated the presence of no new compounds. Redistillation gave a center cut of constant bp 39–40° (0.80 mm): pmr (neat) δ 2.90 (s, 3.5 H, $N(CH_3)_3$), 8.3 (s, 1.0 H, HCOOH), 13.1 (s, 1.0 H, HCOOH). Ratio of HCOOH:$N(CH_3)_3$ = 2.0:1 (62 mm), 2.6:1 (0.80 mm).

A mixture of 29.8 g (0.645 mol) of formic acid and 39.9 g (0.215 mol) of tributylamine was distilled through a 3-in. Bantamware Vigreux column to afford a center cut of constant bp 70° (0.92 mm); pmr (neat) δ 1.2–3.2 (m, 14 H, $N[(CH_2)_3CH_3]_3$), 8.50 (s, 1.0 H, HCOOH), 13.80 (s, 1.0 H, HCOOH). Redistillation gave a center cut of constant bp 134° (55 mm); pmr (neat) δ 1.2–3.2 (m, 12 H, $N[(CH_2)_3CH_3]_3$), 8.50 (s, 1.0 H, HCOOH), 13.6 (s, 1.0 H, HCOOH). Vpc (as above) and infrared examination indicated the presence of no new covalent compounds. Ratio of HCOOH:$N[(CH_2)_3CH_3]_3$ = 2.0:1.0 (0.92 mm), 2.3:1.0 (55 mm).

General Procedure for Reaction of Olefins and Sulfur Dioxide.—To a rapidly stirred solution of 0.100 mol of the olefin and 0.05 g of phenothiazine (to inhibit polymerization) in the desired solvent system maintained at 100 ± 2° under a reflux condenser was added 0.0500 mol of sulfur dioxide on a stream of nitrogen over a period of 1 hr (3 hr where noted). The sulfur dioxide was condensed in a graduated tube and measured by volume (2.24 ± 0.01 ml) based on a density of 1.43 g/ml at its boiling point (−10°).[18] The nitrogen purging was continued for 0.25 hr and the mixture was poured onto ice and filtered. The solid was washed with water and dried to yield the sulfone, disulfide, or sulfur. The filtrate was concentrated and extracted with ether. After washing with sodium bicarbonate and water, the extract was dried ($MgSO_4$ or Na_2SO_4) and the solvent was removed to afford the disulfide in cases where it was liquid. (See Table VII.)

TABLE VII
SPECIFIC CONDITIONS

Condition	Solvent system (molar ratios)	Weight used, g
A	HCOOH (3.0)–NMe_3 (1.0)	19.8
B	HCOOH (3.0)–NMe_3 (1.0)	39.6
C	CH_3COOH (1.7)–NH_4OOCH (1.0)	34.6
D	HCOOH (1.2)–NH_4OOCH (1.0)	25.6
E	HCOOH (3.0)–NMe_3 (1.0)	9.9

Phenyl 2-Carboxamidoethyl Sulfone (9).—A solution of 8.21 g (0.0500 mol) of sodium benzenesulfinate, 3.55 g (0.0500 mol) of acrylamide, 0.05 g of phenothiazine, 13.6 g (0.216 mol) of ammonium formate, and 21.0 ml (0.366 mol) of acetic acid was heated at 100° under nitrogen for 1.25 hr. The mixture was poured onto ice and filtered to yield a total of 9.55 g (90%) of colorless needles: mp 127.0–127.5° (lit.[19] mp 126–127°); pmr (25% w/w CF_3COOH) δ 2.99 (2 H, t, J = 6 Hz), 3.75 (12 H, t, J = 6 Hz), 7.8 (6 H, m).

(17) P. Allen, Jr. and L. Reich, *J. Phys. Chem.*, **64**, 1928 (1960); J. Kice and K. Bowers, *J. Amer. Chem. Soc.*, **84**, 605 (1962).

(18) See reference in footnote *i* of Table I.

(19) O. Achmatowicz and J. Michalski, *Rocz. Chem.*, **30**, 243 (1956).

Basic Cleavage of Phenyl 2-Carboxamidoethyl Sulfone (9).—This was carried out by the general method of Bradley[20] using 5.30 g (0.136 mol) of sodamide, 35 ml of piperdine, and 6.60 g (0.0310 mol) of the sulfone. It yielded 10.7 g of nearly colorless powder. This material was shown to contain sodium hydroxide by titration with acid. From the integral ratios of the aliphatic to aromatic signals the ratio of sodium 2-carboxamidoethyl sulfinate to sodium benzenesulfinate was calculated to be about 2:1.

Reaction of Sodium 2-Carboxamidoethyl Sulfinate (6a) and Acrylamide (1a).—A solution of 4.0 g of the mixture of salts (**6a** and **1a**), 1.0 g of acrylamide, and 10 ml of formic acid was refluxed 1 hr and poured onto ice. Filtration yielded 0.60 g of stout needles, part melted at 115°, rest at 205–210°. Tlc of the solid showed spots of R_f 0.00 and 0.23. Bis(2-carboxamidoethyl) sulfone and phenyl 2-carboxamidoethyl sulfone have R_f of 0.00 and 0.23, respectively.

Exchangeability of Bis(2-carboxamidoethyl) Sulfone (2a). 1. In Sodium Formate–Acetic Acid–Deuterium Oxide.—A mixture of 3.50 g (0.0168 mol) of the sulfone, 7.35 g (0.108 mol) of ammonium formate, 11.5 ml (0.636 mol) of deuterium oxide, and 21.0 ml (0.368 mol) of acetic acid was heated at 100° under nitrogen for 1.25 hr. The mixture was cooled and filtered. The solid was washed with ether and dried to yield 3.54 g of colorless solid, mp 215–218°. A blank solution of 0.2500 g (0.001200 mol) of starting material, 0.0580 g (0.0005680 mol) of pivalic acid, and 0.75 ml of trifluoroacetic acid was examined by pmr. Ratio of CH_2:CH_2 (sulfone):CH_3 (pivalic acid) found was 1.00:1.00:1.07; theoretical for no exchange 1.00:1.00:1.03. A solution of 0.2501 g (0.001201 mol) of the product and 0.0593 g (0.0005808 mol) of pivalic acid in trifluoroacetic acid showed a ratio of 1.00:1.00:1.04 *vs.* the theoretical for no exchange 1.00:1.00:1.09.

2. In Trifluoroacetic Acid-*d*.—A solution of 0.1297 g (0.0006227 mol) of the sulfone and 0.0224 g (0.0002194 mol) of pivalic acid in 0.6 g of trifluoroacetic acid-*d* was warmed a few minutes, allowed to stand 24 hr, and examined by pmr. The CH_2:CH_2:CH_3 ratio was found to be 1.38:1.38:1.00 (theoretical for no exchange 1.31:1.31:1.00).

3. Under Reaction Conditions.—A mixture of 1.00 g (0.00481 mol) of the sulfone, 2.10 g (0.00309 mol) of sodium formate, and 6.0 ml (0.10 mol) of acetic acid-d_4 was heated at 100° for 2 hr and then cooled and filtered. The solid was washed with water and ether. Pmr analysis of a solution of 0.1018 g (0.0004887 mol) of the sulfone, 0.0120 g (0.0001175 mol) of pivalic acid, and 0.6 g of trifluoroacetic acid showed a CH_2:CH_2:CH_3 ratio of 1.83:1.83:1.00 (theoretical for no exchange 1.84:1.84:1.00).

Preparation of Bis(2-carboxamidoethyl) Sulfone (2a) in Sodium Formate-*d* and Acetic Acid-d_4.—To a solution of 1.21 g (0.0170 mol) of acrylamide, 1.25 g (0.0184 mol) of sodium formate-*d*, 0.01 g of phenothiazine, and 2.50 ml (0.0438 mol) of acetic acid-d_4 was added 0.38 ml (0.0085 mol) of sulfur dioxide in the usual manner over a 1-hr period. The mixture was cooled, filtered, washed with 10 ml of water and ether, and dried to afford 0.55 g (31%) of colorless solid, mp 216–218° dec. The pmr spectrum of a 25% solution in trifluoroacetic acid showed broad singlets at δ 3.8 and 3.2 in a 1.15:1.00 ratio.

Preparation of Bis(2-carboxamidoethyl) Sulfone (2a) Using Sodium Formate-*d*. Run A.—To a solution of 2.42 g (0.0341 mol) of acrylamide, 0.05 g of phenothiazine, 2.50 g (0.0367 mol) of sodium formate-*d*, and 7.0 ml (0.122 mol) of acetic acid at 100° was added 0.76 ml (0.0170 mol) of sulfur dioxide on a stream of nitrogen over a period of 1 hr. After stirring 0.25 hr, the mixture was poured onto ice to give 1.85 g (52%) of solid. Ether washing and recrystallization gave colorless needles, mp 228.5–229.0°. Pmr integrations of the signals at δ 3.8 and 3.2 gave an average (three runs) ratio of 0.96:1.00, respectively.

Run B.—This was carried out as run A but using only one-half the amount of acetic acid (3.50 ml, 0.061 mol). Pmr analyses yielded an average integral ratio of 0.90:1.00 for the signals at δ 3.8 and 3.2, respectively.

Statistical Calculation of Integral Ratios (α:β).—Assuming complete exchange of the acidic protons of acetic acid and the NH protons of the amide groups, the initial percentage of deuterium present was calculated. The final proportion of deuterium was calculated differently for the various possible mechanisms. For the termolecular mechanism with no exchange of protons in the intermediate sulfinic acid, the final number of protons and deuterons was the same as the initial. For the termolecular mechanism with exchange of the protons α to the sulfinyl group in the sulfinic acid the final total number of protons is equal to the initial number plus the number of moles of formate ion theoretically utilized. For the three-step mechanism with exchange of the intermediate sulfinic acid, the final number of protons and deuterons is equal to the initial number plus the number of moles of formate ion theoretically utilized. For the three-step mechanism with exchange of the acidic proton and the protons α to the sulfinic acid group in the intermediate sulfinic acid, the final number of protons and deuterons is equal to the initial number plus the number of moles of formate ion theoretically used and twice the number of moles of sulfinic acid generated. The initial and final percentages of protium were averaged for calculation of the area ratios.

Reaction of Acrylamide (1a) and Sulfur Dioxide in Molten Ammonium Formate.—To a solution of 20.5 g (0.324 mol) of ammonium formate, 7.10 g (0.100 mol) of acrylamide, and 0.05 g of phenothiazine at 135° was added 2.24 ml (0.050 mol) of sulfur dioxide over 1 hr. No solid precipitated when the mixture was poured onto ice. The mixture was taken to dryness and extracted with hot methanol to yield about 10 g of a solid–liquid mixture. Tlc showed spots of R_f 0.06 and 0.81. R_f's of knowns are as follows: ammonium formate, 0.06; acrylamide, 0.46; propionamide, 0.32; bis(2-carboxamidoethyl) sulfone, 0.00; bis(2-carboxamidoethyl) disulfide, 0.37. The spot of R_f 0.81 was not identified.

Reaction of Acrylamide (1a), Sulfur Dioxide, and Sodium Borohydride in Methanol.—To a solution of 6.35 g (0.0894 mol) of acrylamide, 0.85 g (0.022 mol) of sodium borohydride, 0.05 g of phenothiazine and 25 ml of methanol at 50° was added 2.0 ml (0.0046 mol) of sulfur dioxide over a period of 1 hr. No solid formed when the mixture was poured onto ice. The odor of sulfur dioxide was noted.

Reaction of Sodium Benzenesulfinate with Ammonium Formate–Acetic Acid.—A solution of 8.21 g (0.0500 mol) of sodium benzenesulfinate, 0.05 g of phenothiazine, 13.6 g (0.216 mol) of ammonium formate, and 21.0 ml (0.366 mol) of acetic acid was heated at 100° for 1.25 hr under nitrogen. When poured onto ice the mixture yielded no solid. The mixture contained thiophenol as shown by tlc. It was taken to dryness *in vacuo* and extracted with benzene to yield a small amount (~0.05 g) of solid with the odor of burning rubber. The residue was redissolved in water and treated with a saturated solution of ferric chloride to precipitate 4.3 g of the ferric salt of sulfinic acid. In a blank 8.21 g of sodium benzenesulfinate yielded 7.3 g (91%) of the salt.

Reaction of Sodium Benzenesulfinate with 3-Mercaptopropionic Acid (8b).—A solution of 4.25 ml (0.0500 mol) of 3-mercaptopropionic acid, 8.21 g (0.0500 mol) of sodium benzenesulfinate, 13.7 g (0.216 mol) of ammonium formate, and 21 ml (0.366 mol) of acetic acid was heated at 100° for 1.25 hr and then poured onto ice. The aqueous mixture was extracted with ether and washed with water. The aqueous portion on evaporation yielded 1 g (19%) of dithiodipropionic acid (**3b**), mp 151–154°, undepressed with an authentic sample. The ether portion yielded 0.2 g of a malodorous oil. Tlc showed the presence of thiophenol and another component. It was not examined further. A blank run without sodium benzenesulfinate yielded no disulfide.

Reaction of 3-Mercaptopropionic Acid (8b) and Sulfur.—To a stirred solution of 1.20 g (0.0375 g-atom) of sulfur, 6.81 g (0.108 mol) of ammonium formate, and 10.5 ml (0.183 mol) of acetic acid over a 50-min period was added 12.5 g (0.188 mol) of 3-mercaptopropiomc acid. After stirring 25 min, the mixture was allowed to cool and then filtered. The odor of hydrogen sulfide was noted. There was obtained 10.6 g (86%) of colorless solid, mp 155–156° after one recrystallization from water. The pmr spectrum was identical with that of an authentic sample of **3b**.

Reaction of Sulfur Dioxide with Ammonium Formate–Acetic Acid.—To a solution of 13.6 g (0.216 mol) of ammonium formate and 21.0 ml (0.366 mol) of acetic acid at 100° was added 1.80 ml (0.0403 mol) of sulfur dioxide in the usual manner over 1.5 hr. The yellow suspension was then poured into water and filtered to yield 0.4 g (31%) of elemental sulfur, mp 120–121°, which burned with a blue flame to produce sulfur dioxide (lit.[21] mp 120° for amorphous sulfur).

(20) W. Bradley, *J. Chem. Soc.*, 458 (1938).

(21) Reference 5, p 664.

Pmr Analysis of Crude Mixture From Acrylamide Reaction.—The reaction was run in the usual manner using 3.55 g (0.050 mol) of acrylamide, 6.81 g (0.108 mol) of ammonium formate, 10.5 ml of acetic acid, and 1.12 ml (0.0250 mol) of sulfur dioxide. The pmr spectrum (in CF_3COOH) showed signals due to acrylamide (m, δ 6.2 and 6.5), the sulfone (t, δ 3.1 and 3.7), and propionamide (s, J = 7.5 Hz, δ 1.3). The area ratio was about 6:6:1, respectively. No mercaptan was detected, though it could have been obscured by the methyl signal (s, δ 2.2) of acetic acid.

Registry No.—**2a**, 13063-92-8; **2b**, 6291-88-9; **2c**, 3234-31-9; **2d**, 5450-67-9; **3a**, 1002-19-3; **3b**, 1119-62-6; **3c**, 15441-06-2; **3d**, 25055-41-8.

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Sulfonium Salts. IV. Cleavage–α-Substitution Competition of Dibenzylhalosulfonium Salts

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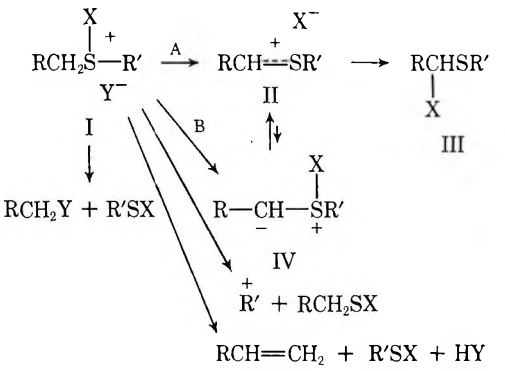
Benzyl sulfide reacts with chlorine, bromine, NCS, and NBS to provide α-halobenzyl benzyl sulfide, benzyl halide, benzylsulfenyl halide, and, where possible, N-benzylsulfenylsuccinimide. The competitive isotope effects, measured in deuteriochloroform and carbon tetrachloride, are consistent with an E2-type elimination from an initially formed halosulfonium salt. The variation of the ratio of cleavage to α-halogenated products is consistent with a rate-determining step involving halide ion attack on a single intermediate when initial concentrations of halogen and sulfide are low, but involving decomposition of aggregates when initial concentrations above about 0.3 M are used.

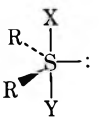
Bromination and chlorination of sulfides bearing an α proton at low temperatures in nonpolar aprotic solvents often leads to the formation of metastable adducts[2] (I) which usually decompose upon warming to give α-halo sulfides[3] (III) (Scheme I). Reactions of

SCHEME I

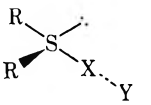


sulfides with chlorine,[3-5] sulfuryl chloride,[5-7] and N-halosuccinimides[8] to produce α-halo sulfides are all considered to proceed through adduct I, generally considered to be a halosulfonium salt.

The largest contributor to the structure of the sulfide–bromine adduct would seem to be ionic on the basis of X-ray,[9] nmr,[9] and conductometric[2d] data. Contributions to the time-averaged structure in solution by the trigonal bipyramidal dihalosulfurane V in analogy with the crystal structure of the adduct of chlorine with bis(p-chlorophenyl) sulfide[10] or the charge transfer type structure[11] VI are not excluded by available data. In fact, the X-ray data[9] is compatible with a much distorted charge transfer structure.



V



VI

In lieu of reorganizing to α-halo sulfides and HX, possibly by way of ylide IV and sulfocarbonium ion II, halosulfonium salts can undergo carbon–sulfur bond rupture to provide sulfenyl halides and alkyl halides directly either by displacement on carbon[12] or by way of stable carbonium ions.[13] Reactions involving carbon–sulfur fragmentations of halosulfonium salts have also been observed.[14]

Results

The reactions of benzyl sulfide with several halogenating agents such as N-chlorosuccinimide (NCS),

(1) Submitted by M. G. Huang in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn.

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(9) G. Allegra, G. E. Wilson, Jr., E. Benedetti, C. Pedone, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970).

(10) N. C. Baenziger, R. E. Buckles, R. J. Maner, and T. D. Simpson, *ibid.*, **91**, 5749 (1969).

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(12) J. M. Stewart and H. P. Cordts, *J. Amer. Chem. Soc.*, **74**, 5880 (1952); J. M. Stewart and C. H. Burnside, *ibid*, **75**, 243 (1953); D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

(13) H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, **78**, 5008 (1956); H. Kwart and L. J. Miller, *ibid.*, **80**, 884 (1958); H. Kwart and R. W. Body, *J. Org. Chem.*, **30**, 1188 (1965); H. Kwart, R. W. Body, and D. M. Hoffman, *Chem. Commun.*, 765 (1967); H. Kwart and P. S. Strilko, *ibid.*, 767 (1967).

(14) G. E. Wilson, Jr. *J. Amer. Chem. Soc.*, **87** 3785 (1965).

N-bromosuccinimide (NBS), chlorine, and bromine were conducted in carbon tetrachloride and in deuteriochloroform at 35°. All went to completion within 30 min, but it was not possible in all cases to obtain systems which were completely homogeneous throughout the course of the reactions. For the bromine and chlorine reactions, the rate of addition of halogen was maintained such that precipitation of the halosulfonium salt was held to a minimum. Product assignments were confirmed by enhancement of the appropriate peaks in the nmr spectra using authentic samples (Table I). Solid benzylsulfenylsuccinimide was removed by filtration from the NCS and NBS halogenations of benzyl sulfide in carbon tetrachloride, before nmr analyses were performed.

TABLE I
CHEMICAL SHIFTS OF COMPONENTS IN THE REACTIONS OF BENZYL SULFIDE WITH HALOGENATING AGENTS

Compound	Protons	δ (CCl_4), Hz	δ ($CDCl_3$), Hz
Hexamethylbenzene		130.0	134.0
$PhCH_2SCH_2Ph$		208.0	213.0
$PhCH_2Cl$		265.5	268.5
$PhCH_2Br$		264.5	269.5
$PhCH_2SCl$		255.5	
$PhCH_2SBr$		253.5	241.0
$PhCHClSCH_2Ph$	CH_2	d, 228.85; d, 240.15	s, 268.5
	CH	343.5	350.0
$PhCHBrSCH_2Ph$	CH_2	s, 237.0	s, 240.5
	CH	344.5	353.5
$(PhCH_2S)_2$		210.0	215.0
$PhCH_2SCD_2Ph$		208.0	213.0
N-Benzylsuccinimide	CH_2Ph		275.5
N-Benzylsulfenylsuccinimide	CH_2Ph		245.5

NCS and NBS halogenation of benzyl sulfide in carbon tetrachloride gave one major product, α-halobenzyl benzyl sulfide (VII), together with the cleavage products benzyl halide (X), benzylsulfenyl halide (VIII), benzyl disulfide (IX), and solid benzylsulfenylsuccinimide (VIII) (Scheme II). That benzylsuccinimide was not formed could be seen when the reaction was conducted in deuteriochloroform in which solvent all the products remained in solution. Bromination of benzyl sulfide in carbon tetrachloride gave initially a solid yellow adduct which disappeared in 1 to 2 min. The reaction products after 30 min showed one major product, α-bromobenzyl benzyl sulfide, and the cleavage products benzyl bromide, benzylsulfenyl bromide, and benzyl disulfide.

Attempts to isolate the α-halobenzyl benzyl sulfides by distillation resulted in rapid decomposition into benzyl halide and other unidentified materials. Failure to isolate these compounds has been reported in several other cases.[4b,7a,b,15] Chlorination of benzyl sulfide gave solely α-chlorobenzyl benzyl sulfide and α,α-dichlorobenzyl benzyl sulfide. Incorporation of chlorine at the α position was established by oxidation of the sulfide to the corresponding sulfone, the nmr of which showed signals at δ 7.39 (s, 5 H), 5.92 (s, 1 H), and 4.40 (q, J = 14.0 Hz, 2 H) ppm. Polyhalogenation at one carbon atom has been observed as general behavior.[4b,6,16]

(15) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.* **26**, 2478 (1961).
(16) L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4089 (1964).

SCHEME II

$$PhCH_2SCH_2Ph + XY \longrightarrow PhCH_2SCHPh + PhCH_2SY + (PhCH_2S)_2 + PhCH_2X + HY$$

VII (X) VIII IX X

X = Cl; Y = Cl, —N(succinimide)

X = Br; Y = Br, —N(succinimide)

The crystalline bromine adduct of benzyl sulfide was isolated at low temperature. This adduct decomposed slowly at room temperature in the solid state to cleavage and α-substitution products. Prolonged storage at 0° also led to decomposition products. The product distributions for halogenations are given in Table II. In general the per cent cleavage increased slightly with increased solvent polarity, but there was no strong trend. NCS chlorination of benzyl sulfide in carbon tetrachloride provided the best conditions for forming the mono-α-substituted product, and bromination with bromine gave the best yield of cleaved products.

TABLE II
DISTRIBUTION OF HALOGENATION PRODUCTS IN CARBON TETRACHLORIDE AND IN DEUTERIOCHLOROFORM SOLUTION

	Carbon tetrachloride[a]		Chloroform-d_1[a]	
	% α substitution	% cleavage	% α substitution	% cleavage
Cl_2	86[b]	0	c	c
Br_2	34.7	64.8	41.5	57.8
NCS	87.2	2.62	77.7	21.6
NBS	60.3	30.4	22.5	77.2

[a] 0.208 M benzyl sulfide at 35° for 30 min. [b] Includes 25% yield of α,α-dichlorobenzyl benzyl sulfide. [c] Quantitative assay was not possible because the internal standard was also chlorinated.

Benzyl sulfide-α-α-d_2 for isotope effect studies was synthesized by a three-step route. Lithium aluminum deuteride reduction of ethyl benzoate and treatment of the product alcohol with thionyl chloride was followed by reaction of the deuterated benzyl chloride with benzyl mercaptide ion to give the desired product. The ir spectrum of this compound shows C–D stretching at 2140 cm^{-1}, and the nmr shows two singlets at δ 3.47 and 7.16 ppm in the ratio of 2:10. From the molecular ions the isotopic composition corrected for ^{13}C, ^{2}H, ^{33}S, and ^{34}S, were calculated to be 0.30% d_0, 1.79 d_1, and 97.9% d_2.

Benzyl sulfide-α,α-d_2 was halogenated at 35° for 30 min in both carbon tetrachloride and deuteriochloroform thus providing α-halobenzyl benzyl sulfides XI and XII. The diastereotopic methylene protons appear as an AB quartet (δ 228.85, 240.15, J = 13.5 Hz) in the case where chlorine is the substituent and as a singlet (δ 237.0 Hz) for the bromine counterpart.

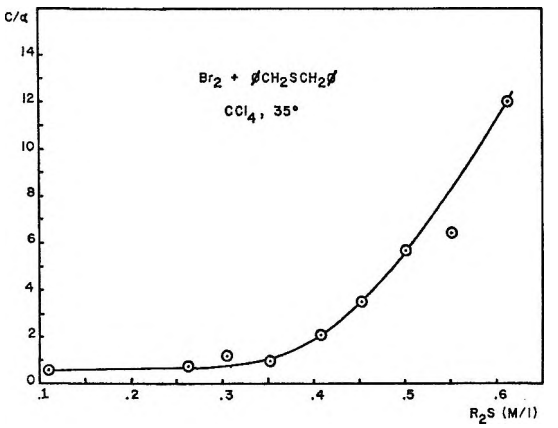


Figure 1.—Concentration dependence of c/α ratio for the halogenation of benzyl sulfide.

PhCHSCD$_2$Ph (X) — XI, X = Cl, Br

PhCDSCH$_2$Ph (X) — XII

For calculation of k_H/k_D, an average of at least four integral sweeps of the methylene and methine areas was used. When the nmr signals were too weak to be integrated directly, the reaction mixture was concentrated; the spectra of the concentrated product mixtures showed that no decomposition of the products had taken place. The competitive deuterium isotope effects for halogenation of benzyl sulfide in deuteriochloroform and carbon tetrachloride are shown in Table III.

TABLE III
KINETIC ISOTOPE EFFECTS IN THE HALOGENATION OF BENZYL SULFIDE AT 35° IN CARBON TETRACHLORIDE AND DEUTERIOCHLOROFORM

	CCl_4	$CDCl_3$
Cl_2	6.55	4.62
Br_2	2.59	2.11
NCS	8.27	5.90
NBS	4.23	3.14

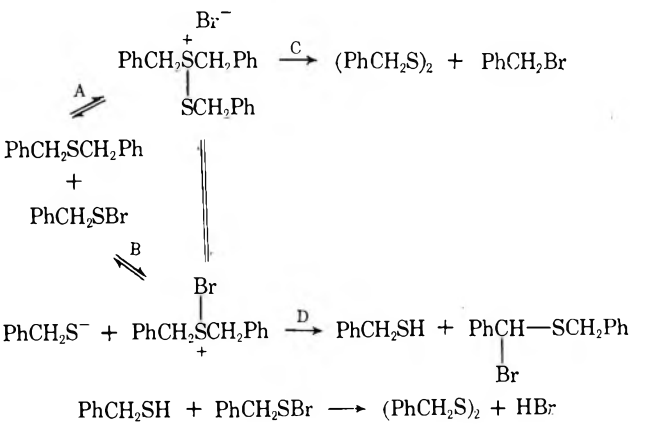
The ratio of cleavage to α-substitution products (c/α) when reaction was complete was examined using equimolar mixtures of bromine and benzyl sulfide over a concentration range of 0.625 to 0.104 M sulfide in carbon tetrachloride. Nmr analysis using hexamethylbenzene as an internal standard was carried out directly on the product mixture after addition of 1 drop of acetone-d_6 to destroy benzylsulfenyl bromide, whose methylene signal interferred with the analysis. The sensitivity of the products to our work-up procedures prevented our obtaining results outside the stated concentration range. Rapid addition of bromide led to instantaneous precipitation of a form of adduct whose rate of dissolution is extremely slow, *ca.* 1 hr for complete disappearance. This could be overcome by addition of bromine over a period of 3–5 min. Slower addition complicates the kinetics as well as the interpretation of the data, but we feel that it is clearly better than the alternative, and that it does not obviate the conclusions. The c/α ratio as a function of initial sulfide concentration is shown in Figure 1.

Discussion

Because both cleavage and Pummerer products are produced in comparable quantities in the halogenation of benzyl sulfide, an opportunity exists in principle to investigate the interrelationship of these two processes. The α-halo sulfide (VII) produced can be rationalized using a generalized Pummerer reaction (Scheme I).[17] Benzyl halide and benzylsulfenyl halide can be considered products of displacement on a halosulfonium salt. Although N-benzylsulfenylsuccinimide could in principle arise through a succinimidylsulfonium salt, we favor the concept of reaction between succinimide and free sulfenyl halide.

The origin of benzyl disulfide, most prominent in the bromination reaction where cleavage is greatest, was not clear. It could arise from direct disproportionation of the displacement product, benzylsulfenyl bromide, or, in one of two ways, from the reaction of the sulfenyl bromide with the sulfide (Scheme III). Although direct disproportionation of benzylsulfenyl bromide cannot definitely be excluded, solutions of this compound were stable with respect to disproportionation for periods longer than the reaction time. Addition of solid benzyl sulfide to a solution of benzylsulfenyl bromide resulted in the formation of α-bromobenzyl benzyl sulfide with only a trace of benzyl bromide. The nmr peaks for the α-bromo sulfide increased in intensity as the reaction proceeded. The absence of benzyl bromide from the products of this reaction excludes the possibility of disulfide formation by way of the thiosulfonium ion intermediate generated from the sulfenyl bromide, pathway C. The alternative, pathway D, explains the data. The halosulfonium salt could, in this case, be generated either directly (pathway B)[18] or by way of the thiosulfonium salt (pathway A).

SCHEME III



The absence of N-benzylsuccinimide from the reaction products in NBS and NCS halogenations is significant. We have shown independently that, under the reaction conditions, benzyl bromide and succinimide do not react. It can now be concluded that neither succinimide nor its anion, if formed, is capable of attacking the α-carbon atom of the halosulfonium salt of the sulfocarbonium ion.

(17) G. E. Wilson, Jr., and R. Albert, *Tetrahedron Lett.*, 6271 (1968).

(18) The formation of a bromosulfonium salt by direct displacement by sulfide on benzylsufenyl bromide is in harmony with the suggestion that sulfenyl bromides possess a positive bromine: N. Kharasch, *Org. Sulfur Compounds*, 1, 387 (1961).

Mechanism of Proton Removal.—One theory of the bimolecular elimination mechanism[19] views this process as embracing three types of transition states. All represent concerted processes but differ in the relative extent to which bonds are ruptured. The transition state may resemble a carbonium ion, the olefinic product, or a carbanion. The type of transition state which obtains is determined by the combined demands of substrate, base, and leaving group. As one moves from a central transition state, a decreased k_H/k_D is expected. The magnitudes of the competitive isotope effects (Table III) for halogenation with NCS and chlorine are clearly most compatible with a relatively central E2 elimination to form a sulfocarbonium ion (Scheme I, path A). They are incompatible with an irreversible ElcB mechanism[20] which represents the only alternative. A similar large isotope effect was obtained by Tuleen and Marcum[8] for NCS chlorination of benzyl phenyl sulfide-α-d_1.

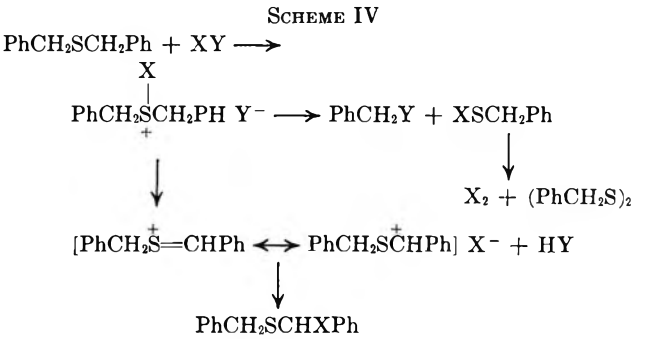
That the methylene protons of chloro sulfide XII are diastereotopically related to each other with a chemical shift between them of 11.3 Hz provides an operational method to examine the possibility of proton exchange at any stage in the reaction. Exchange, if it were to occur to a small extent through an ylide or other route, should provide approximately equal mixtures of two diastereomeric sulfides in which the single methylene protons would lead to a pair of broad singlets located within the quartet of the normal methylene protons of XII. This was rigorously excluded by an experiment in which benzyl sulfide was chlorinated in carbon tetrachloride maintained at saturation with a slow stream of dry deuterium chloride. The nmr of the reaction products at 50-Hz sweep width gave no indication of any deuterium exchange where we estimate that about 5% could have been detected. It is thus clear that exchange does not occur either along the reaction pathway or parallel to it.

The magnitude of k_H/k_D for bromination is somewhat low, but this could be interpreted as arising from a shift to a less synchronous proton removal still lying in the bimolecular region. These results might also be accommodated by an E2S mechanism exactly analogous to the E2C mechanism.[21]

It is interesting that the values of k_H/k_D for the NCS and NBS reactions differ from those with the halogen counterparts. This seems to indicate that the succinimidyl anion is participating to some extent in proton removal.

Concentration Dependence of Product Ratios.—Our preliminary studies indicated a general trend toward increased cleavage with all halogenating agents when the equimolar initial concentrations of sulfide and halogenating agent were raised; however, reproducible data could be obtained only for bromination in carbon tetrachloride. The absence of concentration dependence of c/α at low reactant concentrations coupled with the kinetic isotope effect is consistent with an hypothesis that both cleavage and α-substitution products stem from a common intermediate and that both reactions are first order in both bromosulfonium cation and bromide anion (Scheme IV).[22] It is not consistent with

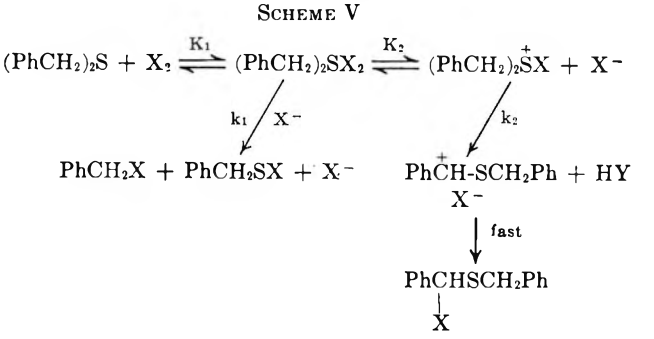
SCHEME IV



participation by any process, such as rate-determining monomolecular carbon–sulfur cleavage of a halosulfonium cation, which is zero order in bromide ion.

At higher concentrations, the explanation must be more complex. One could assume the intervention of two halosulfonium salts, one largely covalent and the other ionic, which proceed to different products by a transformation involving halide ion (Scheme V). Mak-

SCHEME V



ing the assumption that K_1 is large, a kinetic scheme based on this mechanism leads to the time-dependent expression

$$\frac{c}{\alpha} = \frac{k_2 X_0}{2k_1 K_2}\left(\frac{2+\beta t}{2+\beta t}\right)$$

where X_0 is the initial sulfide concentration and $\beta = -k_1 X_0$. Allowing the reaction to go to completion this derivation predicts c/α to be a linear function of the initial sulfide concentration over the entire concentration range.

$$c/\alpha = k_2 X_0/k_1 k_2$$

Postulation that a salt effect might tend to favor bond cleavage as the reactions proceed at the higher concentrations, appears attractive, but this interpretation may be discarded. Ionization of the hydrogen bromide to any large extent in carbon tetrachloride seems unlikely when one considers that K_{diss} for HCl in nitromethane is only 6.0×10^{-7}.[23]

(19) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962).

(20) The kinetic isotope effect for an Elcb reaction, which for the case of an irreversible elimination must be identical when measured competitively and by independent runs, is expected to be unity [D. J. McLennan, *Quart. Rev.*, **21**, 490 (1967); Z. Rapopport, *Tetrahedron Lett.*, 3601 (1968)], and has been measured in one case to be 1.2 [D. J. Cram, and A. S. Wingrove, *J. Amer Chem. Soc.*, **86**, 5490 (1964)].

(21) See, for example, A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968); E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968).

(22) The product ratio does not demand the intervention of free ions in solution nor does it demand that the attacking species be the bromide ion rather than Br_3^- or HBr_2^-. It also does not rule out the possibility that the reactive species are maintained at low concentration by rapid equilibrium processes.

(23) Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Amer. Chem. Soc.*, **91**, 4199 (1969).

A final alternative exists; namely, that in the nonpolar solvents used, aggregation of halosulfonium salts becomes acute at about 0.3 *M*. The aggregates, in which a charge transfer type structure[9] probably exists, then decompose to a higher proportion of cleavage products than do the monomeric ion pairs. Thus, it appears that most appropriate general formation of these events is that shown in Scheme IV with an hypothesis of aggregation at higher concentrations of reactants.

Experimental Section

Materials and Apparatus for the Halogenation of Benzyl Sulfide.—Benzyl sulfide was obtained commercially and recrystallized from ethanol. Commercially available NCS and NBS were purified by recrystallizing from eight times their weight of water. Reagent grade deuteriochloroform, carbon tetrachloride, bromine, 1 *N* sodium thiosulfate solution, and Matheson anhydrous hydrogen chloride and chlorine were used without further purification. Purified hexamethylbenzene was used as an internal standard for quantitative nmr measurements. Nmr determinations were performed on a Varian Associates, Model A-60, spectrometer. Each integration was repeated at least four times to obtain the average value.

General Procedure for Bromination of Benzyl Sulfide.—A stock solution containing 214.3 mg (1 mmol) of benzyl sulfide and 13.5 mg (0.083 mmol) of hexamethylbenzene in 2.4 ml of carbon tetrachloride was delivered by pipet into a 15-ml round-bottomed flask equipped with a calcium chloride drying tube The solution was stirred and equilibrated for at least 10 min in the kinetic bath. A solution containing 159.8 mg (1 mmol) of bromine in 2.4 ml of carbon tetrachloride maintained at constant temperature in the kinetic bath was then added to the flask all at once. The solid adduct initially formed completely disappeared in less than 2 min, and the brown solution was stirred at 35° for 30 min. At the end of this time, to the red solution was added 1 drop of acetone-d_6 to destroy benzyl sulfenyl bromide. The solution was concentrated to about 2 ml by flushing with nitrogen. This concentrated solution was then used for nmr analysis.

General Procedure for Chlorination of Benzyl Sulfide.—Approximately 0.25 ml (1 mmol) of a solution of chlorine in carbon tetrachloride, whose chlorine content was determined by titration against 1 *N* sodium thiosulfate solution,[24] was then added to 4.55 ml of a thermostated stock solution containing 1 mmol of the sulfide in 4.55 ml of carbon tetrachloride. The reaction was carried out at 35° for 30 min and the final solution was concentrated for nmr analysis.

General Procedure for Halogenation of Benzyl Sulfide with NCS and NBS.—To 4.8 ml of a stock solution containing 1 mmol of the sulfide and the internal standard in carbon tetrachloride was added in one portion 1 mmol of solid NCS or NBS. The reaction proceeded as described above. The solid, benzylsulfenylsuccinimide, was removed by filtration, and the filtrate was concentrated for nmr analysis. When the same reaction was performed in deuteriochloroform, all reaction products remained in solution.

Benzyl Alcohol-α-α-d_2.—To 3 g (0.072 mmol) of lithium aluminum deuteride suspended in 225 ml of freshly distilled ether at reflux was added dropwise during a 50-min period 21.2 g (0.14 mol) of ethyl benzoate in 50 ml of ether. The addition was so adjusted that gentle reflux was maintained. The resulting suspension was maintained under reflux for an additional 3 hr. To the final thick slurry, cooled with ice water, was added slowly 5 ml of water and then it was acidified with concentrated sulfuric acid. The mixture was heated under reflux for 1.5 hr and cooled; the clear layer was removed. Ether (250 ml), followed by 2 ml of water and a few drops of concentrated sulfuric acid, was added and the mixture was refluxed for an additional hour, after which it was cooled and filtered. The residual oil after solvent removal was made neutral to litmus paper and was vacuum distilled. The 15.3 g (99%) of product, bp 91–92° (15 mm), was shown by vpc analysis to be slightly contaminated with ethyl benzoate. Nmr analysis of the α-α-dideuteriobenzyl alcohol showed no detectable protons at the benzylic methylene position.

(24) F. Kurzer and J. R. Powell, *Org. Syn.*, **43**, 934 (1963).

Benzyl Chloride-α-α-d_2.—The crude benzyl alcohol-α,α-d_2 was dissolved in 100 ml of benzene, and to this solution was added, dropwise with the temperature maintained at 20–25°, 21.5 g (0.18 mol) of thionyl chloride in 50 ml of benzene. The addition was complete in 45 min, and the resulting solution was heated under reflux for 3 hr. The final solution was cooled, and the solvent was removed under vacuum by rotary evaporator. The residual yellow oil was vacuum distilled giving 11.3 g (87.5%) of benzyl chloride-α,α-d_2, bp 60–65° (15 mm). Vpc analysis of the product showed two components, the larger of which was identified as benzyl chloride-α-α-d_2.

Benzyl Sulfide-α-α-d_2.—To sodium benzylmercaptide prepared from 11.0 g (0.0884 mol) of benzyl mercaptan and 4 g (0.1 mol) of sodium hydroxide pellets in 50 ml of ethanol was added 11.3 g of crude benzyl chloride-α-α-d_2. The addition was carried out at 20–25° and was completed in 15 min. The resulting suspension was heated under reflux for 1 hr. The final brown mixture was cooled, and the organic layer was isolated by decantation. The solvent was removed on a rotary evaporator under vacuum leaving a semisolid mass. To the combined solids was added 1 l. of water to precipitate the product which was removed by filtration, washed twice with cold water, and dried. The yellow solid was recrystallized from 200 ml of ethanol giving 10.2 g (34%) of benzyl sulfide-α,α-d_2: mp 49°; ν_{max}^{KBr} 3010, 2910, 2140, 1595, 1575, 1490, 1450, 1410, 1070, 750, 700 cm^{-1}; nmr (CCl_4) δ 3.47 (s, 2 H), 7.16 (s, 5 H) ppm; mass spectrum *m/e* at 216 (100), 125 (22.1), 124 (22.9), 123 (55.4), 122 (20.3), 94 (38.5), 93 (56.1), 92 (27.5), 91 (51.8), 77 (21.6), 65 (43.2), 51 (22.2), 46 (31.5), 45 (51.8), 39 (25.4); d_0 0.299%, d_1 1.79%, d_2 97.9%.

α-Chlorobenzyl Benzyl Sulfone.—Benzyl sulfide, 2.14 g (0.01 mol), in carbon tetrachloride was chlorinated with NCS in a manner described in the general procedure. After the reaction was complete and solids had been removed by filtration, the reaction mixture was oxidized with *ca.* 0.04 mol of monoperphthalic acid in ether. The sulfone, after work-up, recrystallization from ethanol, and drying, was obtained in 78.5% yield: mp 117–118° (lit. 123°[25], 118°); ν_{max}^{KBr} 3010, 2983, 1600, 1580, 1493, 1452, 1410, 1320 (sulfone), 1135, 775, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.39 (s, 5 H), 5.92 (s, 1 H), 4.40 (q, J = 14.0 Hz, 2 H) ppm.

α,α-Dichlorobenzyl Benzyl Sulfide.—To a solution of 3.21 g (0.015 mol) of benzyl sulfide in 20 ml of carbon tetrachloride was added 4.4 g (0.0325 mol) of sulfuryl chloride at room temperature over a 30-min period according to the procedure of Paquette.[16] The solution was then stirred at room temperature for 1 hr, after which it was evaporated to give a thick oil. Nmr analysis was performed without further purification: nmr ($CDCl_3$) δ 7.83 (m, 2 H), 7.16 (m, 8 H), 4.22 (s, 2 H) ppm.

Benzylsulfenyl Chloride.—Into a solution of 2.47 g (0.01 mol) of benzyl disulfide in carbon tetrachloride solution at −15° was bubbled 0.71 g (*ca.* 0.01 mol) of chlorine during a 10-min period. The resulting red solution was kept at −15° until an nmr measurement was performed. The nmr of this reaction mixture showed no signals for benzyl disulfide. It contained three singlets at δ 7.25, 4.52, and 4.29 ppm.

Benzylsulfenyl Bromide.—To a solution of 739 mg (3 mmol) of benzyl disulfide in carbon tetrachloride at −15° was added 5 ml of carbon tetrachloride containing 480 mg (3 mmol) of bromine. The red solution was stirred at −15° for 20 min before an nmr was taken. The nmr spectrum shows two singlets at 7.30 and 4.24 ppm assignable to the phenyl and methylene protons of benzylsulfenyl bromide, respectively.

To the above mixture at −15° was then added 643 mg (3 mmol) of benzyl sulfide in carbon tetrachloride. The resulting mixture was kept at 35° with constant stirring for 30 min. Nmr analysis at this stage gave, in addition to the weak signal of benzylsulfenyl bromide, the peaks corresponding to α-bromobenzyl sulfide and benzyl disulfide. Nmr analysis after a 1-hr period at 35° gave essentially the same signals except that the intensity of the disulfide peak increased and that of the benzylsulfenyl bromide signal decreased.

N-Benzylsulfenylsuccinimide.—A solution of 14.8 g (0.06 mol) of benzyl disulfide, 10.7 g (0.06 mol) of NBS, and a catalytic amount of benzoyl peroxide in carbon tetrachloride was heated to reflux for 30 min. Work-up followed the published procedure[25] giving a crude solid, recrystallization of which from alcohol gave

(25) H. Böhme, H. Fischer, and R. Frank, *Justus Liebigs Ann. Chem.*, **563**, 54 (1949).

(26) W. Groebel, *Ber.*, **93**, 284 (1960).

7.0 g (53%) of needles: mp 161–162°, lit.[27] 162°; nmr ($CDCl_3$) δ 7.30 (s, 5 H), 4.11 (s, 2 H), 2.65 (s, 4 H) ppm; ν_{max}^{KBr} 2920, 2850, 1720, 1555, 1490, 1419, 1305, 1148, 765, and 713 cm^{-1}.

N-Benzylsuccinimide.—This compound was prepared according to the procedure of Argoria.[28]

Chlorination of Benzyl Sulfide with NCS in the Presence of Deuterium Chloride.—A 15-ml round-bottomed flask equipped with magnetic stirrer was charged with 214 mg (1 mmol) of benzyl sulfide in 4.8 ml of carbon tetrachloride. Into this solution kept at 35° was bubbled a stream of dry deuterium chloride at a rate of one bubble every 10 sec. A 134-mg (1 mmol) portion of solid NCS was then added, and the resulting mixture was continuously stirred under deuterium chloride flow. Nmr analyses of the filtrate after 30 min of reaction showed four peaks for the methylene protons at δ 219, 232.5, 236.5, and 250 Hz downfield from TMS. There were no detectable signals at δ 243.8 and 228.85 Hz as evidenced by expanding this area at 50-Hz sweep width.

(27) W. Tagaki, K. Kikukawa, K. Ando, and S. Oae, *Chem. Ind. (London)*, **38**, 1624 (1964).

(28) A. Argoria, J. Barassi, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 2509 (1963).

Registry No.—Benzyl sulfide, 538-74-9.

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β-Keto Sulfoxides. X. Conversion of Cycloalkanecarboxylic Esters to 1-Cycloalkylpropane-1,2-diones[1]

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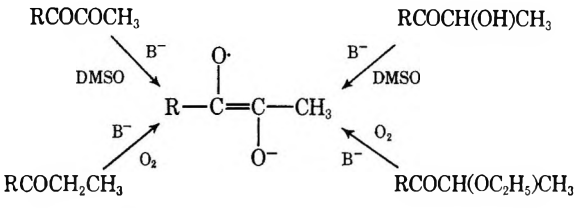
The conversion of cycloalkylcarboxylic esters to cycloalkyl keto sulfoxides ($RCOCH_2SOCH_3$) and hence to α diketones ($RCOCOCH_3$), cycloalkyl ethyl ketones ($RCOCH_2CH_3$), cycloalkyl vinyl ketones [$RCOCH{=}CH_2$, $RCOC(CH_3){=}CH_2$], and α-ethoxy ketones [$RCOCH(OC_2H_5)CH_3$] is described.

The 1-cycloalkylpropane-1,2-diones, or the corresponding hydroxy ketones, were required for the synthesis of a series of semidione radical anions (Scheme I).[2,3] In addition to the previously known routes to

SCHEME I



semidiones,[2] we found during the course of this work that the oxidation of α-alkoxy ketones in basic solution was often an excellent method for the preparation of semidiones. We have developed the synthesis of the diketones from the cycloalkanecarboxylic esters *via* the β-keto sulfoxides,[4,5] as shown in Scheme II.[6,7] The alkylated β-keto sulfoxides[8,9] were also reduced[5,6] to yield the ketones ($RCOCH_2CH_3$) and α-ethoxy ketones

SCHEME II

$$RCO_2C_2H_5 + CH_3SOCH_2^- \longrightarrow \underset{1}{RCOCH_2SOCH_3} \xrightarrow[2.\ CH_3I]{1.\ B^-} \underset{2}{RCOCH(CH_3)SOCH_3} \xrightarrow{H^+} RCOC(OH)(CH_3)SCH_3 \xrightarrow{-CH_3SH} RCOCOCH_3$$

[$RCOCH(OC_2H_5)CH_3$] and pyrolyzed[10] to yield the vinyl ketones (Scheme III).

SCHEME III

$$RCOCH(CH_3)SOCH_3 \xrightarrow{Zn,\ H^+} RCOCH_2CH_3 + RCOCH(OC_2H_5)CH_3$$
$$RCOCH(CH_3)SOCH_3 \xrightarrow{\Delta} CH_3SOH + RCOCH{=}CH_2$$

Results and Discussion

Condensation of the cycloalkanecarboxylic esters with the methylsulfinyl carbanion presented no particular problems.[4,5] The reaction with cyclohexanecarboxylic ester has been previously reported.[5] Yields ranged from 41% with R = cyclopropyl to 74% with R = cyclopentyl or cyclohexyl. The β-keto sulfoxides (**1**) were converted to the enolate anions with sodium hydride in THF and alkylated with methyl iodide to yield $RCOCH(CH_3)SOCH_3$ (**2**) and $RCOC(CH_3)_2SOCH_3$ (**3**) (**a**–**f**, R): **a**, cyclopropyl; **b**, 1-methylcyclopropyl; **c**, cyclobutyl; **d**, cyclopentyl; **e**, cyclohexyl; **f**, 1-methylcyclobutyl.

The cyclopropyl and cyclobutyl compounds were unique in the ease with which dialkylation occurred. Use of a slight excess of methyl iodide and sodium hydride in the alkylation resulted in a mixture of **2a**–**3a**. In **1a** the second methyl group entered at the position α to both the carbonyl and sulfoxide functions to form **3a** exclusively. The cyclobutyl analog (**1c**) reacts with 2.3 equiv of sodium hydride and methyl iodide to yield a mixture of the dimethyl (**3c**) and trimethyl (**3f**) derivatives. Reaction of **1a** with 3.4 equiv of sodium hydride and methyl iodide yielded only **3a**. We believe the lack of methylation at the methine position of **1a** is due to a stereoelectronic effect which places the methine hydrogen in the nodal plane of the carbonyl group

(1) For part IX, see *J. Org. Chem.*, **35**, 2106 (1970). This work was supported by a grant from the Army Research Office (Durham).

(2) G. A. Russell and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 744 (1964).

(3) G. A. Russell and H. Malkus, *ibid.*, **89**, 160 (1967).

(4) H.-D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).

(5) E. J. Corey and M. J. Chaykovsky, *ibid.*, **86**, 1639 (1964); **87**, 1345 (1965).

(6) G. A. Russell and G. J. Mikol, *ibid.*, **88**, 5498 (1966).

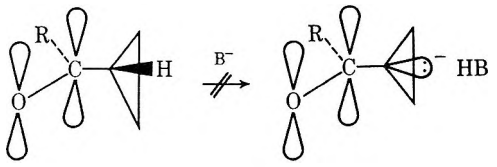
(7) T. L. Moore, U. S. Patent 3,409,673 (Dec 22, 1966).

(8) P. G. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).

(9) G. A. Russell, E. Sabourin, and G. J. Mikol, *ibid.*, **31**, 2854 (1966).

(10) C. A. Kingsbury and D. J. Cram., *J. Amer. Chem. Soc.*, **82**, 1816 (1960).

thereby effectively blocking conjugation between the carbonyl group and a developing carbanion center.



Compound **1a** was reduced by treatment with a fourfold excess of zinc dust in a 3:2 mixture of ethanol–acetic acid by refluxing for 4–5 hr to yield cyclopropyl methyl ketone (62%) and the Pummerer rearrangement product ω-(methylmercapto)-ω-acetoxyacetylcyclopropane (19%). The reduction products of **2a–2e** are summarized in Table I. Table I also lists the pyrolysis products of **2b**, **2d**, **2e**, and **3a–3f** as observed in glpc at 150°.

TABLE I

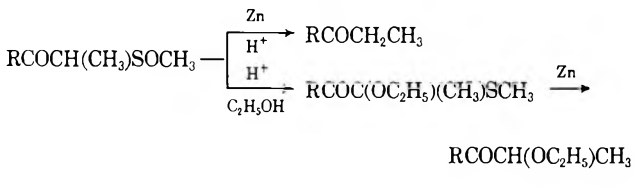
CONVERSION OF β-KETO SULFOXIDES TO KETONES

	Yield, %		
$RCOCH(CH_3)SOCH_3$, R	$RCOCH_3$-CH_3[a]	RCOCH-$(OC_2H_5)CH_3$[a]	$RCOCH{=}CH_2$[b]
Cyclopropyl	36	36	
Cyclopropyl	24[c]	54[c,d]	
1-Methylcyclopropyl	53	8	41
Cyclobutyl[e]		37	
Cyclopentyl	33	41	45
Cyclohexyl	36	40	48
$RCOC(CH_3)_2SOCH_3$, R	RCOCH-$(CH_3)_2$		RCOC-$(CH_3){=}CH_2$
Cyclopropyl			51
Cyclobutyl	34[e]		52[f]
1-Methylcyclobutyl			70[f]
Cyclopentyl			51
Cyclohexyl			53

[a] By refluxing 4–5 hr with acetic acid–ethanol in the presence of excess zinc dust. [b] Gas-liquid chromatography using 2-m 15% Carbowax 20M on Chromosorb W column at 150°. [c] Condition *a* with aqueous acetic acid. [d] $RCOCH(OH)CH_3$. [e] Products isolated by reaction of a mixture of **2c** and **3c**. [f] Conversion of **3f** in a mixture of ~66% **3c** and 34% **3f**.

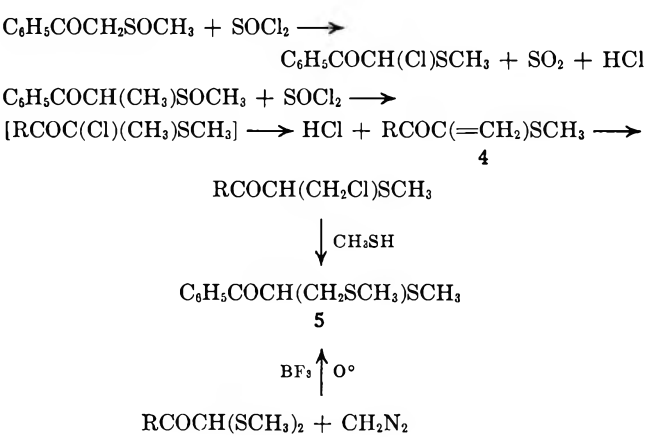
The reduction of the alkylated β-keto sulfoxides appears to involve competing processes to yield the ketone or the Pummerer rearrangement product, Scheme IV.

SCHEME IV



Much more drastic conditions were required to reduce **2** than were encountered in our previous studies with ω-(methylsulfinyl)acetophenone which was easily reduced without ether formation.[6] α substitution generally reduces the ease with which β-keto sulfoxides undergo the Pummerer rearrangement and the yield of the Pummerer rearrangement product.[6,11] Thus treatment of **2a–2e** with thionyl chloride did not yield the α-chloro thio ethers as observed for the unalkylated β-keto sulfoxides.[9,12] Moreover, whereas ω-(methylsulfinyl)acetophenone reacts with thionyl chloride to yield ω-chloro-ω-(methylmercapto)acetophenone,[12] the reaction with the α-methyl derivative yields only the chloromethyl derivative readily characterized as **5**. Apparently, the α-alkyl substituent promotes rearrangement of the α-chloro ketone as shown in Scheme V. Compound **5** was independently synthesized in

SCHEME V



55% yield from the reaction of diazomethane with the methyl mercaptal of phenylglyoxal in ether solution at 0° (boron trifluoride catalysis).

The best yields of isolated diketones were obtained by treatment of the β-keto sulfoxides (**1**) with hydrogen chloride in DMSO solution. Methyl mercaptan was allowed to escape from the reaction flask. Table II

TABLE II

CONVERSION OF β-KETO SULFOXIDES ($RCOCH(CH_3)SOCH_3$) TO α DIKETONES ($RCOCOCH_3$)[a]

R	% yield of diketone
Cyclopropyl	37
Cyclobutyl	39
Cyclopentyl	74
Cyclohexyl	63[b]

[a] Isolated by steam distillation from the reaction of 1 g of keto sulfoxide with a mixture of 2 ml of DMSO, 3 ml of concentrated HCl, and 10 ml of water. [b] Isolated by extraction from the reaction product of 3.2 g of the keto sulfoxide with 15 ml of DMSO and 6 ml of concentrated hydrochloric acid.

gives the yields of the observed products. Other techniques for the conversion of β-keto sulfoxides to dicarbonyl compounds involve the reactions of the keto sulfoxide with iodine or acid plus an oxidizing agent.[7,13] The acid will bring about the Pummerer rearrangement and the oxidizing agent will remove the methyl mercaptan from the equilibrium, $RCOCR'(OH)SCH_3 \rightleftarrows RCOCOR' + CH_3SH$. Cupric acetate precipitates $Cu(SCH_3)_2$ and is a very satisfactory reagent for glyoxal preparation.[6,14]

An alternate route to the 1-cyclopropylpropane-1,2-dione was from the α-hydroxy ketone produced by the reduction of the keto sulfoxide in aqueous acetic acid with zinc dust. The hydroxy ketone was oxidized by

(11) G. A. Russell and G. J. Mikol, "Mechanisms of Molecular Migration," Vol. I., B. S. Thyagarajan, Ed., Interscience, 1968, p 157.

(12) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **35**, 764 (1970).
(13) T. L. Moore, *ibid.*, **32**, 2786 (1967).
(14) G. J. Mikol and G. A. Russell, *Org. Syn.*, **48**, 109 (1968).

cupric sulfate in pyridine to the diketone in a 55% yield.[15] This technique was not extended to the other keto sulfoxides.

The cycloalkyl ethyl ketones could be oxidized to the semidiones in basic solution containing a trace of oxygen (Scheme I). The α-ethoxy derivatives also oxidized to yield the semidione in basic solution. The esr spectra from the α-ethoxy ketones were of particularly high quality, for example, Figure 1 with R = cyclopropyl and 1-methylcyclopropyl. Apparently the process of Scheme VI occurs readily.

SCHEME VI

$$RCOCH(OC_2H_5)CH_3 + B^- \rightleftharpoons RC(O^-)=C(OC_2H_5)CH_3 \xrightarrow{O_2}$$

$$RCOC(OC_2H_5)(CH_3)OO^- \xrightarrow{DMSO} RCOC(OC_2H_5)(CH_3)O^- \longrightarrow$$

$$C_2H_5O^- + RCOCOCH_3 \xrightarrow{DMSO,\ B^-} RC(O^{\cdot})=C(O^-)CH_3$$

Experimental Section

β-Keto Sulfoxides 1.—A 500-ml three-necked flask with a mechanical stirrer, pressure equalized dropping funnel, a fritted suction tube for removal of solvent, and nitrogen inlet and outlet tubes was employed. Sodium hydride in a mineral oil slurry was placed in the flask and the mineral oil removed by stirring thrice with 20 ml of pentane. Dimethyl sulfoxide was added with 1 drop of an antifoaming agent and the mixture stirred at 63° for 2.5 hr. The cycloalkanecarboxylic ester was added slowly at 10°. After 40-min stirring at 25° the products were poured into 300 ml of ice water. The aqueous solution was extracted twice with 20-ml portions of ether and then acidified to pH 2 while cooled in an ice bath. The solution was extracted with seven 60-ml portions of methylene chloride and the organic extracts washed with 20 ml of 10% aqueous sodium bicarbonate solution. The solution was dried ($MgSO_4$) and evaporated to yield an oil which according to tlc contained only minor impurities The oil was further purified by chromatography with ethyl acetate on silica gel or by distillation.

Ethyl cyclohexanecarboxylate (20 g, 128 mmol) with 260 mmol of sodium hydride and 110 ml of DMSO gave 17.8 g (74%) of **ω-(methylsulfinyl)acetylcyclohexane, 1e**: mp 55–57°, lit. mp 62–63°.[5] Ethyl cyclopentanecarboxylate (30 g, 211 mmol) with 420 mmol of sodium hydride and 160 ml of DMSO gave 27 g (74%) of **ω-(methylsulfinyl)acetylcyclopentane, 1d**: bp 123–125° at 0.5 Torr; ir (CCl_4) 1700 (C=O), 1050 cm^{-1} (SO); mass spectrum (70 eV) *m/e* (rel intensity) 158 (7), 97 (23), 69 (100).

Anal. Calcd for $C_8H_{14}SO_2$ (174): C, 55.14; H, 8.09; S, 18.39. Found: C, 55.28; H, 8.01; S, 18.62.

Ethyl cyclbutanecarboxylate (25.6 g, 200 mmol) with 400 mmol of sodium hydride in 155 ml of DMSO gave 14.1 g (44%) of **ω-(methylsulfinyl)acetylcyclobutane, 1c**: bp 129–130° at 1 Torr; mp 60–62°; ir (KBr) 1697 (C=O), 1025 cm^{-1} (SO); mass spectrum (70 eV) *m/e* (rel intensity) 145 (1.6), 144 (11), 97 (2), 83 (32), 55 (100).

Anal. Calcd for $C_7H_{14}SO_2$ (160): C, 52.47; H, 7.55; S, 20.01. Found: C, 52.44; H, 7.62; S, 20.17.

Ethyl cyclopropanecarboxylate (22.8 g, 200 mmol) with 400 mmol of sodium hydride in 155 ml of DMSO gave 12.1 g (41%) of **ω-(methylsulfinyl)acetylcyclopropane, 1a**: bp 114–115° at 0.5 Torr; ir 1700 (C=O), 1038 cm^{-1} (SO); mass spectrum (70 eV) *m/e* (rel intensity) 130 (15), 69 (100), 41 (58).

Anal. Calcd for $C_6H_{10}SO_2$ (146): C, 49.29; H, 6.89; S, 21.92. Found: C, 49.44; H, 6.89; S, 22.13.

Methyl α-methylcyclopropanecarboxylate was prepared by the reaction of 20 g of methyl methacryate in 40 ml of ether at −15° with the diazomethane prepared from 64 g of Diazald. The pyrazoline was decomposed at 110–120° to give 13.4 g (59%) of the ester, bp 119–120°, lit.[16] bp 123–126°. Reaction of 13.4 g (117 mmol) of the ester with 5.17 g (216 mmol) of sodium hydride in 72 ml of DMSO gave 9.1 g (49%) of **1-(methylsulfinylacetyl)-1-methylcyclopropane, 1b**: bp 105–108° at 0.5 Torr; ir (CCl_4) 1675 (C=O), 1047 cm^{-1} (SO); mass spectrum (70 eV) *m/e* (rel intensity) 160 (1.2), 145 (11), 143 (17), 97 (24), 55 (100).

Anal. Calcd for $C_7H_{12}SO_2$ (160): C, 52.47; H, 7.55. Found: C, 52.25; H, 7.50.

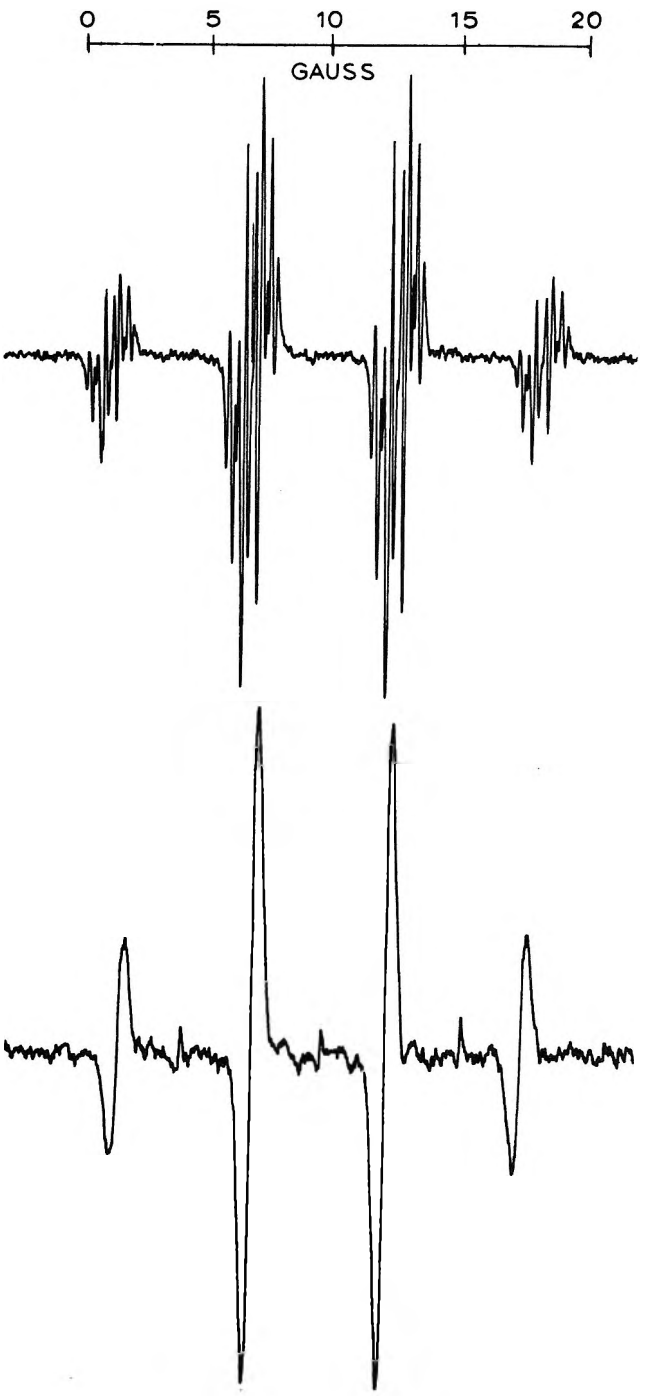


Figure 1.—Top, oxidation, product of 1-ethoxyethyl cyclopropyl ketone in DMSO containing potassium *t*-butoxide; bottom, oxidation product of 1-methylcyclopropyl ethyl ketone in DMSO containing cesium *t*-butoxide.

Methylated β-Keto Sulfoxides 2a–2e, 3a–3f.—Sodium hydride was washed free of mineral oil as described previously and dispersed in THF. A solution of the sulfoxide to be alkylated in THF was added to the sodium hydride at 10°. After 30 min methyl iodide was added slowly. The reaction mixture was stirred for 2–4 hr at 25° and then poured into 400 ml of water containing a trace of sodium thiosulfate. The mixture was extracted seven times with 40-ml portions of methylene chloride and dried over $MgSO_4$. Removal of the solvent left oils which were further purified by chromatography with 3:1 chloroform–hexane or ethyl acetate, from silica gel.

α-(Methylsulfinyl)propionylcyclopropane, 2a, was prepared from 9 g of **1a** (61.6 mmol) by reaction with 63 mmol of sodium

(15) H. T. Clarke and E. E. Drieger, "Organic Syntheses," Coll. Vol. I, 2nd ed, Wiley, New York, N. Y., 1941, p 87.

(16) S Siegel, *J. Amer. Chem. Soc.*, **72**, 3815 (1950).

hydride and 65 mmol of methyl iodide. After a 2.5-hr reaction period, 7.1 g (72%) of **2a** was isolated: ir 1683 (C=O), 1042 cm^{-1} (SO); pmr (60 MHz, CCl_4) δ 0.88–1.20 (m, 4.7, CH_2–CH_2), 1.25–1.60 (m, 4, CCH_3), 1.88–2.25 (m, 1, CH), 3.75–4.1 (m, 1, CH–SO), 2.31–2.38 (t, 3.4, CH_3).

1-(Methylsulfinyl)ethyl 1-methylcyclopropyl ketone, 2b, was prepared from 41.5 mmol of **1b** by reaction with 41.6 mmol of sodium hydride and 41.5 mmol of methyl iodide in 55 ml of THF which gave 5.2 g (72%): ir (CCl_4) 1675 (C=O), 1050 cm^{-1} (SO); pmr (60 MHz, CCl_4) δ 0.70–0.95 (m, 2, $-CH_2$–CH_2), 1.15–1.55 (m, 8), 3.86–4.20 (m, 1, CH), 2.38 (d, 3, $SOCH_3$).

α-(Methylsulfinyl)propionylcyclopentane, 2d, was prepared from 8.7 g (50 mmol) of **1d**, 55 mmol of sodium hydride, and 80 mmol of methyl iodide. A 74% yield of **2d** was isolated: ir (CCl_4) 1700 (C=O), 1055 cm^{-1} (SO); pmr (60 MHz, CCl_4) δ 1.4–2.1 (m, 8, $CH_2CH_2CH_2CH_2$), 2.7–3.5 (m, 0.9, CH), 3.80–4.1 (m, 0.75, COCHSO), 1.2–1.53 (q, 3.8, CH_3), 2.29–2.39 (s, 3.8, $SOCH_3$).

α-(Methylsulfinyl)propionylcyclohexane,[9] **2e**, was prepared in 79% yield from 40 mmol of **1e**, 43 mmol of sodium hydride, and 67 mmol of methyl iodide in 20 ml of THF.

α-(Methylsulfinyl)isopropyl cyclopropyl ketone, 3a, was prepared in 31% yield from 41.5 mmol of **1a**, 65 mmol of sodium hydride, and 65 mmol of methyl iodide. Chromatography of the product from silica gel using chloroform–hexane as the eluent gave **3a** as the first fraction. A second fraction yielded **2a** in 39% yield. Compound **3a** gave mass spectrum (70 eV) *m/e* (rel intensity) 142 (1.4), 110 (15), 41 (71), 69 (100).

Anal. Calcd for $C_8H_{14}SO_2$ (174); C, 55.14; H, 8.10; S, 18.40. Found: C, 55.13; H, 8.25; S, 18.49.

α-(Methylsulfinyl)propionylcyclobutane (2c), 2-(methylsulfinyl) 2-propyl cyclobutyl ketone (3c), and 2-(methylsulfinyl)-2-propyl 1-methylcyclobutyl ketone (3f) were obtained as mixtures by alkylation. A mixture of ~66% **3c** and ~34% **3f** were obtained by the reaction of 27.4 mmol of **1c** with 63 mmol of sodium hydride and 62 mmol of methyl iodide in 45 ml of THF. Pyrolysis on a glpc Carbowax column yielded a mixture of the two vinyl ketones. Reaction of 41.5 mmol of **1c** with 46 mmol of sodium hydride and 45 mmol of methyl iodide yielded a product that contained approximately equal amounts of **2c** and **3c**. Reduction yielded 1-cyclobutyl-2-ethoxy-1-propanone (from **2c**) and isopropyl cyclobutyl ketone (from **3c**).

Pyrolysis of β-Keto Sulfoxides.—Samples of the β-keto sulfoxides of ~50 mg were passed through a glpc column (2 m) of 20% Carbowax on Chromosorb at 145–170° in an Aerograph Autoprep instrument. The products were collected and identified. Keto sulfoxide **2b** (53 mg) at 180° gave 13.9 mg (41%) of **1-methylcyclopropyl vinyl ketone**: ir (CCl_4) 1678 (C=O), 1612 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 0.58–0.84 (m, 2, CH_2–CH_2), 1.02–1.35 (m, 2, CH_2–CH_2), 1.35 (s, 3, CH_3), 5.42–6.46 (m, 3, $CH{=}CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 110 (10), 83 (10), 55 (100), 41 (9).

From 57.5 mg of **2d** there was obtained at 180° 17 mg (45%) of **cyclopentyl vinyl ketone**: ir (CCl_4) 1690, 1675 (C=O), 1610 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.50–1.90 (m, 8, CH_2CH_2-CH_2CH_2), 2.70–3.30 (m, 1, >CH–), 5.56–6.34 (m, 3, $CH{=}CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 124 (13), 97 (8), 83 (80), 69 (75), 55 (100), 41 (90).

Anal. Calcd for $C_8H_{12}O$ (124): C, 77.38; H, 9.74. Found: C, 77.25; H, 9.89.

Cyclohexyl vinyl ketone was prepared from 54 mg of **2e** in 48% yield at 145°: ir (CCl_4) 1695, 1675 (C=O), 1610 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.0–2.0 [m, 10, $(CH_2)_5$], 2.2–2.8 (m, 1, >CH–), 5.5–6.4 (m, 3, $CH{=}CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 138 (8), 110 (5), 97 (10), 83 (51), 55 (100).

Anal. Calcd for $C_9H_{14}O$ (138): C, 78.21; H, 10.21. Found: C, 78.09; H, 10.35.

The keto sulfoxide **3a** (50 mg) at 135° gave 16 mg (51%) of **cyclopropyl isopropenyl ketone**: ir (CCl_4) 1665 (C=O), 1627 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 0.70–1.15 (m, 4, CH_2CH_2), 2.12–2.52 (m, 1, >CH–), 1.85 [d, 3, $-C(CH_3){=}$] 6.00 (s, 1, C=CH), 5.69 (m, 1, C=CH); mass spectrum (70 eV) *m/e* (rel intensity) 110 (14), 69 (100), 41 (56).

Anal. Calcd for $C_7H_{10}O$ (110): C, 76.32; H, 9.15. Found: C, 76.40; H, 9.32.

The mixture of **3c** and **3f** described previously gave about equal amounts of **cyclobutyl isopropenyl ketone** and **1-methylcyclobutyl isopropenyl ketone** when pyrolyzed. Cyclobutyl isopropenyl ketone had ir (CCl_4) 1668 (C=O), 1627 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.8–2.5 (m, 6, $CH_2CH_2CH_2$), 3.4–3.9 (m, 1, >CH–), 1.81 [d, 3, $C(CH_3){=}$], 5.6–5.8 (m, 2, $=CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 124 (4), 109 (14), 83 (8), 69 (100), 55 (71), 41 (72).

Anal. Calcd for $C_8H_{12}O$ (124): C, 77.38, H, 9.74. Found: C, 77.28; H, 9.90.

1-Methylcyclobutane isopropenyl ketone had ir (CCl_4) 1665 (C=O), 1625 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.7–2.8 (m, 6, $CH_2CH_2CH_2$), 1.51 (s, 3, $>CCH_3$–), 1.81 [d, 3, $-C(CH_3){=}$], 5.53–5.78 (m, 2, $=CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 138 (2), 123 (7), 95 (11), 70 (12), 69 (100), 68 (11), 41 (95).

Anal. Calcd for $C_9H_{14}O$ (138): C, 78.21; H, 10.21. Found: C, 78.01; H, 10.04.

α-(Methylsulfinyl)isopropyl cyclopentyl ketone (52 mg) gave 18 mg (51%) of **cyclopentyl isopropenyl ketone** at 145°: ir (CCl_4) 1672 (C=O), 1631 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.5–1.9 [m, 8, $(CH_2)_4$], 3.15–3.54 (m, 1, >CH–), 1.81 [d, 3, $-C(CH_3){=}$], 5.68–5.86 (m, 2, $=CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 138 (11), 110 (7), 97 (22), 69 (100), 55 (8), 41 (73).

α-(Methylsulfinyl)isopropyl cyclohexyl ketone (53 mg) gave 20 mg (53%) of **cyclohexyl isopropenyl ketone** at 145°: ir (CCl_4) 1670 (C=O), 1630 cm^{-1} (C=C); pmr (60 MHz, CCl_4) δ 1.0–2.0 (m, 10, $(CH_2)_5$, 2.73–3.5 (m, 1, >CH–), 2.82 [d, 3, $-C(CH_3){=}$], 5.67–5.83 (m, 2, $=CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 152 (21), 110 (22), 83 (59), 69 (95), 55 (100), 41 (97).

Conversion of 2a and 2c–2e to α Diketones.—The β-keto sulfoxides (1 g) were dissolved in 2 ml of DMSO, 3 ml of concentrated hydrochloric acid, and 10 ml of water. After stirring for 1.5 hr under a stream of nitrogen the mixture was heated to a gentle boil. The nitrogen stream aided in carrying over drops of water and a yellow oil which were collected in a receiver in an ice bath. The distillate was extracted with methylene chloride, which was dried ($MgSO_4$) and concentrated. From 2 g of **2a** there was obtained 520 mg (37%) of **1-cyclopropylpropane-1,2-dione**: bp 43–44° at 12 Torr; ir (CCl_4) 1710, 1690 cm^{-1} (C=O); pmr (60 MHz, CCl_4), δ 0.99–1.10 (m, 4, CH_2CH_2), 2.5–2.9 (m, 1, >CH–), 2.26 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 112 (9.5), 69 (100), 43 (61), 41 (76).

Anal. Calcd for $C_6H_8O_2$ (112): C, 64.27; H, 7.19. Found: C, 64.08; H, 7.29.

From **2c** (2 g, 11.5 mmol) there was obtained 560 mg (39%) of 1-cyclobutylpropane-1,2-dione as a yellow oil: bp 53–54° at 12 Torr; ir 1708 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 1.7–2.5 (m, $CH_2CH_2CH_2$), 3.6–4.1 (m, >CH–), 2.25 (s, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 126 (5), 83 (29), 43 (51), 55 (100).

Anal. Calcd for $C_7H_{10}O_2$ (126): C, 66.64; H, 7.99. Found: C, 66.47; H, 8.08.

Compound **2d** (1 g) yielded 0.55 g (74%) of **1-cyclopentylpropane-1,2-dione**: bp 33–35° at 0.6 Torr; ir (CCl_4) 1712 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 1.6–2.1 [m, 7.4 $(CH_2)_4$], 3.2–3.7 (m, 1 >CH–), 2.29 (s, 3 CH_3); mass spectrum (70 eV) *m/e* (rel intentisy) 140 (3), 97 (25), 69 (100), 43 (32).

Anal. Calcd for $C_8H_{12}O_2$ (14): C, 68.54; H, 8.62. Found: C, 68.29; H, 8.47.

Keto sulfoxide **2e** (3.22 g) was stirred in a mixture of 15 ml of DMSO and 6 ml of concentrated hydrochloric acid for 24 hr at 25° and allowed to stand for another 12 hr. The mixture was diluted with 60 ml of water and extracted thrice with 10 ml portions of chloroform. Drying ($MgSO_4$) and removal of solvent gave a yellow oil. Column chromatography on silica gel with chloroform as the eluent separated the diketone and another product from more polar compounds. A 2nd chromatograph with ethyl acetate as the eluent gave 1.54 g (63%) of **1-cyclohexylpropane-1,2-dione**: bp 26–28° at 0.5 Torr; ir (CCl_4) 1710 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 1.1–2.0 [m, 9.6 $(CH_2)_6$], 2.75–3.30 (m, 1, >CH–), 2.25 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 154 (1), 111 (10), 83 (51), 43 (46), 41 (100).

Anal. Calcd for $C_9H_{14}O_2$ (154): C, 70.09; H, 9.14. Found: C, 70.22; H, 9.23.

Methyl Hemimercaptal of 1-Cyclohexylpropane-1,2-dione by Pummerer Rearrangement of 2e.—Compound **2e** (0.80 g) was stirred for 24 hr at 25° in a mixture of 1.8 g of DMSO, 11 ml of water, and 1.6 ml of concentrated hydrochloric acid. The solution was extracted with 30 ml of methylene chloride. Drying and removal of the solvent left 0.75 g (94%) of the hemimercaptal as a yellow oil: ir (CCl_4) 3400 (OH), 1703 cm^{-1} (C=O); pmr

(60 MHz, CCl_4) δ 1.1–2.0 (m, 13.5, C_6H_{11}, CH_3), 1.71 (s, CH_3), 2.28 (m, 3, SCH_3), 5.30 (s, 1, OH).

ω-(Methylmercapto)-ω-(acetoxy)acetylcyclopropane.—This compound was prepared from the anion of **1a** prepared from 3.40 g (23.3 mmol) of **1a** in 40 ml of THF by reaction with 25 mmol of sodium hydride. At 60° a solution of 1.98 g (25 mmol) of pyridine and 1.89 g (24 mmol) of acetyl chloride in 30 ml of methylene chloride was added rapidly. The reaction mixture was allowed refluxed for 3 hr and allowed to stand for 48 hr. It was then diluted with 150 ml of methylene chloride, poured into 100 ml of water, and extracted with 10% aqueous sulfuric acid. The methylene chloride solution was washed with water and dried over $MgSO_4$ and the solvent evaporated. Chromatography from silica gel with 3:1 chloroform–hexane yielded 3.7 g (84%) of the Pummerer rearrangement product: ir (CCl_4) 1755 (ester C=O), 1708 (cyclopropyl carbonyl), 1218 cm^{-1} (ester); pmr (60 MHz, CCl_4) δ 0.84–1.20 (m, 4, CH_2CH_2), 1.9–2.4 (m, 1, >CH–), 2.03, 2.13 (s, 3, CH_3), 5.98 [s, 1, $-CH(SCH_3)(O_2CCH_3)$]; mass spectrum (70 eV), *m/e* (rel intensity) 188 (2), 145 (6), 130 (8), 69 (90), 47 (13), 43 (100), 41 (49).

Anal. Calcd for $C_8H_{12}SO_3$ (188): C, 51.04; H, 6.43; S, 17.03. Found: C, 50.88; H, 6.46; S, 17.15.

1-Phenyl-2-(methylmercapto)-3-chloropropanone.[17]—ω-Methyl-ω-(methylsulfinyl)acetophenone (9.75 g, 50 mmol) was dissolved in 200 ml of CH_2Cl_2 at 0° under nitrogen. Thionyl chloride (6 g, 50 mmole) was added and the reaction mixture allowed to warm to room temperature. After 2 hr the solvent was removed under vacuum to yield 10.9 g of a yellow oil containing (by pmr) approximately 85% 1-phenyl-2-methyl-3-chloropropane (SCH_3, δ 1.96) and 10% ω-methyl-ω-(methylmercapto)acetophenone.

1-Phenyl-2,3-di(methylmercapto)propanone.[17]—The crude 1-phenyl-2-(methylmercapto)-3-chloropropanone prepared from 1.96 g of ω-methyl-ω-(methylsulfinyl)acetophenone was treated in CH_2Cl_2 with 15 ml of methylmercaptan and 0.75 ml of triethylamine. The reaction was allowed to stir for 3 hr under nitrogen, the solvent evaporated, and the crude residue taken up in 100 ml of ether, washed with dilute aqueous sodium bicarbonate, dried, and concentrated to yield a yellow semisolid residue. Chromatography on 20 × 60 cm plates coated with Merck PF_{254} with $CaSO_4$ binder (80%) Merck silica gel H (20%), with elution by 1:1 cyclohexane–cyclopentane yielded 0.14 g (7.7%) of 1-phenyl-2-(methylmercapto)propanone and 1.87 g (83%) of 1-phenyl-2,3-di(methylmercapto)propanone: mp 44–45° from pentane; pmr (60 MHz, $CDCl_3$) δ 1.97, 2.13 (s, 3, SCH_3), an ABX multiplet with A = 2.87, B = 3.26, X = 4.41 (m, 3, $CHCH_2$, J_{AX} = 6.9, J_{BX} = 8.1, J_{AB} = 13.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 226 (50), 179 (90), 163 (15), 121 (75), 105 (100).

Anal. Calcd for $C_{11}H_{14}OS_2$ (226): C, 58.40; H, 6.24; S, 28.29. Found: C, 58.36; H, 6.23; S, 28.25.

Reduction of β-Keto Sulfoxides 1a, 2a–2d, 3a–3c.—Amalgamated aluminum foil in aqueous THF, or zinc powder in ethanol–acetic acid failed to reduce **1e** in 1.5 hr at 25°. Keto sulfoxide **1a** (1.83 g, 12.5 mmol) in 12 ml of ethanol was added to 7.8 ml of glacial acetic acid and 4.05 g (62 mg atom) of zinc. After 4 hr of refluxing, 0.65 g (62%) of **cyclopropyl methyl ketone**, bp 106–111°, was obtained. The distillation residue (0.44 g) was **ω-(methylmercapto)-ω-acetoxyacetylcyclopropane** (19%). Treatment of 2.5 g (15.6 mmol) of **2a** in 25 ml of refluxing solvent for 5 hr with 5.1 g (78 mg atom) of zinc powder gave a product that glpc showed to consist of 550 mg (36%) of **cyclopropyl ethyl ketone** and 805 mg (36%) of **α-ethoxyethyl cyclopropyl ketone**. Samples of cyclopropyl ethyl ketone isolated by glpc had ir (CCl_4) 1695 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 0.60–0.96 (m, 4, CH_2CH_2), 1.6–2.1 (m, 1, >CH–), 2.3–2.7 (q, 2, CH_2CH_3), 0.9–1.15 (m, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 98 (10), 69 (100), 57 (7.5), 43 (6), 41 (50). α-Ethoxyethyl cyclopropyl ketone gave a semicarbazone, mp 142–143°. The ketone had ir (CCl_4) 1695 (C=O), 1107 cm^{-1} (ether); pmr (60 MHz, CCl_4), δ 0.70–1.0 (m, 4, CH_2CH_2), 1.1–1.3 (m, 6, CH_3), 2.0–2.5 (m, 1, >CH–), 3.6–3.9 (q, 1, $>CHOC_2H_5$), 3.3–3.6 (q, 2, CH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 98 (5.8), 73 (66), 69 (20), 45 (100), 43 (11), 41 (20).

Keto sulfoxide **2b** (2.88 g, 16.5 mmol) after 12 hr at 25° and 4 hr at reflux yielded 1.57 g of an oil that was distilled to give 0.98 g (53%) of **1-methylcyclopropyl ethyl ketone**, bp 68–72° at 36 Torr, and **1-methylcyclopropyl 1-ethoxyethyl ketone** (214 mg, 8%). 1-Methylcyclopropyl ketone had ir 1685 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 0.48–0.70 (m, 2, CH_2CH_2), 0.83–1.27 (m, 5, CH_2CH_2, $CHCH_3$), 1.32 (s, 3, $>C(CH_3)-$), 2.20–2.54 (q, 2, CH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity 112 (11), 83 (42), 57 (20), 55 (100), 41 (7). The α-ethoxy ketone had ir (CCl_4) 1690 (C=O), 111) cm^{-1} (ether); pmr (60 MHz, CCl_4) δ 0.48–0.75 (m, 2, CH_2CH_2), 1.08–1.30 (m, 5, CH_2CH_2 and CH_2CH_3), 1.19 [s, 3, $>C(CH_3)-$], 1.30–1.4, (d, 3, $>CHCH_3$), 3.2–3.6 (q, 2, CH_2CH_3), 3.9–4.2 (q, 1, CH); mass spectrum (70 eV) *m/e* (rel intensity) 110 (3), 83 (16), 73 (71), 55 (29), 45 (100), 41 (5).

A mixture of mono- and dimethylated **1c** (1.8 g, ~10 mmol) yielded 410 mg (34%) of **cyclobutyl isopropyl ketone** and 590 mg (37%) of **α-ethoxy ethyl cyclobutyl ketone**. Cyclobutyl isopropyl ketone had ir (CCl_4) 1704 cm^{-1} (C=O); pmr (60 MHz), CCl_4) δ 1.8–2.6 (m, 7.7, $(CH_2)_3$ and >CH–) 0.97, 1.06 (d, 6, CH_3), 3.0–3.6 (m, 1, cyclobutyl methine); mass spectrum (70 eV) *m/e* (rel intenstiy) 126 (2), 112 (2), 83 (28), 57 (17), 55 (100), 43 (17).

Anal. Calcd for $C_8H_{14}O$ (126): C, 76.14; H, 11.18. Found: C, 76.25; H, 11.24.

The α-ethoxy ketone had ir (CCl_4) 1708 (C=O), 1107 cm^{-1} (ether); pmr (60 MHz, CCl_4) δ 1.06–1.29 (m, 6, CH_3), 1.8–2.3 [m, 6, $CH_2)_3$], 3.3–3.7 (m, 1, >CH–), 3.2–3.56 (q, 2, CH_2CH_3), 3.5–3.9 (q, 1, $CHCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 112 (4), 73 (85), 55 (25), 45 (100), 43 (7).

Reduction of **2d** (2.95 g, 15.7 mmol) yielded 660 mg (33%) of **ethyl cyclopentyl ketone**, bp 72–80° at 11 Torr, lit.[18] 174–175° at 760 Torr, and 1.11 g (4%) of **α-ethoxyethyl cyclopentyl ketone**: bp 86–94° at 11 Torr, semicarbazone mp 150–151°; ir (CCl_4) 1710 (C=O), 1107 cm^{-1} (ether); pmr (60 MHz, CCl_4) δ 1.1–1.3 (m, 6, CH_3), 1.5–1.9 [m, 8, $CH_2)_4$], 3.0–3.4 (m, 1, CH–), 3.25–3.6 (q, 2, CH_2CH_3), 3.5–3.9 (q, 1, CH_3CH); mass spectrum (70 eV) *m/e* (rel intensity) 126 (5), 97 (4), 73 (100), 69 (27), 45 (97).

Anal. Calcd for $C_{10}H_{18}O_2$ (170): C, 70.55; H, 10.66. Found: C, 70.35; H, 10.62.

Keto sulfoxide **2e** (2.0 g, 10 mmol) yielded 510 mg (36%) of **cyclohexyl ethyl ketone**, bp 89–92° at 12 Torr, lit. bp 88–89° at 19 Torr, semicarbazone mp 147–149, lit.[19] mp 150–152°, and 740 mg (40%) of **α-ethoxyethyl cyclohexyl ketone**: bp 93–104° at 11 Torr, semicarbazone mp 151–152°; ir (CCl_4) 1709 (C=O), 1112 cm^{-1} (ether): pmr (60 MHz), (CCl_4), 1.08–1.32 (m, 6, CH_3), 1.2–2.0 [m, 10, $(CH_2)_5$], 2.5–2.9 (m, 1, CH–), 3.3–3.6 (q, 2, CH_2CH_3), 3.55–3.92 (q, 1, $CHCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 140 (3), 111 (2), 109 (2), 83 (14), 73 (100), 55 (15), 45 (84).

The reduction of **2a** (2.04 g 12.7 mmol) in 8.2 ml of acetic acid and 12 ml of water by refluxing with 4.25 g (65 mg-atoms) of zinc powder yielded 296 mg (24%) of **cyclopropyl ethyl ketone** and 782 mg (54%) of **cyclopropyl methyl acyloin**: ir (CCl_4) 3450 (OH), 1690 cm^{-1} (C=O); pmr (60 MHz, CCl_4) δ 0.80–1.18 (m, 4, CH_2CH_2), 1.30, 1.42 (d, 3, $CHCH_3$), 1.75–2.17 (m, 1, >CH–), 3.32 (m, 1, OH), 4.1–4.5 [q, 1, CH(OH)]; mass spectrum (70 eV) *m/e* (rel intensity) 113 (1) 112 (9), 69 (100), 43 (78), 42 (81), 41 (6).

Registry No.—**1a**, 25183-65-7; **1b**, 25183-66-8; **1c**, 25183-69-1; **1d**, 25183-70-4; **2a**, 25183-71-5; **2b**, 25183-72-6; **2d**, 25183-73-7; **3a**, 25183-74-8; 1-methylcyclopropyl vinyl ketone, 25183-75-9; cyclopentyl vinyl ketone, 25183-76-0; cyclohexyl vinyl ketone, 2177-34-6; cyclopropyl isopropenyl ketone, 4663-37-0; cyclobutyl isopropenyl ketone, 25183-79-3; 1-methylcyclobutyl isopropenyl ketone, 25183-80-6; cyclopentyl isopropenyl ketone, 25183-81-7; cyclohexyl isopropenyl ketone, 25183-82-8; 1-cyclopropylpropane-1,2-dione, 15940-89-3; 1-cyclobutylpropane-1,2-dione, 15940-91-7; 1-cyclopentylpropane-1,2-dione, 15940-93-9; 1-cyclohexylpropane-1,2-dione, 13898-90-3; 1-cyclohexylpropane-1,2-dione methyl hemimercaptol, 25183-87-3; ω-(methylmercapto)-ω-(acetoxy)acetylcyclopropane, 25183-88-4; 1-phenyl-2,3-di(methylmercapto)propanone, 25172-45-6; cyclopropyl methyl ke-

(17) Experiment performed by Dr. L. A. Ochrymowycz.

(18) G. Veron and H. M. Mitchovich, *Bull. Soc. Chim. Fr.*, **45** [4], 961 (1929).

(19) H. Meerwein, *Justus Liebigs Ann. Chem.*, **419**, 167 (1919).

tone, 765-43-5; cyclopropyl ethyl ketone, 6704-19-4; cyclopropyl α-ethoxyethyl ketone, 25111-29-9; cyclopropyl α-ethoxyethyl ketone (semicarbazone), 25111-30-2; 1-methylcyclopropyl ethyl ketone, 25111-31-3; 1-methylcyclopropyl 1-ethoxyethyl ketone, 25111-32-4; cyclobutyl isopropyl ketone, 25111-33-5; α-ethoxyethyl cyclobutyl ketone, 25111-34-6; α-ethoxyethyl cyclopentyl ketone, 25111-35-7; cyclohexyl ethyl ketone, 1123-86-0; α-ethoxyethyl cyclohexyl ketone, 25111-37-9; α-ethoxyethyl cyclohexyl ketone (semicarbazone), 25111-38-0; cyclopropyl ethyl acyloin, 25111-39-1.

Organic Disulfides and Related Substances. XXIX. Studies in the Chemistry of Sulfenamides[1a-c]

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A variety of sulfenamides, $R^1SNR^2R^3$, were prepared and generalizations were sought for the chemical and physical properties of the class. Of syntheses studied, the smoothest was through reaction of sulfenyl chlorides with amines or amides. Thermal stability decreased from R^1 = *n*-butyl to 2-acetamidoethyl, suggesting an anchimeric effect in the latter; it decreased also with enhanced basicity of NR^2R^3 [*e.g.*, for $R^1 = AcNH(CH_2)_2$, stability for $R^2 + R^3$ = phthaloyl > $R^2 = R^3$ = alkyl], presumably because of an increased rate of proton transfer. The sulfenamides studied were quite stable to light. In their spectra, the predominant EI fragmentation reactions were C–S and N–S cleavage, with or without hydrogen rearrangement depending upon the nature of R^1, R^2, and R^3; ir and Raman spectra showed no useful characteristic absorption for the S–N bond. In their chemical reactions, sulfenamides with electrophiles characteristically gave products consistent with attack on NR^2R^3, followed by nucleophilic cleavage of the S–N bond (*e.g.*, with an alkyl or sulfonyl halide, carbon disulfide, and an isothiocyanate); however, with isocyanates and electron-deficient alkenes the preferred course seemed to be for elimination reactions, which can be formulated as concerted ones. The general pattern of nucleophilic attack was followed in conversion of sulfenamides by thiols to disulfides. In their biological properties, inactivity of several sulfenamides as antiradiation drugs indicated that NR^2R^3 may not be a promising latentiating group for radioprotective thiols.

Sulfenamides, which have the generalized structure **1** of eq 1, have been known for many years, but we are

$$R^1SCl + HNR^2R^3 \longrightarrow R^1SNR^2R^3 + HCl \quad (1)$$
3 **1, 4–17**

$$\downarrow {}^1/_2Cl_2$$

$${}^1/_2R^1SSR^1$$
2

$R^1 = AcNHCH_2CH_2$ (for 2–11)

4, $R^2 = H$; $R^3 = p\text{-}C_6H_4CO_2Me$
5, $R^2 = H$; R^3 = 2-benzothiazolyl
6, $R^2 = R^3 = C_2H_5$
7, $R^2 + R^3 = (CH_2)_5$
8, $R^2 + R^3 = (CH_2)_2O(CH_2)_2$
9, NR^2R^3 = 1-benzimidazolyl
10, $R^2 + R^3$ = *o*-phthaloyl
11, $R^2 = H$; $R^3 = p\text{-}CH_3C_6H_4SO_2$
12, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$
13, $R^1 = n\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
14, $R^1 = t\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
15, $R^1 = C_2H_5$; $R^2 = R^3 = C_2H_5$
16, $R^1 = t\text{-}C_4H_9$; $R^2 = R^3 = C_2H_5$
17, $R^1 = t\text{-}C_4H_9$; $R^2 = H$; $R^3 = C_6H_5$

unaware of any effort to develop a unified theory of their chemistry.[2] Because of the possibility that the NR^2R^3 function might be an effective latentiating group for medicinally useful thiols,[3] we had occasion to prepare a variety of sulfenamides for testing as antiradiation drugs. Investigation thus became possible of the chemistry of typical sulfenamides in the hope of developing concepts useful for rationalizing and predicting chemical and physical properties of this class of compounds.

Preparation.—As a thiol, 2-acetamidoethanethiol was chosen because both it[3a] and the corresponding amine[3b] afford protection against ionizing radiation. As eq 1 shows, its disulfide (**2**) was converted to the sulfenyl chloride (**3**), which then was allowed to react with amines or amides to give the sulfenamides, **1**. This method was preferred to two others tried. Aminolysis of an acetamidoethanethiolsulfonate ($R^1SO_2SR^1$), which is an equilibrium reaction,[4] gave no pure, isolable sulfenamides; the product ratio was the same after 4 days as after 0.5 hr by tlc. Although this method often succeeds,[4] the properties of the acetamido products are not suited to the usual technique. The sulfenyl thiocyanate route[5] gave poor yields; thus crude **8** was obtained in only 30% yield (*vs.* 86% from **3**) and even then showed a strong –SCN band at 2200 cm^{-1} which could not be removed by washing with water. Furthermore, the preparation of 2-acetamidoethanesulfenyl thiocyanate was difficult because of its solubility properties.

The sulfenyl chloride, **3**, was obtained in quite variable yields, usually about 60%, by chlorinolysis of the disulfide in methylene chloride at temperatures in the range of −40 to −25° (eq 1). A lower temperature did not increase the yield of **3**; for example, **10** was

(1) (a) Paper XXVIII: L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts No. DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Presented in part at the Symposium on Organosulfur Chemistry, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 14–18, 1969 (Abstracts, Paper ORGN 26), and at the Third International Cork Mechanisms Conference, University College, Cork, Ireland, Sept 29–Oct. 3, 1969. (d) To whom inquiries should be addressed.

(2) For reviews see (a) N. Kharasch, S. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 304 (1946); (b) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, N. Y., 1958, p 279; (c) E. Riesz, *Bull. Soc. Chem. Fr.*, 1449 (1966).

(3) For discussions, see (a) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964); (b) L. Field, B. J. Sweetman, and M. Bellas, *ibid.*, **12**, 624 (1969).

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obtained in 70% yield by preparing **3** at −35° and in 45% yield at −50°.

Sulfenamides then were generated by adding the cold solution of **3** to excess amine in methylene chloride (**6–8**) or to equivalent amounts of the amine or amide with triethylamine added as the acid scavenger. The only exception to this method was with **10**, where potassium phthalimide was used. With ammonia or the primary amines ethyl glycinate and 1-aminoadamantane, reaction of **3** was unpromising. The first two sulfenamides could not be isolated, but their water solubility probably was a contributing reason; a little material was obtained using ammonia which had a promising ir spectrum, but it decomposed extensively in 3 days. The crude product from 1-aminoadamantane (73% yield) also could not be purified because of extensive decomposition. With primary aromatic or heterocyclic amines, the reaction was more satisfactory. Considerable loss occurred with **4** (55% crude yield to 11% pure), but it may be attributed at least partly to the need for chromatography since **5**, which crystallized well, was obtained pure in 63% yield. With secondary amines, crude yields of 55–103% for **6–8** dropped only to 29–51%; the possibly beneficial effect of structure was complemented, however, by the ease of removing the amine impurity by washing with water and by evaporation. Benzimidazole was included among the secondary amines because the amine function is part of a ring and because it protects against; ionizing radiation *per se*.[6]

1-Benzylpiperazine gave crude sulfenamide in 103% yield but, although tlc and nmr indicated good purity, a satisfactory analysis could not be obtained; marked darkening at 50° during a few minutes suggested notable heat sensitivity. With phthalimide, **10** was obtained in 45% yield. With *p*-toluenesulfonamide, a low yield of 21% **11** probably mainly reflects difficulties in purification. With succinimide, no pure sulfenamide; was obtained. Composition of all of the sulfenamides **4–11** was assured by elemental analysis, and the structures were confirmed by ir, nmr, and mass spectrometry (the mass spectrum of **11** could not be obtained however, because of decomposition during attempted volatilization).

Some impressions gained from the foregoing syntheses and purifications deserve mention. Strong basicity of the amine (R^2R^3NH of eq 1) led to products that were frequently more difficult to purify since they decomposed at temperature above 60° (darkening of products) and slowly even at *ca.* 25° (*e.g.*, strong amine odor from **6** after a week). The sulfenamide derived from isobutylamine could not be purified by short-path distillation (0.05 mm, <80°), as were **6–8**, because of decomposition. The less basic aryl or heterocyclic counterparts were more easily handled, probably in part because they were crystalline. Secondary alkylamines succeeded better than primary ones of similar basicity, and difficulties with products from 1-benzylpiperazine and to a lesser extent benzimidazole and 2-aminobenzothiazole probably were caused by the second basic function. The less basic phthalimide derivative **10** worked best. These observations suggest that lower basicity and a higher degree of substitution of the amine facilitate synthesis and purification, as does sparing solubility (with **5**, **9**, and **10**). Our impression as to the R^1S moiety is that the known compounds[7] where NR^2R^3 is 1-piperidyl and where R^1 was ethyl (**12**), *n*-butyl (**13**), or *t*-butyl (**14**) were roughly comparable to one another in ease of preparation and purification (yields of 55–90%), and that **12–17** were markedly superior in stability and ease of purification to compounds where R^1 was 2-acetamidoethyl. These impressions led us to study qualitatively the rates of decomposition of some typical sulfenamides.

Stability toward Heat and Light.—Comparison of some thermal stabilities are shown in Table I. Two

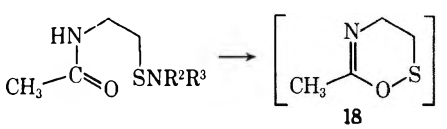
TABLE I

COMPARISON OF THERMAL STABILITIES OF TYPICAL SULFENAMIDES, $R^1SNR^2R^3$ (1)

Compd	R^1	R^2, R^3	Temp, °C	Time, min	Estimated decomposition, %
5	$AcNH(CH_2)_2$	2-Benzothiazolyl, H	155	20	>80
8	$AcNH(CH_2)_2$	$-(CH_2)_2O(CH_2)_2-$	140	20	>80
10	$A(cNHCH_2)_2$	*o*-Phthaloyl	155	20	<20
13	*n*-Butyl	$-(CH_2)_5-$	140	80	<5
16	*t*-Butyl	Et, Et	100	4 days	~0

factors decreased the thermal stability: (1) the presence in R^1 of a group capable of anchimeric participation in cleavage of the S–N bond (thus **13** and **16** are more stable than **5**, **8**, or **10**); (2) increased basicity of the nitrogen atom of NR^2R^3 (thus **10** is more stable than **5** or **8**). Two additional factors noted by others are worth adding: (3) an increased number of substituents on the nitrogen increases the stability,[8,9] a point consistent with the greater ease mentioned above of preparing pure sulfenamides from secondary than from primary amines; (4) substitution of electron-withdrawing substituents into R^1 also increases the thermal stability; thus a 5-carbomethoxy- or 5-acetyl-2-thiazolesulfenamide is more stable than the 5-methyl derivative.[8]

Products from the decomposition of **5**, **8**, and **10** always included the amine (R^2R^3NH), suggesting that the reaction shown in eq 2 might play a major role in thermal decomposition through anchimeric participation of the acetamido group, although we could find no evidence of the heterocycle **18**. It is tempting to conclude that the greater stability of the phthalimide derivative **10** results from the decreased ability of the nitrogen atom to remove a proton from the amide group to give phthalimide and **18** as required by eq 2. Analysis



18

of the residue from decomposition of **8** by glpc and mass spectrometry showed only morpholine and N-acetylmorpholine; apparently the sulfur fragment is not volatile. Prolonged heating of the diethylamino com-

(6) R. Rinaldi and Y. Bernard, *C. R. Acad. Sci.*, **258**, 6251 (1964).

(7) C. M. Himel, U. S. Patent 2,807,615 (1957); *Chem. Abstr.*, **52**, 14706 (1958).

(8) J. J. D'Amico, M. W. Harman, and R. H. Cooper, *J. Amer. Chem. Soc.*, **79**, 5270 (1957).

(9) E. L. Carr, G. E. P. Smith, Jr., and G. Alliger, *J. Org. Chem.*, **14**, 921 (1949).

TABLE II

RELATIVE INTENSITIES OF PRODUCT IONS FROM COMPETING FRAGMENTATION REACTIONS IN THE EI MASS SPECTRA OF SULFENAMIDES, $R^1SNR^2R^3$

					Eq 3		Eq 4,	Eq 5		Eq 6,
Compd	R^1	R^2, R^3	M^+	M − 1	R^1 [M − SNR^2R^3]	SNR^2R^3 [M − R^1]	HSN-R^2R^3 [M − (R^1 − 1)]	NR^2R^3 [M − R^1S]	R^1S [M − NR^2R^3]	HNR^2R^3 [M − (R^1S − 1)]
4[a]	$AcNH(CH_2)_2$	*p*-$C_6H_4CO_2Me$, H	4	<1	6	<1	<1	3	4	61
5	$AcNH(CH_2)_2$	2-Benzothiazolyl, H	2	<1	18	<1	1	4	22	100
6	$AcNH(CH_2)_2$	C_2H_5, C_2H_5	2	<1	26	2	<1	100	4	1
7	$AcNH(CH_2)_2$	$(CH_2)_5$	12	<1	100	5	3	40	5	9
8	$AcNH(CH_2)_2$	$(CH_2)_2O(CH_2)_2$	13	<1	Y[b]	14 − X[c]	3	100 − Y[b]	X[c]	16
9	$AcNH(CH_2)_2$	1-Benzimidazolyl	2	<1	7	<1	<1	7	Y[b]	100 − Y[b]
10[d]	$AcNH(CH_2)_2$	*o*-Phthaloyl	2	<1	16	2	1	<1	10	55
12[e]	C_2H_5	$(CH_2)_5$	68	42	54	68	14	52	44	14
13	*n*-C_4H_9	$(CH_2)_5$	35	4	29	31	16	100	3	64
14	*t*-C_4H_9	$(CH_2)_5$	25	<1	86	25	100	10	3	2
16[f]	*t*-C_4H_9	C_2H_5, C_2H_5	19	<1	38	10	57	2	1	2
17	*t*-C_4H_9	C_6H_5, H	15	<1	59	4	100	31	15	60

[a] The base peak is *m/e* 120 corresponding to the metastable loss of 31 (OMe) from *m/e* 151 (*p*-$H_2NC_6H_4CO_2Me$). [b] These two fragments fall at the same nominal mass, total intensity 100%. [c] These two fragments fall at the same nominal mass, total intensity 14%. [d] The base peak is at *m/e* 117 and may correspond to heterocycle **18**. [e] The base peak is *m/e* 55, presumably a fragment from the piperidine ring. [f] The base peak is *m/e* 90 corresponding to the metastable loss of 15 (CH_3) from *m/e* 105.

pound **6** followed by glpc and mass spectrometric analysis resulted in detection of five volatile products. Three of these seemed identifiable from the mass spectra (*cf.* Experimental Section): N,N-diethylacetamide, presumably from reaction of diethylamine with **6** (amide interchange), N,N-diethylthioacetamide, and N,N-diethyl-N′-acetylthioglycinamide, $AcNHCH_2C(S)NEt_2$. Tlc analysis suggested that other (nonvolatile) products also were formed, but these were not investigated. Under these same conditions the *t*-butyl compound **16** was essentially unchanged.

The trends in thermal stability of sulfenamides thus resemble those suspected from the synthesis and seem to be for improved stability of sulfenamides containing the more weakly basic amine moieties or containing R^1S groups unlikely to afford anchimeric assistance to cleavage of the S–N bond; with R^1S=$AcNHCH_2CH_2S$, elimination of the amine moiety and subsequent amide-transfer reactions are likely.

All of the sulfenamides seemed quite stable to light. In ambient light over a period of several months we saw no changes in sulfenamides **4**–**17** which would suggest adverse effects. For example, the refractive indices of **7** and **8** did not differ significantly whether they were stored for 1 month in ambient light or in the dark. An attempt to photolyze N-(*t*-butylthio)-N,N-diethylamine (**16**) in cyclohexane–cyclohexene failed to change the sulfenamide (glpc), and 75% of the **16** was recovered. However, light reportedly does accelerate the rate of decomposition of thiazolesulfenamides.[9]

Spectra.—Nmr spectra were done routinely. The only noteworthy feature was with the carbomethoxyphenylsulfenamide (**4**), in which half of the aromatic A_2B_2 system, presumably those protons *ortho* to the nitrogen, were shifted downfield 26 Hz relative to the corresponding protons in the amine. This shift (probably reflecting decreased electron density on nitrogen, and hence in the aromatic ring) parallels the reported decreased basicity of sulfenamides.[10] This effect could arise from pπ–dπ bonding between nitrogen and sulfur.

The EI mass spectra of 12 sulfenamides were studied to determine the fragmentation reactions responsible for their mass spectra. As shown by Table II, R^1 of $R^1SNR^2R^3$ was primary alkyl, tertiary alkyl, or 2-acetamidoethyl, while R^2R^3 comprised alkyl, aryl, or heterocyclic groups. Examination of the data of Table II suggests that there are four predominant fragmentation reactions: C–S cleavage (eq 3), C–S cleavage with hydrogen rearrangement (eq 4), S–N cleavage (eq 5), and S–N cleavage with hydrogen rearrangement to the nitrogen fragment (eq 6).

$$R^1SNR^2R^3 \longrightarrow R^{1(\cdot \text{ or } +)} + SNR^2R^{3(+ \text{ or } \cdot)} \quad (3)$$

$$\longrightarrow (R^1 - H) + H(SNR^2R^3)\cdot^+ \quad (4)$$

$$\longrightarrow R^1S^{(\cdot \text{ or } +)} + NR^2R^{3(+ \text{ or } \cdot)} \quad (5)$$

$$\longrightarrow (R^1S - H) + HNR^2R^3\cdot^+ \quad (6)$$

Eq 3 shows the most consistently important fragmentation reaction, C–S cleavage with the charge remaining on the R^1 fragment. That the relative abundance of the charged fragment containing no heteroatom [*i.e.*, of $(R^1)^+$ in **12**–**14**, **16**, and **17**] is greater than that of $(SNR^2R^3)^+$ probably results from the slower rate of decomposition of $(R^1)^+$ ion relative to the $(SNR^2R^3)^+$ fragment. Another notable feature, the decreased abundance of $(SNR^2R^3)^+$ when R^1 = $AcNHCH_2CH_2$, can be attributed to relatively greater stability of the 2-acetamidoethyl carbonium ion than of $(SNR^2R^3)^+$. Examination of the relative intensities of the ions in the mass spectrum of **4** as a function of electron energies suggests that the *m/e* 86 ion, $(AcNHCH_2CH_2)^+$ or an isomer, is probably cyclic since its abundance (%Σ) shows an increase as the electron energy is lowered (1.6%Σ^{40} at 18 eV to a maximum of 18%Σ^{40} at *ca.* 14 eV), the same behavior shown by McLafferty-type rearrangement ions in the spectrum. The mass spectrum of 2-acetamidoethyl disulfide (**2**) also shows this C–S cleavage reaction giving an intense *m/e* 86 ion. Labeling of **2** by washing with deuterium oxide caused the *m/e* 86 ion to shift to *m/e* 87 in accordance with the assigned structure. Presumably, substitution of any group in R^1 which will stabilize a carbonium ion will similarly decrease the relative intensity of $(SNR^2R^3)^+$ with respect to that seen with simple alkyl groups.

(10) R. T. Major and L. H. Peterson, *J. Amer. Chem. Soc.*, **78**, 6181 (1956).

Eq 4, C–S cleavage with hydrogen rearrangement, can be seen from Table II to play a role, but it is important only when R^1 does not contain the acetamido moiety of **4–10**. The relative abundance of $(HSNR^2R^3)\cdot^+$ increases with an increasing number of β-hydrogen atoms (*cf.* *t*-butyl > ethyl ~ *n*-butyl, Table II), suggesting a preference for transfer of a β-hydrogen atom over transfer from other locations. (The structure $HSNR^2R^3$ implies only that the hydrogen atom has been transferred to SNR^2R^3 and that it probably is bound to sulfur or nitrogen.)

Eq 5, cleavage of the S–N bond, does not give intense ions in all of the spectra, although such ions are seen to some extent in all spectra. The $(NR^2R^3)^+$ fragment may be formed by any of three routes: simple S–N bond cleavage (eq 5), simple C–S cleavage (eq 3) followed by loss of a sulfur atom, or C–S cleavage with hydrogen rearrangement (eq 4) followed by loss of 33 (SH). The absence of metastable ions for any of these secondary fragmentations reactions did not allow decision among these possibilities. Except with **4**, **5**, **9**, **10**, and **16**, $(NR^2R^3)^+$ is significantly intense. In all of these except **16**, competitive fragmentation reactions probably prevail (eq 6). With **16**, further decomposition of $(NR^2R^3)^+$ may explain its low abundance since only one bond needs to be broken to produce a mass loss whereas in the cyclic amine two bonds must be broken for a mass loss other than hydrogen. In the cleavage of the S–N bond (eq 5) with formation of $(R^1S)^+$, the ions from **8** and **9** at *m/e* 118 may be doublets and therefore deceptively large. The R^1S^+ ion from **12**, *m/e* 61, probably is correctly assigned since the *m/e* 63 ion is more than large enough to account for the expected contribution from the ^{34}S isotope (6% of *m/e* 61).

Eq 6, showing N–S cleavage with hydrogen rearrangement, leads to ions of relative intensity exceeding 20% only in **4**, **5**, **9**, **10**, **13**, and **17**. Of these, only **13** lacks an unsaturated substituent on nitrogen. The high intensity of $(HSNR^2R^3)\cdot^+$ from **13** may result from the ease of hydrogen transfer from the γ carbon to nitrogen with simultaneous formation of two neutral fragments, thioformaldehyde and propene. The other compounds (**4**, **5**, **9**, **10**, and **17**) have unsaturated groups that should allow a McLafferty-type rearrangement.

Summarization in terms of structures also is informative. All of the sulfenamides show molecular ions (except **11**, where only *p*-toluenesulfonamide could be seen). The 2-acetamidoethyl derivatives (**4–10**) characteristically show lower intensity molecular ions than the unsubstituted compounds (**12–14**, **16**, and **17**), and ions at *m/e* 86 of moderate to high intensity corresponding to C–S cleavage with retention of the charge on the R^1 fragment. With the acetamidoethyl compounds, S–N cleavage either with or without rearrangement dominates the spectra (eq 5 and 6). Cleavage of the S–N bond occurs predominantly without hydrogen rearrangement when the nitrogen substituents are alkyl (eq 5); however, with unsaturated substituents on nitrogen, cleavage with hydrogen rearrangement predominates (eq 6). The S-*n*-alkylsulfenamides, **12** and **13**, show all four fragmentation reactions (eq 3–6); however, the S-*t*-alkyl derivatives (**14**, **16**, and **17**) show predominantly C–S cleavage with and without rearrangement (eq 3 and 4), except for **17** in which the aromatic ring allows S–N cleavage with hydrogen rearrangement (eq 6).

We also examined the ir and laser-Raman spectra of several sulfenamides to determine whether there is an easily recognized characteristic frequency for the S–N bond. Seven simple sulfenamides were chosen for the ir studies: **12–15**, **17**, morpholine sulfide (**19**), and piperidine sulfide (**20**). Compounds **19** and **20** were chosen for help in seeking characteristic bands because any characteriestic frequency seen with the simple sulfenamides should be modified in **19** and **20** by coupling of the two S–N modes owing to the common sulfur atom. Raman spectra of four of these simple sulfenamides were determined; the laser-Raman spectra of **5**, **10**, and **11** could not be determined because of fluorescence, although the compounds were pure by ordinary criteria. Ir bands in common seemed either weak, without Raman counterparts, or with counterparts in **19** and **20** which seemed to rule out their being characteristic for S–N stretching (*cf.* Experimental Section). There appears to be no strong, consistent band present throughout the series that is not assignable to other portions of the molecule. The ir or Raman spectra thus do not seem to afford a good diagnostic tool for detection of sulfenamides. An incidental point is that a band at *ca.* 830 cm^{-1} previously assigned to S–N stretching in piperidine polysulfides[11] may result instead from piperidine ring vibrations, since the authors state that it is present in piperidine sulfide (**20**) as well, where one might expect the S–N stretching frequencies to be different owing to coupling because of the common sulfur atom.

Reactions with Electrophiles.—Sulfenamides (**1**) are unstable to acids.[12] For example, N-sulfenyl protecting groups are removed in peptide synthesis using hydrogen chloride, which results in formation of sulfenyl chlorides,[12a] and eq 7 provides a basis for iodo-

$$R^1SNR^2R^3 + HX \longrightarrow RSX + HNR^2R^3 \qquad (7)$$

metric determination of **1**.[13,14] Boron trichloride[15] and diborane[16] also cleave **1**, although amine sulfides reportedly form complexes with boron trifluoride.[17] It seems likely that the instability of **1** to acids results from coordination of an electrophilic species with the nitrogen lone pair, followed by displacement of the protonated nitrogen fragment, HNR^2R^3, by nucleophilic attack on sulfur. With this in mind as a principle for electrophiles in a general sense, reaction of **1** with electrophiles seemed likely to result in S–N cleavage and in formation of a variety of sulfenyl derivatives.

Methyl iodide reacted as such an electrophile. Thus N-(*n*-butylthio)piperidine (**13**) or N-(ethylthio)piperidine (**12**) gave *n*-butyl or ethyl disulfide, iodine, and presumably N,N-dimethylpiperidinium iodide (eq 8).

$$\begin{array}{ccccc} [R^1SN(CH_3)R^2R^3]^+I^- & \longrightarrow & [R^1SI] & + & CH_3NR^2R^3 \\ \uparrow & & \downarrow & & \downarrow CH_3I \\ R^1SNR^2R^3 + CH_3I & & {}^1/_2R^1SSR^1 + {}^1/_2I_2 & & (CH_3)_2N^+R^2R^3I^- \end{array} \qquad (8)$$

(11) C. N. R. Rao, R. Venkataraghavan, and T. R. Kasturi, *Can. J. Chem.*, **42**, 36 (1964).

(12) (a) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963). (b) H. Rheinboldt and F. Mott, *Ber.*, **72**, 668 (1939).

(13) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).

(14) W. Groebel, *Chem. Ber.*, **92**, 2887 (1959).

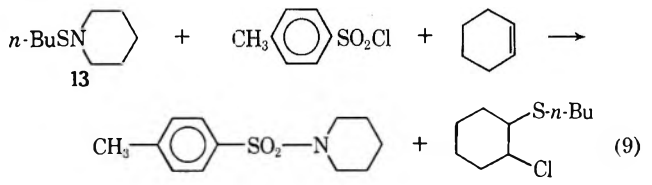
(15) H. Nöth and G. Mikulaschek, *ibid.*, **97**, 709 (1964).

(16) H. Nöth and G. Mikulaschek, *ibid.*, **94**, 634 (1961).

(17) A. B. Burg and H. W. Woodrow, *J. Amer. Chem. Soc.*, **76**, 219 (1954).

n-Butyl disulfide was identified by ir, nmr, and glpc comparison with an authentic sample, and 102% of the iodine required by eq 8 was titrated after 1 hr with **12** at room temperature.

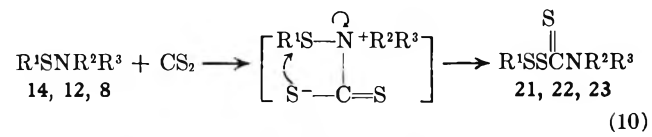
Reaction of N-(*n*-butylthio)piperidine (**13**) with *p*-toluenesulfonyl chloride, in the presence of cyclohexene as a trap for the sulfenyl chloride, gave as the only major products N-tosylpiperidine and 2-chlorocyclohexyl *n*-butyl sulfide (eq 9). These products were



(9)

identified by glpc mass spectrometric analysis and comparison of their mass spectra with those of authentic materials.

Carbon disulfide, considered as an electrophile, should react with sulfenamides to give trithiopercarbamates, as shown by eq 10. Blake has reported products from



(10)

14, 21, $R^1 = t\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
12, 22, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$
8, 23, $R^1 = AcNH(CH_2)_2$; $R^2 + R^3 = (CH_2)_2O(CH_2)_2$

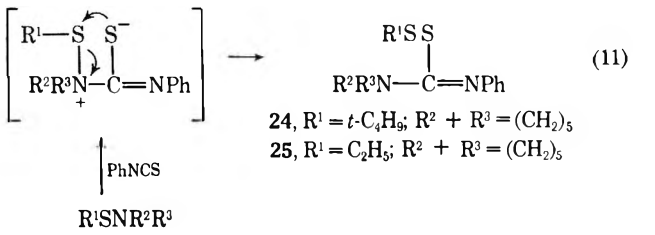
this type of reaction to be disulfides and tetrasubstituted thiuram disulfides;[18] these probably resulted from disproportionation of the primary product in the case of a N,N-disubstituted sulfenamide. The products reported from carbon disulfide and a monosubstituted sulfenamide were an isothiocyanate and a thiol[9,18] (decomposition). 2-Benzothiazolesulfenamide did not react.[9]

Reaction of N-(*t*-butylthio)piperidine (**14**) with carbon disulfide was very slow but gave **21** in 50% yield. The structure of **21** was assigned from its spectra and was confirmed by a reported independent synthesis from the appropriate dithiocarbamate and 2-methylpropane-2-sulfenyl chloride.[19] Reaction of N-(ethylthio)piperidine (**12**) was very fast and exothermic, possibly because of much less shielding with R^1 = Et than with R^1 = *t*-Bu; **22** resulted in 95% yield (eq 10). Although **22** was an oil which was difficult to purify, presumably because of disproportionation, the ir spectrum clearly showed the thioamide function, the nmr spectrum demonstrated the presence of ethyl and piperidyl groups, and the mass spectrum gave a molecular ion with the proper isotope distribution. The base peak in the spectrum was at *m/e* 128, as with **21**, and must result from loss of the ethyl group and two sulfur atoms. The acetamidosulfenamide **8** also reacted rapidly with carbon disulfide, giving **23** in 100% yield. The spectra of **23** were consistent with expectations.

(18) E. S. Blake, *J. Amer. Chem. Soc.*, **65**, 1267 (1943). After the presentation of our work as is mentioned in ref 1c and the submission of the present paper, a report appeared by J. E. Dunbar and J. H. Rogers that also described the new reaction of carbon disulfide with sulfenamides, but with other sulfenamides than those discussed here [*J. Org. Chem.*, **35**, 279 (1970)].

(19) C. M. Himel and L. O. Edmonds, U. S. Patent 2,792,394 (1957); *Chem. Abstr.*, **52**, 1282 (1958).

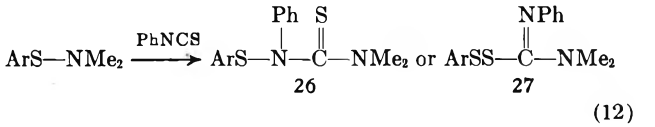
The general principle suggested for reaction of electrophiles predicts that isothiocyanates should react according to eq 11. As with carbon disulfide, reactions reported with isothiocyanates have varied with the



(11)

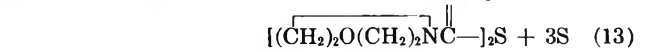
24, $R^1 = t\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
25, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$

degree of nitrogen substitution. N,N-dimethylperchlorobenzenesulfenamide reportedly gave the N-sulfenylthiourea **26** (eq 12),[20] instead of isomer **27** that



(12)

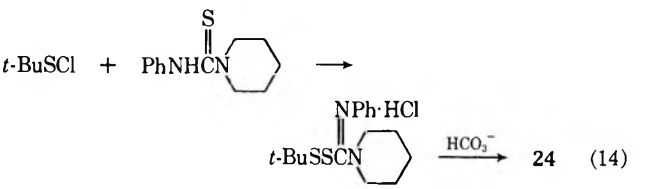
one would expect. Morpholine disulfide with methyl isothiocyanate gave the formamidine sulfide of eq 13,[21]



(13)

which could be formed reasonably by loss of sulfur from the type of product predicted by eq 11. 2-Benzothiazolesulfenamide and an isothiocyanate gave 2-benzothiazolyl disulfide,[9] presumably from the initial product, and *o*-nitrobenzenesulfenamide gave *o*-nitrophenyl disulfide.[22]

We found that N-(*t*-butylthio)piperidine (**14**) reacted very slowly with phenyl isothiocyanate. The reaction was nearly complete only after 1 month (by ir). It gave a low melting solid, **24** (eq 11). The ir and mass spectrum supported the assigned structure. The ir spectrum showed a strong band at 1590 cm^{-1} (>C=NPh), and the mass spectrum showed the correct molecular weight with the expected enhancement of the M + 2 peak due to two sulfur atoms and the base peak at *m/e* 187 corresponding to loss of the *t*-butyl group and two sulfur atoms. An independent synthesis gave identical **24** (eq 14). Both formation of a hydrochlo-



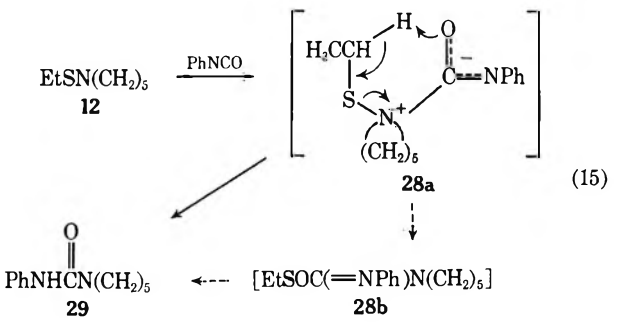
(14)

ride salt of **24** and the failure of **24** to oxidize iodide to iodine further argue against formulation as the isomeric N-sulfenylthiourea. As with carbon disulfide, the ethyl derivative **12** reacted much faster than **14**; reaction was complete by ir in 5 min. The product (**25**) apparently disproportionated more readily than **24**, a characteristic of resistance noted before with *t*-

(20) G. Oertel, H. Malz, and H. Holtschmidt, *Chem. Ber.*, **97**, 891 (1964).
(21) R. W. Saville, *ibid.*, 2880 (1958).
(22) F. Kurzer and W. Tertiuk, *ibid.*, 1571 (1958).

butyl disulfides.[23] The structure of **25** follows from its spectra and (like **24**) from its failure to oxidize iodide ion to iodine. The ir spectrum of **25** shows a strong band at 1590 cm^{-1} (>C=NPh) and the nmr spectrum shows phenyl, ethyl, and piperidyl groups. The mass spectrum shows the expected molecular ion with the expected enhancement of the M + 2 peak, and also a base peak at *m/e* 187 resulting from loss of the ethyl group and two sulfur atoms.

Reaction of N-(ethylthio)piperidine (**12**) with phenyl isocyanate in principle should give **28b** (eq 15), probably an unstable compound. Sulfenamides derived

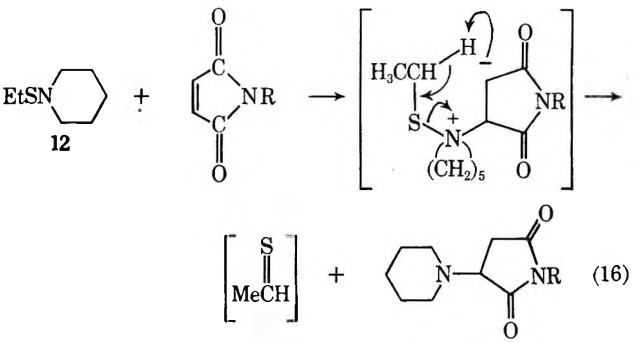


(15)

from ammonia have been reported to react with aryl isocyanates to give the N-sulfenylureas;[9,24,25] hydrogen transfer from nitrogen in an intermediate like **28a** must occur. With N-alkyl substituted sulfenamides, the product is the urea derivative of the amine,[9,24] the sulfur fragment being lost. This result has been explained by D'Amico as resulting from a thiol-catalyzed decomposition of the sulfenamide.[24] Reaction of **12** with phenyl isocyanate at 90° for 3 days gave **29** as the only isolable product, along with much dark, intractable material; the identity of **29** was confirmed by independent synthesis from piperidine and phenyl isocyanate. Presumably either **28a** or **28b** decomposes by abstraction of a hydrogen atom α to sulfur to give the urea and thioacetaldehyde, the latter undergoing further reactions to give the dark color. We prefer this mechanism *via* **28a** to **29** to that of D'Amico since we have no evidence for decomposition of **12** under the reaction conditions. It should be noted that the isocyanate reaction (eq 15) proceeds more slowly than the isothiocyanate reaction (eq 11).

Having in mind the previously mentioned general principle, we attempted to prepare sulfenyl acetates by treating **12** with acetic anhydride. Others have used acetic anhydride to convert 2-aminothiazolesulfenamides to the corresponding 5-thiazolyl sulfides[26] and N-monoalkylsulfenamides to bisthioamines, $(R^1S)_2NR^2$.[27] Glpc and mass spectrometric analysis of the products obtained from **12** showed only N-acetylpiperidine and ethyl disulfide, but ethanesulfenyl acetate would be expected to be quite unstable.

With electron-rich olefins (vinyl ethers) and cyclic olefins (cyclohexene), **13** failed to react in 4 days at 100°, as determined by the absence of change in the intensity of the olefinic protons relative to other peaks in the nmr spectrum. With electron-deficient olefins, eliminations resembling that of eq 15 occurred. Qualitatively, the rate of reaction seemed to follow the degree of electron deficiency (tetracyanoethylene > N-ethyl- or N-phenylmaleimide > ethyl acrylate). The reaction with N-phenylmaleimide was studied because of the ease of monitoring the reaction by nmr and uv. Reaction of N-phenylmaleimide with N-(ethylthio)piperidine (**12**) at 90° for 16 hr gave as the only isolable product the compound resulting from addition of piperidine to N-phenylmaleimide (eq 16). The formation of **30** may be



(16)

a concerted process which requires the presence of α-hydrogens, since the *n*-butyl derivative **13** reacts similarly with N-ethylmaleimide, while the *t*-butyl derivative **14** reacts much more slowly (3 days at 90° gave only a trace of **30**, although this result also could be attributed to the larger *t*-butyl group, as with eq 10 and 11). A stepwise mechanism seems less likely since **12** and **16** showed no decomposition after 16 hr at 90°. The adduct **30** (47% yield from **12**) was identical with **30** obtained from piperidine and N-phenylmaleimide.

Ethyl acrylate and N-(ethylthio)piperidine (**12**) reacted to 60% completion only after 3 days at 77°. Analysis of the product mixture still later by glpc and mass spectrometry showed the presence of both **12** and a new compound with mol wt 185 (**32**). Analogy with eq 16 suggested that **32** was ethyl β-(1-piperidyl)-propionate (eq 17). The mass spectrum of **32** showed

$$\underset{\mathbf{12}}{EtSN(CH_2)_5} + CH_2{=}CHCO_2Et \longrightarrow \underset{\mathbf{32}}{(CH_2)_5NCH_2CH_2CO_2Et} + [CH_3CHS] \quad (17)$$

only one intense ion, *m/e* 100, corresponding to loss of piperidine from the molecular ion. An ir spectrum of the reaction mixture after nearly complete reaction was very similar to that of the proposed propionate. Preparative tlc ultimately gave **32** identical with the adduct of piperidine and ethyl acrylate.[28] No pure sulfur-containing fragment could be identified.

The general pattern suggested at the outset for reaction with electrophiles thus seems to be borne out with disubstituted sulfenamides in that attack first occurs upon the nitrogen. Thereafter, if a counterion has been expelled (*e.g.*, halide) it attacks the sulfur, effecting nucleophilic displacement of the nitrogen fragment. If an internal charge center has been developed, however, it is now clear that this may not *only* attack SR^1 (as in eq 10, 11) but in other situations may give the effect of abstracting a proton from R^1S (as in eq 15–17).

(23) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).
(24) J. J. D'Amico, *ibid.*, **26**, 3436 (1961).
(25) F. Kurzer, *J. Chem. Soc.*, 3360 (1953).
(26) E. Hoggarth, *ibid.*, 110 (1947).
(27) J. C. Conly, U. S. Patent 2,860,142; *Chem. Abstr.*, **53**, 7199 (1959).
(28) E. Philippi and E. Galter, *Monatsh. Chem.*, **51**, 253 (1929).

Although the foregoing reactions seem best formulated as being heterolytic, it certainly would be unwise to assert that homolysis does not play a role. One is particularly dubious about ruling out homolysis in the elimination reactions in view of the more vigorous conditions used. Further study on the possible involvement of homolysis would be worthwhile.

One further reaction of an electrophilic nature should be added for the sake of completeness, that of carbonyl compounds (eq 18).[24,29] This reaction works well for

$$R_2CO + R^1SNH_2 \longrightarrow R_2C = NSR^1 + H_2O \quad (18)$$

benzaldehyde and acetone,[29] but with cyclohexanone and dicarbonyl compounds thioalkylation may occur.[24]

Reactions with Nucleophiles.—Reactions of sulfenamides with nucleophiles seem to proceed in a straightforward manner. Thus Grignard reagents,[30] thiols,[31] and amines[9,32] effect displacement on sulfur to give sulfides, disulfides, and sulfenamides respectively. The general reaction seems to be that of eq 19.

$$R^1SNR^2R^3 + (Nu)^- \longrightarrow RS(Nu) + R^2R^3N^- \quad (19)$$

Nucleophilic attack of one sulfenamide on another seemed likely to result in metathesis (eq 20). How-

$$R^1SNR^2R^3 + R^4SNR^5R^6 \rightleftharpoons R^1SNR^5R^6 + R^4SNR^2R^3 \quad (20)$$

ever, when the ethyl and *t*-butylsulfenamides **12** and **16** were heated either neat or with amine or thiol catalysts no change occurred in up to 16 hr at 90°. In a similar experiment, **16** was heated with piperidine for 12 days at 90° with no metathesis evident. Although no amine or sulfenamide exchange took place in these experiments, the lack of reaction may have resulted from the steric effect of the *t*-butyl group.

Interest in the chemistry of disulfides prompted us to examine nucleophilic displacement on the acetamidoethyl derivatives **5** and **10** to evaluate their use for the synthesis of unsymmetrical disulfides. Reaction of **10** with 2-acetamidoethanethiol, with triethylamine as a catalyst, gave the symmetrical disulfide **2** in 93% yield. No reaction occurred in the absence of triethylamine. Reaction of **5** or **10** with *p*-toluenethiol proceeded rapidly, in the absence of base, to give 2-*p*-tolyldithio-1-acetamidoethane (**33**) in about 61–70% yield; however, the product from **10** contained some phthalimide and was difficult to purify. An unsuccessful effort was made to develop a general method for preparing unsymmetrical disulfides by a similar route using N-tosyloxyphthalimide. If reaction of the tosyloxyphthalimide with a thiol gave a sulfenamide, reaction with a second thiol should give the unsymmetrical disulfide and phthalimide. This method failed because α-toluenethiol did not react with N-tosyloxyphthalimide. An elegant capitalization along similar lines has been reported recently by Mukaiyama and Takahashi.[33] They prepared a sulfenamide by reaction of one thiol with diethyl azodicarboxylate and then converted this sulfenamide in 75–90% yield to unsymmetrical disulfides using a second thiol.[33] In our experience, a highly nucleophilic aminothiol may behave poorly in this synthesis owing to attack of the first thiol on the sulfenamide as it forms, thus leading to a symmetrical disulfide in the first stage.

Biological Properties.—Toxicities and antiradiation activities of typical products are being evaluated by means outlined earlier.[3] Preliminary results indicate that none of the sulfenamides and related products led to significant protection in mice against ionizing radiation.[34] Results thus far suggest therefore that NR^2R^3 is surprisingly unpromising as a latentiating group for biologically active thiols.

Experimental Section[35]

Materials.—Preparations were performed as reported for N-phenymaleimide,[36] 2-acetamidoethyl disulfide (**2**),[37] N-(*t*-butylthio)piperidine (**14**),[7] N-(*n*-butylthio)piperidine (**13**),[7] N-(ethylthio)piperidine (**12**),[7] N-(*t*-butylthio)aniline (**17**),[7] and N-(ethylthio)diethylamine (**15**).[10] Satisfactory melting points or analysis by glpc or nmr were obtained for all the above-listed compounds. Morpholine sulfide (**19**) and piperidine sulfide (**20**) were gifts from J. L. Richards, to whom we are grateful. All other materials were purchased and used without purification.

2-Acetamidoethanesulfenyl Chloride (3).—Illustratively, a solution of 2.00 g (8.48 mmol) of 2-acetamidoethyl disulfide (**2**) in 75 ml of CH_2Cl_2 was cooled to −35°. Chlorine (0.4 ml, 8.8 mmol), previously collected in a Dry Ice–acetone cooled vessel, was allowed to evaporate during 15 min into the stirred solution. After 10 min, the amount of **3** was determined by iodometric titration;[38] 2 ml of the solution of **3** required 3.39 ml of 0.0731 *N* sodium thiosulfate solution (0.248 meq) (55% yield). Reasonable stability of **3** was found at −35°, since titration at intervals up to 2.5 hr gave the same result. In the preparation of sulfenamides, however, the amount of sulfenyl chloride specified is simply twice the number of mols of disulfide used, the assumption being made that the yield was theoretical from the disulfide as the limiting reagent.

General Procedure for Synthesis of Sulfenamides. A.—The **3** from *ca.* 2 g (8.5 mmol) or 4 g (17 mmol) of **2** and an equimolar quantity of Cl_2, 0.4 ml (8.8 mmol) or 0.8 ml (17.6 mmol), was

(29) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 3072 (1957).

(30) H. Gilman and C. C. Vernon, *Recl. Trav. Chim. Pays-Bas*, **48**, 743 (1929).

(31) A. Fontana, F. Marchiori, L. Moroder, and E. Scoffone, *Tetrahedron Lett.*, 2985 (1966).

(32) L. H. Howland, U. S. Patent 2,382,793; *Chem. Abstr.*, **40**, 368 (1946).

(33) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

(34) We are indebted for these evaluations to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck, and Miss Marie Grenan, all of the Walter Reed Army Institute of Research, Washington, D. C. Preliminary ALD_{50}[3b] results (mg/kg) for compounds follow: **5**, 240; **6**, 475; **8**, 130; **10**, 45; **11**, 150; **13**, 75; **14**, 430; **21**, 800; **23**, 60; **24**, > 300. Thus far, **5** has led only to 17% survival at 180 mg/kg (0% at 90) and **23** only to 7% survival at 30 mg/kg (0% at 15). The other compounds just mentioned were completely inactive when tested at *ca.* 0.3–0.6 × ALD_{50}. Other compounds remain to be tested.

(35) Melting points are corrected, and boiling points are uncorrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Mass spectra were obtained with an LKB Model 9000 instrument, operating at 70 eV, source temperature 250°, and accelerating potential 3.5 kV, unless specified otherwise, using either direct-inlet or gas chromatographic (glass, 6-ft 1% SE-30 on a Gas Chrom Q column) inlet systems; the instrument was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to Mr. Charles Wetter for these spectra. In the mass spectra, peaks of relative intensity lower than 5% are reported only for products of eq 3, 4, 5, or 6, or elsewhere when thought important. Ir spectra were obtained using a Beckman Model IR-10 with films of liquids and KBr pellets of solids; absorptions are given in cm^{-1}, "s" signifying strong (other reported were medium). Glpc analyses were obtained using a 6-ft stainless-steel 10% SE-30 on Chromosorb P column, injection port 250°, detector 220°, column temperature 130–170°. Nmr spectra were obtained with a Varian Model A-60 with TMS as internal standard in CCl_4 unless otherwise noted. Raman spectra were obtained with a Cary Model 81 instrument. We thank the National Science Foundation for departmental grants GP-1683 and GP-6932 respectively toward purchase of the latter two instruments. Unless otherwise stated, reactions were done at room temperature. Moist extracts were dried using the anhydrous reagent specified, and solvents were evaporated at reduced pressure with a rotary evaporator. Short-path distillations were done in a conventional falling-drop apparatus with a path length of *ca.* 1–2 cm or less.

(36) M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, *Org. Syn.*, **41**, 93 (1961).

(37) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(38) N. Kharasch and M. M. Wald, *Anal. Chem.*, **27**, 996 (1955).

added slowly (*ca.* 0.3 hr) to a solution of the amine or amide, 17 or 34 mmol, in CH_2Cl_2 at $-20 \pm 10°$. Either an excess of the amine was used (usually *ca.* 2.5 mol of total amine/mol RSCl) or Et_3N was present (*ca.* 1.5 mol/mol RSCl). The solution was stirred for 1.5 hr during which time it warmed to *ca.* 25°; it was then washed with water to remove amine salts or excess amine, dried ($MgSO_4$ or Na_2SO_4), and evaporated to dryness under reduced pressure. Crude products then were purified by column chromatography, short-path distillation, or recrystallization (*vide infra*).

B. Applications of Procedure A. N-(2-Acetamidoethylthio)-*p*-carbomethoxyaniline (4).—The crude product from 5.1 g (34 mmol) of methyl *p*-aminobenzoate by A (55% **4** by nmr analysis) was chromatographed over Florisil in $CHCl_3$ to give 1.0 g (11% yield). Two recrystallizations from ethyl acetate gave mp 98–100°; nmr ($CDCl_3$) δ 2.00 (s, 3, $CH_3C(=O)N$), 2.70 (m, 2, CH_2–S), 3.50 (m, 2, CH_2–NH), 3.85 (s, 3, CH_3O), 6.45 (s, 1, NH Ar), 7.10 (m, 3, 2ArH and Ac NH), and 7.90 (m, 2, 2ArH); mass spectrum *m/e* (rel intensity) 270 (0.3), 269 (0.7), 268 (4), 182 (0.2), 152 (6), 151 (61), 150 (3), 121 (9), 120 (100), 118 (4), 92 (31), 91 (5), 87 (7), 86 (6), 84 (9), 72 (15), 65 (25), 64 (5), 63 (6), 60 (8), 45 (20), 44 (9), 43 (100), and 42 (9).

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.58; H, 6.01; N, 10.42.

N-(2-Acetamidoethylthio)-2-aminobenzothiazole (5).—The CH_2Cl_2 solution from A (17 mmol of **2**) after the water wash and before drying, was chilled at 5° for 3 hr and filtered: yield of **5**, 5.1 g (56%), mp 140–141° (dec). Partial evaporation of the filtrate and chilling gave an additional 0.6 g (7%) of **5**, mp 140–142° (dec). Recrystallization from EtOH–H_2O gave pure **5**: mp 142–143°; nmr (C_5D_5N) δ 2.05 (s, 3, $CH_3C(=O)N$), 3.15 (m, 2, CH_2S), 3.80 (m, 2, CH_2NH), 7.0–8.0 (m, *ca.* 4, Ar), 8.57 (s, $w_{1/2}$ 14 Hz, 1, $NHCH_2$), and 8.74 (s, 1, NHS); mass spectrum *m/e* (rel intensity) 269 (0.2), 268 (0.2), 267 (2), 182 (1), 152 (5), 151 (13), 150 (100), 149 (4), 123 (21), 122 (6), 118 (22), 117 (2), 109 (6), 96 (22), 86 (18), 76 (5.4), 75 (12), 72 (5.3), 69 (13), 60 (18), 45 (7), 44 (13), 43 (33), and 42 (5).

Anal. Calcd for $C_{11}H_{13}N_3OS_2$: C, 49.35; H, 4.89; N, 15.69; S, 23.95. Found: C, 49.29; H, 4.91; N, 15.63; S, 24.09.

N-(2-Acetamidoethylthio)-N,N-diethylamine (6).—The crude product from Et_2NH (excess) and the **3** from 8.5 mmol of **2**, 1.78 g (55%) of a pale yellow oil, $n^{25}D$ 1.4905, was chromatographed over Florisil in benzene. A middle fraction, the fourth of seven ($n^{26}D$ 1.4913), was analyzed. Crude **6** also was purified by short-path distillation (70°, 0.08 mm) to give pure **6**: $n^{25}D$ 1.4899 (*ca.* 70% yield in distillation, net yield 39%); nmr (neat) δ 1.12 (t, 6, CH_3CH_2), 1.95 (s, 3, $CH_3C(=O)N$), 2.9 (m, 6, CH_2–CH_3 and CH_2–S), 3.35 (m, 2, CH_2–NH), and 8.20 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 192 (0.07), 191 (0.4), 190 (2), 118 (4), 104 (2), 86 (26), 73 (1), 72 (100), 58 (7), 56 (6), 44 (32), 43 (29), and 42 (20).

Anal. Calcd for $C_8H_{18}N_2OS$: C, 50.49; H, 9.43; N, 14.72; S, 16.85. Found: C, 50.77; H, 9.52; N, 14.41; S, 17.05.

N-(2-Acetamidoethylthio)piperidine (7).—The crude **7** from **3** (34 mmol, theory) and excess piperidine was obtained in 103% yield (7.0 g, $n^{28}D$ 1.5125). A 6.0-g portion was purified by short-path distillation (80°, 0.08 mm) to give 3.0 g (51%) of pure **7**: $n^{28}D$ 1.5160; nmr δ 1.48 (m, 6, $-(CH_2)_3-$), 1.95 (s, 3, $CH_3C(=O)N$), 2.5–3.1 (m, 6, $-(CH_2)_2N$ + $-CH_2S$), 3.45 (m, 2, CH_2-NH), and 7.81 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 204 (0.7), 203 (2), 202 (12), 119 (3), 118 (5), 117 (3), 116 (5), 87 (6), 86 (100), 85 (9), 84 (40), 83 (5), 60 (9.5), 56 (10), 55 (20), 44 (44), 43 (30), 42 (27), and 41 (9).

Anal. Calcd for $C_9H_{18}N_2OS$: C, 53.43; H, 8.97; N, 13.84; S, 15.85. Found: C, 53.24; H, 8.72; N, 13.69; S, 15.91.

N-(2-Acetamidoethylthio)morpholine (8).—The crude **8** from **3** (*ca.* 34 mmol theory) by A, 6.0 g (86%) of pale yellow oil $n^{28}D$ 1.5154, was purified by short-path distillation (80°, 0.1 mm) to give a slightly yellow oil: 2.0 g (29%); $n^{28}D$ 1.5150; nmr δ 1.96 (s, 3, $CH_3C(=O)N$), 2.9 (m, 6, $-CH_2NS$ + $-CH_2S$), 3.1–3.8 (m, 6, CH_2O + CH_2NH), and 7.88 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 206 (0.7), 205 (2), 204 (13), 119 (3) 118 (14), 88 (7), 87 (16), 86 (100), 76 (6), 72 (8), 57 (30), 56 (47), 55 (7), 54 (40), 42 (18), and 41 (6).

Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.05; H, 7.89; N, 13.72; S, 15.70. Found: C, 46.96; H, 7.79; N, 13.62; S, 15.49.

N-(2-Acetamidoethylthio)benzimidazole (9).—The crude **9** from **3** (34 mmol theory) and 4.0 g (34 mmol) of benzimidazole was crystallized from acetone to give 2.2 g of white needles (28%). Partial evaporation of the solvent gave an additional 1.2 g, total yield 42%. Two recrystallizations from acetone gave **9** of mp 118–121° (dec); nmr ($CDCl_3$) δ 1.92 (s, 3, $CH_3C(=O)N$), 2.8–3.7 (m, 4, NCH_2CH_2S), 7.1–7.9 (m, 5, 4ArH + NH), and 8.02 (s, 1, $-N=CH-N-$); mass spectrum *m/e* (rel intensity) 237 (0.2), 236 (0.5), 235 (2.0), 119 (21), 118 (100), 117 (7), 91 (26), 90 (11), 86 (7), 76 (5), 65 (14), 64 (15), 63 (52), 59 (5), 52 (6), 44 (7), and 43 (25).

Anal. Calcd for $C_{11}H_{13}N_3OS$: C, 56.14; H, 5.57; N, 17.86; S, 13.63. Found: C, 56.13; H, 5.67; N, 17.82; S, 13.42.

N-(2-Acetamidoethylthio)phthalimide (10).—The crude **10** from 31.4 g (170 mmol) of the potassium salt of phthalimide and **3** (176 mmol) was crystallized from MeOH to give 20.0 g (45%) of **10**, mp 144–149°. Concentration of mother liquor gave 9.0 g of phthalimide. Recrystallization from MeOH gave pure **10**: mp 149–150°; nmr ($CDCl_3$) δ 2.08 (s, 3, $CH_3C(=O)N$), 3.0 (m, 2, CH_2S), 3.4 (m, 2, CH_2NH), 6.85 (s, $w_{1/2}$ 20 Hz, 1, NH), and 7.9 (m, 4, ArH); mass spectrum *m/e* (rel intenstiy) 266 (0.1), 265 (0.2), 264 (2), 205 (17), 179 (1), 178 (2), 160 (8), 149 (7), 148 (68), 147 (55), 130 (31), 119 (6), 118 (10), 117 (100), 105 (7), 104 (51), 103 (17), 102 (69), 86 (16), 84 (20), 77 (56), 76 (66), 75 (37), 74 (15), 72 (13), 60 (29), 59 (5), 58 (15), 50 (30), and 44 (24).

Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.58; H, 4.58; N, 10.61; S, 12.14. Found: C, 54.91; H, 4.63; N, 10.46; S, 12.33.

N-(2-Acetamidoethylthio)-*p*-toluenesulfonamide (11).—The solution of crude **11** from **3** (34 mmol theory) and 5.8 g (34 mmol) of *p*-toluenesulfonamide (using Et_3N) was washed with a solution of 3.2 g (80 mmol) of NaOH in 100 ml of H_2O. The aqueous layer then was cooled and brought to pH 4 with 50% AcOH. The resulting solid was removed by filtration and dried to give 6.3 g (64%) of crude **11**,[39] mp 99–120°.

The solid was chromatographed over silica gel (Baker 60–200 mesh; 180 g) in EtOAc to give 2.1 g (21%) of **11**. Recrystallizations from Me_2CO gave pure **11**: mp 120.5–121°; nmr ($CDCl_3$) δ 1.97 (s, 3, $CH_3C(=O)N$), 2.41 (s, 3, CH_3Ar), 3.2–3.9 (m, 4, NCH_2CH_2S), 5.32 (s, $w_{1/2}$ = 13 Hz, 1, $NHSO_2$), 6.9 (s, $w_{1/2}$ = 25 Hz, 1, $NHC(=O)-$), 7.30 (m, 2, 2 ArH), and 7.80 (m, 2, 2 ArH).

Anal. Calcd for $C_{11}H_{16}N_2O_3S_2$: C, 45.81; H, 5.59; N, 9.71; S, 22.23. Found: C, 45.89; H, 5.52; N, 9.56; S, 21.88.

N-(*t*-Butylthio)-N,N-diethylamine (16).—2-Methyl-2-propanesulfenyl chloride, from chlorination of *t*-butyl disulfide at *ca.* 25°, was added dropwise to excess diethylamine in petroleum ether at 5°. The resulting mixture was washed twice with water and distilled (20-cm Vigreux column) to give pure **16**: bp 48° (8.0 mm); $n^{28}D$ 1.4479; nmr δ 1.08 (t, 6, CH_3CH_2), 1.20 (s, 9, $(CH_3)_3$), and 2.97 (q, 4, CH_2CH_3).

Anal. Calcd for $C_8H_{19}NS$: C, 59.56; H, 11.87. Found: C, 59.36; H, 11.91.

Thermolysis.—Thermolyses were carried out on neat samples in open vessels (**5**, **8**, **10**, and **13**) for the time shown in Table I, or for 4 days in a sealed ampoule (**6** and **16**). Analysis of the products was accomplished by tlc (acetone, Brinkmann F-254 precoated analytical plates) for acetamidoethyl derivatives and are qualitative estimates based on visually estimated spot intensities. Volatile products from **6**, **8**, and **13** were analyzed by glpc and mass spectrometry. **N-(*n*-butylthio)piperidine (13,** 1.00 g) after 20 min at 140° showed no new peaks or change in the ratio of the original peak heights of **13** and *n*-butyl disulfide in the sample used as a standard. Further heating (1 hr) caused slight darkening but no change by glpc analysis. **N-(2-Acetamidoethylthio)phthalimide (10,** 10 mg) after 20 min at 155° gave a nearly colorless residue. Tlc analysis, by comparison with **10** and phthalimide, showed a large spot corresponding to **10** and only a trace of phthalimide.

N-(2-Acetamidoethylthio)morpholine (8, 10 mg), after 20 min at 140° gave a dark residue. Tlc analysis by comparison with pure **8** showed only a small spot corresponding to **8** and other spots not identified. Glpc and mass spectrometric analysis starting at 40° and programming for an increase of 10°/min, showed only the presence of morpholine and N-acetylmorpholine, mol wts (ms) 87 and 129 respectively. **N-(2-Acetamidoethylthio)-2-aminobenzothiazole (5,** 10 mg) after 20 min at 155° left a dark residue. Tlc analysis by comparison with **5** and 2-aminobenzothiazole showed only a trace of **5** and a large spot corresponding to 2-aminobenzothiazole.

(39) This separation of **11** was based on information on the physical properties of compounds like **11** kindly supplied to us by Professor Robert B. Scott of the University of Mississippi.

N-(2-Acetamidoethylthio)-N,N-diethylamine (6, 2.00 g), in a sealed ampoule was heated at 100° for 4 days. Tlc analysis of the reaction mixture showed only a small portion of the mixture to be 6. Glpc–mass spectrometric analysis, starting at 60°, programmed at 5°/min to 230°, showed five volatile products.

Spectral data for the products follow. The first product, N,N-diethylacetamide [*m/e* (rel intensity) 115 (22), 100 (18), 86 (4), 72 (16), 58 (100), 44 (34), 43 (34) and 30 (22)], was identified by comparison of its mass spectrum with that reported.[40] The yield of the second product was small and it could not be identified. The third product [*m/e* (rel intensity) 131 (81), 130 (17), 102 (17), 72 (16), 70 (30), 61 (44), 59 (67), 58 (15), 56 (10), 44 (100), 42 (68), and 30 (12)] showed a molecular ion at *m/e* 131; the intensity of *m/e* 133 (4% of 131) suggested the presence of a sulfur atom; loss of 29 (C_2H_5) and 72 (NEt_2) as well as presence of a strong peak at *m/e* 59, $(CH_3CS)^+$, are consistent with assignment as N,N-diethylthioacetamide. The fourth product, also the glpc peak of largest intensity, had the mass spectrum *m/e* (rel intensity) 188 (34), 154 (10), 129 (18), 116 (39), 88 (75), 82 (30), 72 (65), 60 (67), 56 (55), 54 (22), 44 (43), 43 (100), 42 (37), and 30 (78); it showed a molecular ion at *m/e* 188; *m/e* 190 (5% of *m/e* 188) suggests a sulfur atom. The presence of intense ions at *m/e* 30 ($CH_2NH_2^+$), 43 (CH_3CO^+), and 60 ($CH_3C(=O)NH_2^+$) suggest the presence of an N-substituted acetamide. The *m/e* 72 (Et_2N^+) ion suggests that the second nitrogen is present as an N,N-diethyl group. Thus N,N-diethyl-N′-acetylthioglycinamide, $AcNHCH_2C(S)NEt_2$, seems a good possibility since similar compounds have been observed in the decomposition of α-ketosulfenamides.[41] The fifth component of the mixture was not assigned a structure: mass spectrum *m/e* (rel intensity) 150 (23), 120 (38), 87 (63), 86 (20), 72 (100), 56 (80), 44 (87), 43 (76), 42 (33), and 30 (23). Under the same conditions (4 days, 100°), **16** was recovered unchanged ($n^{28}D$ = 1.4485).

Attempted Photolysis.—In a quartz vessel, N-(*t*-butylthio)-N,N-diethylamine, **16** (2.00 g), in 500 ml of cyclohexane and 10 ml of cyclohexene was irradiated for 18 hr using a 100-W Hanovia lamp. Partial evaporation of the solvent (total residual wt, 2.4 g), followed by glpc and mass spectrometric analysis showed the presence of only starting material. Complete evaporation (80° at *ca.* 15 mm) gave 1.5 g (75%) of **16**, which was identified by its ir spectrum.

Mass Spectra.—Mass spectra were obtained using the direct-inlet system for **2** and **4–10** and using the glpc-inlet system for **12–14**, **16**, and **17**. In the latter case, reported intensity values were from two identical scans.

Mass spectra, *m/e* (rel intensity), not reported above follow: **12**, 145 (68), 144 (42), 118 (4), 117 (14), 116 (68), 104 (10), 89 (14), 88 (7), 87 (7), 85 (14), 84 (52), 83 (13), 62 (16), 61 (44), 60 (21), 59 (10), 58 (5), 57 (20), 56 (30), 55 (100), 54 (14), 53 (9), 47 (13), 46 (10), 45 (14), 44 (21), 43 (18), 42 (65), 41 (45), 40 (43), and 29 (54); **13**, 173 (35), 172 (4), 117 (16), 116 (31), 89 (3), 86 (13), 85 (64), 84 (100), 75 (7), 62 (12), 61 (18), 60 (17), 59 (8), 57 (29), 56 (32), 55 (88), 54 (12), 53 (9), 47 (16), 46 (10), 45 (16), 44 (16), 43 (23), 42 (64), 41 (68), and 40 (5); **14**, 173 (25), 118 (11), 117 (100), 116 (25), 89 (3), 84 (10), 75 (8), 62 (7), 61 (15), 60 (11), 59 (17), 58 (5), 57 (86), 56 (23), 55 (45), 54 (7), 53 (7), 46 (5), 45 (7), 44 (8), 43 (36), 42 (38), 41 (97), and 40 (7); **16**, 161 (19), 105 (57), 104 (10), 90 (100), 89 (1), 76 (10), 74 (2), 73 (2), 62 (8), 61 (6), 59 (8), 58 (14), 57 (38), 56 (10), 48 (5), 46 (7), 44 (13), 42 (34), and 41 (46); **17** (70 eV), 181 (15), 127 (5), 126 (8), 125 (100), 124 (4), 97 (6), 93 (60), 92 (31), 89 (15), 80 (6), 79 (15), 77 (17), 66 (21), 65 (26), 63 (5), 57 (59), and 56 (18); (12 eV), 181 (68), 127 (5), 126 (8), 125 (100), 105 (60), 57 (9), and 56 (15).

Ir and Raman Spectra.—All compounds were done neat. The most noteworthy absorptions in cm^{-1} were as follows. For **EtSN(CH$_2$)$_5$** (**12**), ir spectrum 685, 860, 930 (s), 1040 (s), 1060, 1100, 1050, 1220 (s), 1270, and 1375 and Raman spectrum 525, 635, 660, 690, 840 (s), 1040 (s), 1060, and 1270 were obtained. For ***n*-BuSN(CH$_2$)$_5$** (**13**): ir 685, 860, 930 (s), 1040 (s), 1060, 1100, 1150, 1225 (s), 1270 (s), 1295, and 1370. For ***t*-BuSN(CH$_2$)$_5$** (**14**): ir 860, 925 (s), 950, 1040 (s), 1060 (s), 1100, 1160 (s), 1220 (s), 1260, and 1365 (s). For **EtSNEt$_2$** (**15**): ir 690, 728 (s), 1175, and 1380; Raman 525, 770, 790 (s), 1010 (s), 1036, and 1214. For ***t*-BuSNHPh** (**17**): ir 690 (s), 750 (s), 890, 1165, 1175, 1240, 1290, and 1365. For **morpholine sulfide** (**19**): ir 680, 930 (s), 950, 1060, 1100 (s), 1260, 1300, and 1365; Raman 370, 480, 600 (s), 680 (s), 850 (s), 1030 (s), 1055, 1210, and 1305. For **piperidine sulfide** (**20**): ir 450, 670, 820, 850, 910, 930, 1030, 1100, 1150, 1210 (s), 1270, 1295, 1340, and 1365; Raman 552 (s), 675 (s), 840 (s), 1050 (s), 1150, 1219, 1260, 1273, 1290, and 1436. For the other sulfenamides (**4-11**, **16**), the ir spectra showed no unexpected features and did not need to be added to the typical spectra above.

Reactions of Sulfenamides with Electrophiles. A. With Methyl Iodide.—A solution of 0.83 g (4.8 mmol) of **13** (slightly contaminated with *n*-butyl disulfide) in 2 ml of MeI was allowed to stand overnight; the reaction mixture darkened rapidly. Titration of the mixture in EtOH–H_2O with 42.0 ml of 0.073 *N* $Na_2S_2O_3$ showed 3.06 mequiv (64%) of iodine. The titrated solution was evaporated to near dryness, diluted with water, and extracted with CH_2Cl_2, yield 0.54 g (126%) of *n*-butyl disulfide, identified by ir, nmr, and glpc-peak enhancement. Similarly, 87.0 mg (0.503 mmol) of **13** in 1 ml of MeI gave 0.376 mequiv of I_2 (75%). A solution of 125 mg (0.86 mmol) of **12** in 1 ml of MeOH and 1 ml of MeI, allowed to stand for 1 hr, gave 0.88 mequiv (102%) of I_2.

B. With *p*-Toluenesulfonyl Chloride.—An equimolar mixture of **13** (1.73 g, 10 mmol) and *p*-toluenesulfonyl chloride (1.90 g, 10 mmol) in 10 ml of cyclohexene was allowed to stand for 15 days. Analysis of the product mixture by glpc and mass spectrometry, starting at 100°, programmed at 10°/min, showed the principal products to be 1-*p*-toluenesulfonylpiperidine [mass spectrum *m/e* (rel intensity) 239 (25), 238 (20), 155 (24), 92 (13), 91 (67), 85 (6), 84 (100), 83 (36), 65 (25), 63 (7), 57 (6), 56 (14), and 55 (31)], which had a mass spectrum identical with that of the product prepared by reaction of piperidine with *p*-toluenesulfonyl chloride,[42] and 2-chlorocyclohexyl *n*-butyl sulfide [mass spectrum *m/e* (rel intensity) 208 (3.1), 207 (1.5), 206 (8.3), 171 (8.1), 129 (9.1), 116 (6.0), 91 (5.4), 88 (5.4), 82 (9.5), 81 (100), 79 (25), 75 (9.8), 73 (6.8), 71 (7.2) 67 (14), and 61 (10.2)], which had a mass spectrum identical with that of an authentic sample. For the preparation of authentic **2-chlorocyclohexyl *n*-butyl sulfide**, *n*-butyl disulfide (17.8 g, 0.1 mol) in petroleum ether was chlorinated with 0.1 mol of Cl_2 at −30°, and the product then was added to excess cyclohexene. Removal of solvent left pale yellow oil; distillation (90–91°, 1.2 mm) gave 8.4 g (20%); glpc and mass spectrometry showed the presence of both *cis* and *trans* isomers.

Anal. Calcd for $C_{10}H_{19}ClS$: C, 58.04; H, 9.26. Found: C, 57.88; H, 9.20.

C. With Carbon Disulfide.—For the reaction of **N-(*t*-butylthio)piperidine** (**14**), 2.7 g (16 mmol) of **14** in 10 ml of ether was added to 20 ml of CS_2. The mixture slowly turned yellow. It was let stand until the reaction was complete (*ca.* 21 days), as determined by weight gain after removal of solvent. The product was recrystallized from methanol by dissolution at *ca.* 50° and then chilling in Dry Ice: yield of colorless **21**, 2.00 g (50%); mp 56–57°; nmr ($CDCl_3$) δ 1.35 (s, 9), 1.74 (m, 6), 4.19 (m, 4); mass spectrum *m/e* (rel intensity) 251 (0.3), 250 (1), 249 (2), 130 (5), 129 (8), 128 (100), 84 (12), 77 (8), 72 (39), 69 (60), 59 (11), 57 (29), 56 (25), 55 (17), 53 (5), 45 (7.6), 42 (18), and 41 (90). Independent synthesis of **21** was achieved by treating piperidinium N-pentamethylene dithiocarbamate in water with 2-methyl-2-propanesulfenyl chloride in petroleum ether, essentially as reported;[43] recrystallization of the crude **21** (MeOH) gave **21** in 60% yield. Further recrystallization gave colorless **21** having constant mp 59–61° and an ir spectrum identical with that of the previous reaction product.

Anal. Calcd for $C_{10}H_{19}NS_3$: C, 48.15; H, 7.68. Found: C, 48.24; H, 7.57.

With N-(Ethylthio)piperidine (**12**), addition of CS_2 (10 ml) to 1.00 g of **12** (6.9 mmol) resulted in rapid evolution of heat. After 0.5 hr, evaporation of excess CS_2 left 1.44 g (95% yield) of bright yellow oil ($n^{27}D$ 1.6284), which gave only one spot on tlc (3:1 heptane–benzene, silica gel). Short-path distillation (70°, 0.1 mm), gave 1.30 g of **22**, $n^{27}D$ 1.6274. In another experiment a solution of 4.00 g (27.6 mmol) of **12** in 50 ml of dry ether was added dropwise to 30 ml of CS_2. The solution became yellow

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and after 2 hr the solvent was evaporated to give 5.90 g (97%) of yellow oil, n^{27}D 1.6275. Short-path distillation (80°, 0.05–0.1 mm) gave n^{26}D 1.6259. Another distillation (60°, 0.025 mm) gave n^{26}D 1.6257; nmr δ 1.35 (t, 3, CH_3CH_2), 1.80 (s, $w_{1/2}$ = 7 Hz, 6, $(CH_2)_3$), 2.90 (q, 2, CH_2CH_3), and 4.20 (s, $w_{1/2}$ = 11 Hz, 4, CH_2N); mass spectrum *m/e* (rel intensity) 223 (0.4), 222 (0.7), 221 (2.5), 220 (4), 130 (5), 129 (9), 128 (100), 93 (17), 84 (20), 77 (20), 76 (10), 72 (80), 70 (6), 69 (72), 67 (7), 65 (7), 64 (19), 61 (12), 60 (12), 59 (25), 58 (18), 56 (51), 55 (24), 54 (13), 53 (10), 46 (15), 45 (45), 43 (7), 42 (40), and 41 (100).

Anal. Calcd for $C_8H_{15}NS_3$: C, 43.40; H, 6.83. Found: C, 43.63; H, 7.00.

With **N-(2-Acetamidoethylthio)morpholine** (**8**) a solution of **8**, 0.35 g (1.7 mmol), in CH_2Cl_2 was added dropwise to 1 ml of CS_2. After the initial exothermic reaction, the yellow mixture was let stand for 0.5 hr. Removal of the solvent gave 0.48 g (100%) of crystalline **23**, mp 86–89°. Two recrystallizations from EtOAc gave **23** having constant mp 96–98°; ir 3270, 3100, 1645, 1550, 1420, 1220 cm^{-1}; mass spectrum *m/e* (rel intensity) 282 (0.4), 281 (0.4), 280 (2.4), 195 (3), 163 (5), 132 (5), 131 (8), 130 (100), 118 (8), 87 (9), 86 (66), 77 (5), 76 (29), 75 (6), 60 (15), 59 (7), 57 (10), 56 (10), 45 (6), 44 (12), 43 (30), and 42 (8).

Anal. Calcd for $C_9H_{16}N_2O_2S_3$: C, 38.54; H, 5.75; S, 34.30. Found: C, 38.73; H, 5.87; S, 34.13.

D. With Phenyl Isothiocyanate.—N-(*t*-Butylthio)piperidine (**14**, 1.90 g, 10.9 mmol) and PhNCS (1.47 g, 10.9 mmol) were allowed to stand until change ceased in the ir spectrum (30 days). A small portion of the oil (n^{26}D 1.5774) was purified by short-path distillation (65°, 0.002 mm) to give an oil (n^{26}D 1.5890), which crystallized when seeded with a crystal from the still. The undistilled product was recrystallized twice from heptane using these seeds (Dry Ice cooling) to give **24**: yield, 1.8 g (54%); constant mp 39–41°; ir 1610, 1590, 1490, 1450, 1390, 1370, 1225, 1175, 1160, 1115, 1000, 750, and 690 cm^{-1}; nmr δ 1.22 (s, 9), 1.67 (s, $w_{1/2}$ = 4 Hz, 6 $(CH_2)_3$), 3.5 (s, $w_{1/2}$ = 10 Hz, 4, CH_2N), and 6.7–7.5 (m, 5); mass spectrum *m/e* (rel intensity) 308 (0.2), 219 (4), 188 (15), 187 (100), 131 (14), 77 (20), 69 (7), 57 (8), and 55 (7).

Anal. Calcd for $C_{16}H_{24}N_2S_2$: C, 62.29; H, 7.84; S, 20.80. Found: C, 62.23; H, 7.81; S, 20.65.

For the independent synthesis of **24**, 2-methyl-2-propanesulfenyl chloride from *t*-butyl disulfide (39 mmol) and 1.8 ml of liquid Cl_2 (39 mmol) in 75 ml of petroleum ether at 25° was added dropwise to 17.2 g of N-phenyl-N′-pentamethylenethiourea (78 mmol) in 150 ml of 1:1 CH_2Cl_2–Et_2O at 5°, and the mixture was stirred at 5° for 1 hr. The solution then was washed with 35% HCl and then water, and the organic layer then was evaporated to dryness to give 16.0 g of the HCl salt of **24** (60%), mp 140–141°; recrystallization from benzene gave an analytical sample, mp 140–141°.

Anal. Calcd for $C_{16}H_{25}ClN_2S_2$: C, 55.71; H, 7.30. Found: C, 56.10; H, 7.29.

A suspension of the hydrochloride (3.44 g, 10.0 mmol) was neutralized with 2 equiv of aqueous Na_2CO_3. Immediate extraction with Et_2O, evaporation, and recrystallization (heptane, Dry Ice–acetone bath) gave 2.30 g (75%) of **24**, mp 39–41°. The ir spectrum was identical with that of **24** obtained from the isothiocyanate reaction.

N-(Ethylthio)piperidine (**12**, 0.29 g, 2.0 mmol) and PhNCS (0.27 g, 2.0 mmol) were allowed to stand for 1 day, even though by ir analysis the reaction is complete in 5 min. The product (**25**) then was purified by short-path distillation (65°, 0.002 mm) to a constant refractive index of n^{26}D 1.6108; yield 0.44 g, 79%; nmr ($CDCl_3$) δ 1.08 (t, 3, CH_3), 1.3–1.9 (s, $w_{1/2}$ = 5 Hz, 6, $(CH_2)_3$), 2.48 (q, 2, CH_2CH_3), 3.50 (s, $w_{1/2}$ = 10 Hz, 4, CH_2N), and 6.5–7.4 (m, 5, Ph); ir 1610, 1590 (>C=N), 1500; mass spectrum *m/e* (rel intensity) 280 (0.3), 219 (5), 188 (14), 187 (100), 131 (12), 119 (5), 109 (5), 84 (6), 77 (18), 69 (9), 55 (7), 51 (6), 42 (5), and 41 (18).

Anal. Calcd for $C_{14}H_{20}N_2S_2$: C, 59.96; H, 7.19; S, 22.86. Found: C, 60.16; H, 7.24; S, 23.03.

E. With Phenyl Isocyanate.—Phenyl isocyanate (2.16 g, 18.2 mmol) and N-(ethylthio)piperidine, **12**, (2.64 g, 18.2 mmol) were heated on a steam bath (*ca.* 90°) for 3 days. The dark crystalline mass was then triturated with CCl_4. Crystalline material was removed and recrystallized from CCl_4 to give 2.14 g (58%) of white crystals identified by nmr as N-pentamethylene-N′-phenylurea (**29**), mp 167–171°, lit.[44] mp 171–172°; the ir spectrum was identical with that of **29** prepared from PhNCO and piperidine.[44]

F. With Olefins.—N-Phenylmaleimide (86 mg, 0.5 mmol) and **N(ethylthio)piperidine**, (**12**, 73 mg, 0.5 mmol) were heated at 90° for 16 hr. The mixture at first became light red. It then turned very dark and the maleate chromophore (*ca.* 220 mμ) disappeared. Upon dissolution of the product in CCl_4, 60 mg (47%) of dark N-phenyl-2-(1-piperidino)succinimide, **30**, crystallized, mp 130–131°. Recrystallization (CCl_4) gave still dark **30**, mp 130–131°. Tlc and ir showed this **30** to be identical with colorless **30**, mp 133–135° (dec), obtained by mixing equimolar amounts of N-phenylmaleimide and piperidine: nmr ($CDCl_3$) δ 1.52 (s, $w_{1/2}$ = 9 Hz, 6, $(CH_2)_3$), 2.1–3.1 (m, 6, CH_2N + $CH_2C(=O)$), 3.87 (m, 1, $NCHC(=O)$), and 7.33 (m, 5, ArH); ir (Nujol) 1700 (s), 1595, 1500, 1165, 770, 750, and 695 cm^{-1}; mass spectrum *m/e* (rel intensity) 258 (3), 175 (5), 138 (8), 119 (10), 112 (6), 111 (72), 110 (16), 96 (45), 91 (11), 85 (6), 84 (100), 83 (8), 82 (12), 77 (8), 70 (7), 69 (12), 68 (8), 64 (8), 57 (7), 56 (13), 55 (40), 54 (20), and 51 (5).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 69.68; H, 7.03.

For the reaction of **N-ethylmaleimide**, 125 mg (1.00 mmol), and 173 mg (1.00 mmol) of **N-(*n*-butylthio)piperidine** (**13**) were dissolved in 0.5 ml of CCl_4. After 10 hr at 100°, the reaction, based on the intensity of the nmr peak at 6.70 δ, appeared *ca.* 50% complete. Partial purification by preparative tlc (Brinkmann precoated plates, silica gel F-254; Me_2CO) and analysis by glpc and mass spectrometry showed the presence of **13** and a second compound presumed to be N-ethyl-α-(1-piperidyl)-succinimide (**31**): mass spectrum *m/e* (rel intensity) 210 (8), 181 (5), 138 (10), 111 (30), 96 (50), 84 (100), and 55 (60).

For the reaction of **ethyl acrylate** with **N-(ethylthio)piperidine** (**12**), equimolar amounts were combined in an nmr tube, and the progress of the reaction was determined by comparing the integral ratio of the total of olefinic protons, with that of the CH_2O group. After 3 days at 77°, the reaction was *ca.* 60% complete. Glpc and mass spectrometric analysis of the reaction mixture, after standing 2 weeks more at *ca.* 25° showed the presence of a new compound [mass spectrum *m/e* (rel intensity) 185 (3), 101 (6), 100 (100), 98 (5), 84 (5), 56 (5), 55 (9), 42 (10), and 41 (9)] presumed to be ethyl β-(1-piperidyl)propionate (**32**). Comparison of the ir spectrum of either the crude product or of **32** purified by preparative glpc with that of **32** prepared by addition of piperidine to ethyl acrylate[28] showed both to be identical with it; its picrate had mp 124–126° (lit.[45b] mp 131.5°).

G. With Acetic Anhydride.—Acetic anhydride (0.45 g, 4.5 mmol) and **N-(ethylthio)piperidine** (**12**, 0.62 g, 4.3 mmol) were mixed and the progress of the reaction was followed by glpc. After 3 hr, the reaction appeared to be *ca.* 50% complete, and the products were analyzed by glpc and mass spectrometry. In addition to **12**, the other products seen evidently were ethyl disulfide (mass spectrum mol wt 122) and N-acetylpiperidine (mass spectrum mol wt 127). Acetic anhydride and **N-(*t*-butylthio)-piperidine** (**14**) were mixed and the extent of reaction determined by glpc. No reaction occurred at *ca.* 25° in up to 3.5 hr. Heating at 90° for 0.5 hr apparently gave *ca.* 50% reaction. The products determined by distillation at 50–120° (*ca.* 25 mm) and infrared analysis were *t*-butyl disulfide and N-acetylpiperidine.

Reactions of Sulfenamides with Nucleophiles.—N-(2-Acetamidoethylthio)phthalimide (**10**, 264 mg, 1 mmol) was added to 120 mg (1.01 mmol) of 2-acetamidoethanethiol in 10 ml of MeOH and 80 μl of Et_3N. Four days later the solution gave a negative nitroprusside test and was evaporated to dryness. Two washes with EtOH left 100 mg (68%) of phthalimide, mp and mmp 227–229°. The EtOH washes were evaporated and the residue was triturated with benzene to give 220 mg (93%) of **2**, mp 87–89° (lit.[37] mp 92–93°), identified by comparison of its ir spectrum with that of **2**.

N-(2-Acetamidoethylthio)-2-aminobenzothiazole (**5**, 0.22 g, 0.82 mmol) suspended in 25 ml of CH_2Cl_2 was allowed to react with *p*-thiocresol (0.100 g, 0.80 mmol). After the **5** had completely dissolved, the solution was washed twice with 20-ml portions of 10% HCl, dried, and evaporated to dryness to give 0.14 g (70%) of 2-(*p*-tolyldithio)-1-acetamidoethane (**33**); this **33** was pure by tlc and was identified by comparison of its ir spectrum with that of authentic material.[37]

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N-(2-Acetamidoethylthio)phthalimide (**10**, 0.78 g, 3.0 mmol) in 5 ml of CH_2Cl_2 was allowed to react with *p*-thiocresol (0.36 g, 2.9 mmol). After a brief exothermic reaction, phthalimide precipitated and was removed by filtration. The filtrate was evaporated to dryness, and the residue was crystallized from benzene to give 0.43 g (61%) of **33** slightly contaminated (ir) with phthalimide; the ir spectrum was similar to that of authentic **33**, and tlc using 1:1 heptane–acetone separated a major product identical with authentic **33**.

Attempted Equilibration of Two Sulfenamides.—A 1:1 mixture of **12** and **16** was heated at 90° for 16 hr. Glpc analysis (10-ft column of 10% SE-30 on Gas Chrom Q at 160°) showed the presence of only **12** and **16**.

Registry No.—**4**, 25116-48-7; **5**, 25116-49-8; **6**, 25116-50-1; **7**, 25116-51-2; **8**, 25116-52-3; **9**, 25116-53-4; **10**, 25158-14-9; **11**, 25116-54-5; **12**, 25116-55-6; **13**, 25116-56-7; **14**, 3060-70-6; **16**, 25116-77-2; **17**, 25116-78-3; **19**, 5038-11-9; **20**, 25116-80-7; **21**, 25110-35-4; **22**, 25110-36-5; **23**, 25110-37-6; **24**, 25110-38-7; **24** HCl, 25110-39-8; **25**, 25110-40-1; **30**, 25110-41-2.

Photoaddition of Diphenylacetylene to Tetrahydro-2-quinolones[1]

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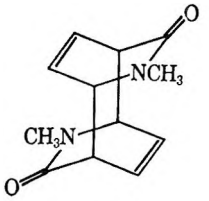
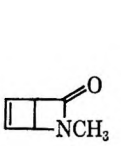
Diphenylacetylene has been observed to undergo photocycloaddition to a series of cycloalkano-2-pyridones **4** at 3500 Å to give the pentacyclic lactams **8**, the cyclobutene derivatives **16**, and the insoluble dimer **7**. Formation of **8** probably proceeds *via* the Diels–Alder adduct (4 + 2 addition) followed by photoreorganization. The pentacyclic lactams were highly labile to aqueous acid and base reverting back to starting materials, whereas the N-methyl derivatives were smoothly rearranged in methanolic acid to benzamides, **11**. Irradiation of **8** at 2537 Å resulted in rearrangement to the cyclobutene systems, **16**, a hitherto unknown photolytic reaction. This behavior was found to be general for a series of cycloalkano-2-pyridones containing various alkyl substitution and ring size.

Investigation of the photochemical behavior of simple 2-pyridones has been limited to the formation of dimers, **1**,[3–5] and valence isomers, **2**.[6] Recently,[7] the cycloaddition of olefins to the related carbostyril system has resulted in the cyclobutane derivative, **3**. Thermally induced cycloadditions to pyridones have also been observed in a few instances.[8–10] However, no photocycloadditions to pyridones have been described.[2] In view of the ready availability[11] of a series of cycloalkanopyridones, **4**, obtained by oxidative cyclization of cyano ketones, **5**, it was convenient to examine the photocycloaddition reaction with a suitable unsaturated substrate, *e.g.*, diphenylacetylene.



1



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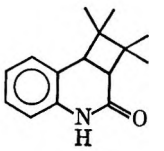
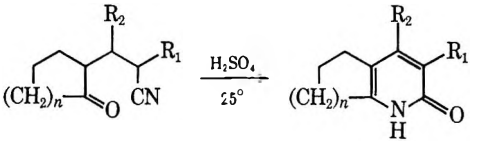


3

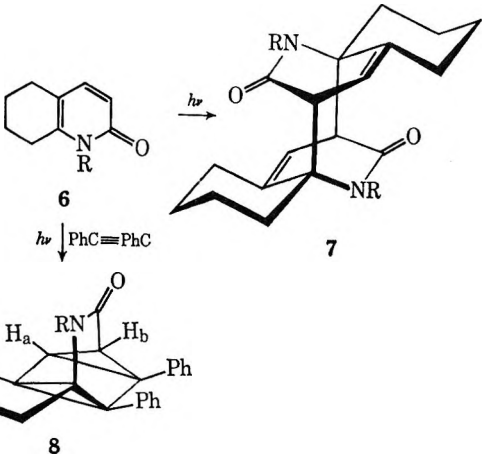


5 **4**

R_1 = H, Me
R_2 = H, Me
n = 1-3

Results and Discussion

Dimer Formation.—When a methanol–hexane solution of the 2-quinolone, **6** (R = H), and diphenylacetylene was irradiated (Pyrex) for 15 hr a crystalline material deposited along the walls of the vessel. The quantity of solid product was observed to increase with increasing exposure to the light source. The elemental analysis and mass spectrum under all practical ionizing conditions were identical with those of the starting material; yet the infrared spectrum displayed a single nonconjugated lactam band at 1660 cm^{-1} (Nujol) unlike the two strong bands (1653, 1625 cm^{-1}) present in **6** (R = H). Further, the melting point at various heat-



6 **7** **8**

(1) (a) This study supported by the National Institutes of Health (NIGMS-RG-06248-09) and the Greater New Orleans Cancer Association. (b) Address all inquiries to A. I. Meyers, Department of Chemistry, Wayne State University, Detroit, Mich. 48202.

(2) Taken from the Ph.D. Dissertation of P. Singh, June 1969. Preliminary accounts have already appeared (a) A. I. Meyers and P. Singh, *Chem. Commun.*, 576 (1968); (b) A. I. Meyers and P. Singh, *Tetrahedron Lett.*, 4073 (1968).

(3) W. A. Ayer, R. Hayatsu, P. de Mayo, S. T. Reid, and J. Stothers, *ibid.*, 648 (1961).

(4) L. A. Paquette and G. Slomp, *J. Amer. Chem. Soc.*, **85**, 765 (1963).

(5) E. C. Taylor and R. O. Kan, *ibid.*, **85**, 776 (1963).

(6) E. J. Corey and J. Streith, *ibid.*, **86**, 950 (1964).

(7) G. R. Evanega and D. L. Fabiny, *Tetrahedron Lett.*, 2241 (1968).

(8) B. S. Thayagarajan and K. Rajagopalan, *Tetrahedron*, **19**, 1483 (1963).

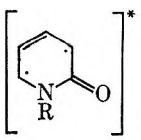
(9) L. Bauer, C. L. Bell, and G. E. Wright, *J. Heterocycl. Chem.*, **3**, 393 (1966).

(10) R. M. Acheson and P. A. Taskar, *J. Chem. Soc. C*, 1542 (1967).

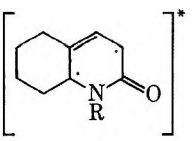
(11) A. I. Meyers and G. Garcia Munoz, *J. Org. Chem.*, **29**, 1435 (1964).

ing rates was identical with that of **6** attesting to its thermal instability. The total insolubility of the photoproduct in all common solvents precluded the use of nmr for structural information. It was therefore concluded that the solid product was a labile dimer of **6** and assigned the structure **7** (R = H) based upon the analogous photodimerization leading to **1**. An attempt at examining its nmr spectrum in trifluoroacetic acid, which did give a homogeneous solution, proved to be useless since the spectrum was that of the monomer, **6**. The irradiation of **6** (R = H) was repeated in the absence of diphenylacetylene and resulted in the same product thus eliminating any concern over the role played by the diphenylacetylene in the dimerization. Since the available data on the dimer left much to be desired with regard to a firm structure elucidation, efforts were made to alter its solubility properties so that further spectral data could be obtained.[4] Nevertheless, all attempts to convert **7** (R = H) into **7** (R = Me) resulted in reversal to the monomer. Surprisingly, **6** (R = Me), obtained smoothly using sodium hydride and methyl iodide on **6** (R = H), failed to produce any trace of dimer **7** (R = Me) upon irradiation. Additional experiments designed to characterize **7** fully (R = H; $LiAlH_4$ reduction, acidic or alkaline hydrolysis, catalytic reduction) likewise met with facile reversal to the monomer. A report[12] on the X-ray study of the dimer of N-methyl-2-pyridone (**1**) reveals that the C–C bond distance between the two pyridone rings is considerably greater (1.60 Å) than a normal C–C bond distance. In the present case, with the added bulk of the cyclohexane ring, it is conceivable that the amount of strain is greatly enhanced thus supporting its highly labile nature. The fact that the N-methyl derivative **6** (R = Me) failed to dimerize seems to be in further accord with the hypothesis that the added bulk of the N-methyl group prevents the joining of the two pyridone rings. Similarly, the 3-methyl derivative, **6b**, failed to yield any dimer, whereas the 4-methylpyridone, **6c**, did produce the dimer upon irradiation. This is also an expected result since the 3-methyl groups in the dimer would reside at the positions which link the two pyridone systems causing increased crowding, while the 4-methyls are attached to an sp^2 carbon and add little to the steric bulk between the joined rings.[13]

The photoinduced formation of the 3,6 "diradical" (**9**) in 2-pyridones has been suggested[4] as the excited species responsible for the dimerization leading to **1** and it is quite likely that a similar species (**10**) would be formed in the cycloalkanopyridone series, although the question regarding the multiplicity of **9** and **10** should be left open.



9

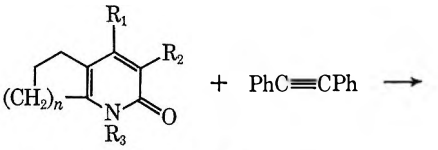


10

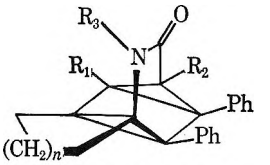
(12) M. Laing, *Proc. Chem. Soc.*, 343 (1964).

(13) Preliminary X-ray data show that the compound crystallizes in the centrosymmetric space group $P2_1/c$ with two dimer formula weights in the unit cell. Hence, unless it consists of four monomer units (contrary to the chemical evidence) it must be either a dimer which itself possesses a center of symmetry or else be disordered. However, since it scatters well out to $2\theta = 140°$ (using filtered Cu Kα radiation) it does not seem likely that it is disordered. The structure determination by direct methods is progressing satisfactorily and will be reported at a later date.

Photocycloaddition with Diphenylacetylene.—The filtrate obtained after removal of the dimer **7** (R = H), produced a residue which consisted of four products (tlc) in varying amounts. The major product (21%) was obtained *via* preparative layer chromatography and shown to be a 1:1 adduct of diphenylacetylene and the pyridone (elemental and mass analyses). All the spectroscopic data (ir, nmr, uv) were consistent with the pentacyclic lactam, **8** (R = H) (Experimental Section). Similar photocycloaddition occurred when the N-methylpyridone, **6a**, was irradiated in the presence of diphenylacetylene. The pentacyclic lactam, **8a**, was obtained in low yield (8%) and, as already stated, no dimer was found among the products. Examination of several related pyridones (**6b–6g**) under similar reaction conditions produced the pentacyclic lactams (**8b–8g**) in 13–49% yield and several minor products to be discussed later.



6, $n = 2$; $R_1 = R_2 = R_3 = H$



8, $n = 2$; $R_1 = R_2 = R_3 = H$

a, $n = 2$; $R_1 = R_2 = H$; $R_3 = Me$
b, $n = 2$; $R_1 = R_3 = H$; $R_2 = Me$
c, $n = 2$; $R_1 = Me$, $R_2 = R_3 = H$
d, $n = 2$; $R_1 = H$; $R_2 = R_3 = Me$
e, $n = 2$; $R_1 = R_3 = Me$; $R_2 = H$
f, $n = 1$; $R_1 = R_2 = R_3 = H$
g, $n = 1$; $R_1 = Me$; $R_2 = R_3 = H$

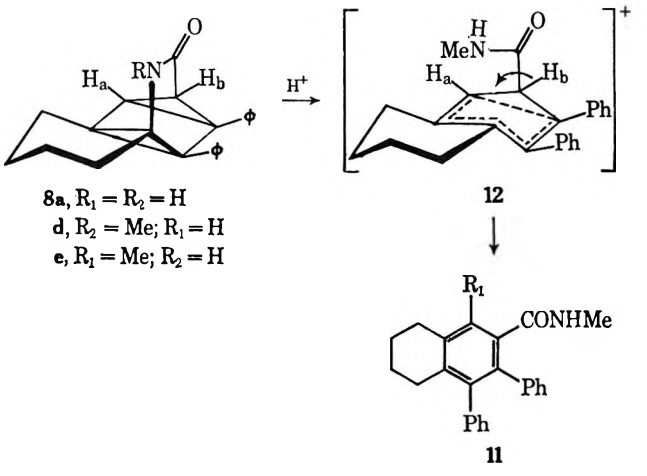
The only unique feature present in the nmr spectra of the pentacyclic lactams is the long range coupling between R_3 and R_2 when both are present as protons. Thus, the expected doublet of R_2 = H is split further into a doublet of doublets at 100 MHz (J = 1, 3 Hz) when R_3 = H. This long range coupling through the amide carbonyl group was found to be absent when the NH proton was exchanged by deuterium, irradiated for spin decoupling, or replaced by a methyl group.[14]

In order to accumulate some chemical evidence to support the structures of the photoadducts, a solution of **8** in methanolic potassium hydroxide was heated for several hours and produced considerable amounts of diphenylacetylene and the starting pyridone **6**. Reversal to starting materials was also found to occur in hot, acidic methanol. The fact that the presence of acid or base was responsible for the reversal of the pentacyclic lactams was clearly established when it was found that **8** was completely stable in boiling toluene even after prolonged heating. The driving force for the reversal is believed to be a function of the aromatic

(14) All the nmr spectra for the pentacyclic lactams and the deuterium exchanged analogs may be found in the doctoral dissertation of P. S., University Microfilms, Ann Arbor, Mich.

stability[11,15] of **6** and on this basis it was decided to examine the N-methyl derivative, **8a**.[16] The latter could also be readily obtained by alkylation of **8** by use of sodium hydride–methyl iodide. Alkaline treatment of **8a** resulted only in complete recovery of the pentacyclic lactam in sharp contrast to the lability of the normethyl system (**8**) under the same conditions.

On the other hand, treatment with methanolic hydrochloric acid produced a new product (tlc) along with small amount of diphenylacetylene undoubtedly due to reversal of **8a** to its components. After purification (tlc) the acid-generated product exhibited an NH band at 3440 cm^{-1} and the amide carbonyl at 1648 cm^{-1}. Elemental analysis and the mass spectrum revealed it to be an isomer of **8a**. A precise mass determination of 341.17756 (calcd 341.17796) indicated that the molecule possessed fourteen sites of unsaturation and/or rings. The uv spectrum exhibited the *o*-terphenyl chromophore (230 mμ) and the nmr spectrum (60 and 100 MHz) was in complete agreement with the assigned structure **11** (R = H). The facile rearrangement of **11** from **8a** may be formulated by protonation, either at nitrogen or oxygen, which produces a positively charged nitrogen atom followed by C–N bond rupture. The resulting delocalized cation **12** then loses a proton forming the aromatic system. Similar results were obtained when the dimethyl derivative, **8e**, was treated with methanolic acid solution, affording the 1-methyl derivative, **11** (R_1 = Me). The dimethyl lactam, **8d**, provided an interesting example in that the C-methyl group was in a position to block aromatization of the cation, **12**. When **8b** was refluxed in acidic medium, the product was again **11** (R_1 = Me) which can only have arisen *via* a methyl migration in **12**. Comparison



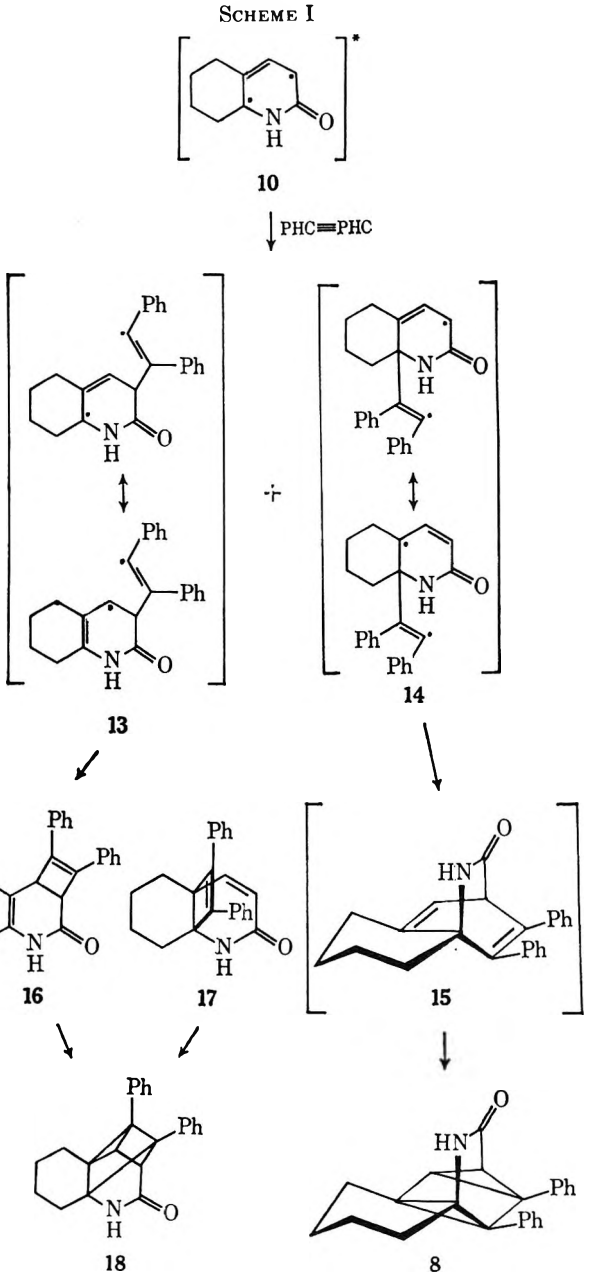
8a, $R_1 = R_2 = H$
d, R_2 = Me; $R_1 = H$
e, R_1 = Me; $R_2 = H$

12

11

of the benzamide derivatives obtained from **8e** and **8d** confirmed their identity. It is to be noted here that also present in the reaction were the starting pyridones, **6a, d, e**, owing to some reversal under acidic conditions. The formation of the benzamides, **11**, support the site of addition of diphenylacetylene to the pyridones **6** as being at positions 3 and 9. If, as previously stated, the excited intermediate, **10**, may be envisioned as being responsible for dimerization of the pyridones, then it is significant that the presence of diphenylacetylene results in an apparent interception of the dimerization process. However, if the pyridone dimer is formed, not by a combination of two excited species, but instead by the excited pyridone adding to ground-state pyridone in a stepwise fashion, intervention by the acetylene is not unexpected. The latter appears to be the case since increasing the concentration of diphenylacetylene did result in an increase in pentacyclic lactam yield. The process leading to **8** may be formulated (Scheme I) as an

SCHEME I



attack by the diradical on ground-state diphenylacetylene[17] producing either **13** and/or **14** which proceed to the homoconjugated diene **15** and/or **16**. The former,

(15) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 860 (1961). The ring current model, upon which these authors have based their conclusions, has been generally used to justify the use of chemical shifts as a qualitative criterion of aromatic character. However, quantitative conclusions in this regard have been challenged by various authors; see P. Beak, J. Bonhan, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, **90**, 1569 (1968), and references cited therein.

(16) The reduction in aromatic character was seen by examining the nmr spectrum of **6a** which showed the 3-H and 4-H doublets centered at 6.33 and 7.04 ppm, respectively. This is compared with the normethyl pyridone (**6**) which exhibited the 3-H and 4-H resonances at 6.35 and 7.17 ppm.

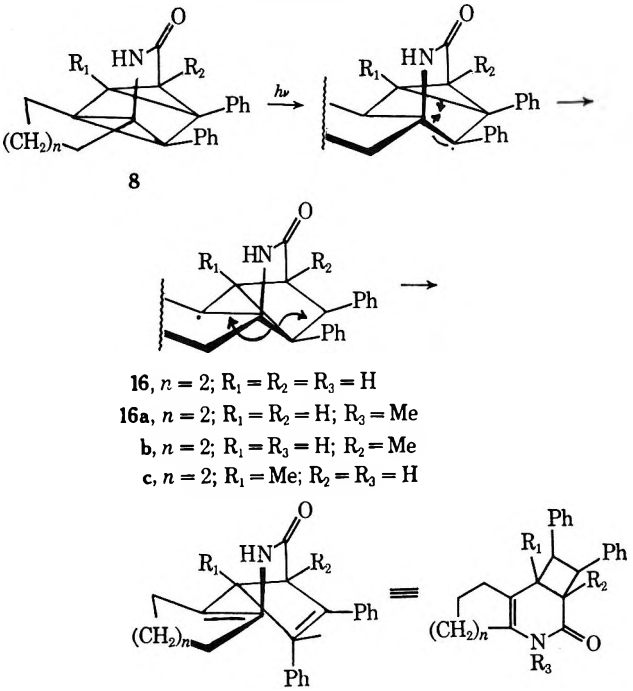
(17) The hypothesis that an activated pyridone attacks ground-state diphenylacetylene rather than vice versa was supported by the fact that the irradiation of a solution of diphenylacetylene at 3500 Å after 16 hr did not give rise to any new products.

under the influence of light, readily rearranges to the pentacyclic lactam **8**. The reorganization of **15** to **8** is now a well-known phenomenon having been observed in a variety of heterocyclic[18] and homocyclic[19] systems.

Scheme I also suggests that the initial adducts **13** and **14** should also provide the cyclobutene derivatives, **16** and **17**. Removal of the three additional bands from the preparative layer plate provided a small quantity of another product along with minute quantities of two additional components. The larger of these products exhibited elemental and mass spectral analyses consistent with **16**, **17**, or **18**. However, the infrared spectrum revealed absorption at 3390 and 1655 cm^{-1}, typical of the enamide moiety and the uv spectrum exhibited maxima at 226, 266, and 288 mμ. These spectral data are consistent with cyclobutene[20] and enamide[3,21] moieties present in **16**. The nmr spectrum was also in agreement with the *cis*-fused cyclobutenopyridone and details are presented in the Experimental Section. The two very minor products isolated from the preparative plate could not be fully characterized although both possessed molecular ions at 341 indicating that they were 1:1 adducts of the pyridone and diphenylacetylene. It is to be noted that, although we were not able to obtain meaningful quantities of the two additional products for complete characterization, both **16** and **17** might be expected *via* valence tautomerization to produce **18** in accord with a previous observation in the naphthalene series.[22] At this stage of the study, the comment concerning **17** and **18** must be regarded as speculative.

Photoisomerization of Pentacyclic Lactams 8.—The pentacyclic lactams **8** represent a highly strained system and it is well known that many analogous systems exhibit considerable photolability.[23] With this view in mind, we investigated the behavior of the pentacyclic lactams, **8**, by irradiation at 2537 Å, an energy source higher than that from which they were formed (3500 Å). When a benzene solution of **8** was irradiated, the starting material rapidly disappeared (tlc) and two new products formed in highly disproportionate amounts. The major product was isolated (tlc) and found to be identical with the cyclobutenopyridone, **16**, formed from diphenylacetylene and **6** (R = H). The conversion of **8** to **16** was 60%. Similar behavior was noted when the pentacyclic lactams **8a–8c** were irradiated in benzene solution. During the irradiation, it was observed that small amounts of diphenylacetylene were also produced. This suggested the possibility that reversal of **8** to its components may be occurring followed by recombination to give **16** directly. This pathway was precluded by the fact that no cyclobutenopyridone was found when the pyridone **6** and diphenylacetylene was irradiated (2537 Å) in methanol–ether (a solvent which also allowed conversion of **8** to **16**). When diphenylacetylene and **6** were irradiated (2537 Å) in benzene for 6 hr, a trace of the cyclobutenopyridone was observed (tlc) but no pentacyclic lactam **8** could be detected. It is thus evident that the formation of **16** from **8** is proceeding by a unimolecular process. The fact that the isomerization is fast in benzene (60% conversion in 4 hr) compared to methanol–ether (<10% in 12 hr) may be attributed to the efficient transfer of energy from benzene to the pentacyclic lactam **8**. Regarding the small amounts (1–2%) of cyclobutenopyridone formed from the pyridone **6** and diphenylacetylene during irradiation at 3500 Å, this was found to be a competing process originating from the postulated intermediates **13** and **14**. Confirmation of this was gathered when the pentacyclic lactam **8** showed no trace of the cyclobutenopyridone **16** upon prolonged exposure to light at 3500 Å under the usual conditions. On the other hand, the cyclobutenopyridone was essentially stable to prolonged irradiation both at 2537 and 3500 Å producing only trace decomposition products. Thus, although the 2 + 2 cycloaddition of diphenylacetylene to the pyridones proceeds in poor yields in contrast to similar cycloadditions,[22,24] the photoisomerization of **8** occurs rather efficiently. See Scheme II.

SCHEME II



The photoisomerization of **8** to **16** at 2537 Å does not appear to have any close analogy in literature. The photoisomerization[25,26] of phenylcyclopropanes (**19**) to propenes has only a remote resemblance to this isomerization since the former involves a hydrogen trans-

(18) H. Prinzbach, R. Fuchs, and R. Kitzing, *Angew. Chem., Int. Ed. Engl.* **7**, 67 (1968); G. R. Zeigler and G. S. Hammond, *J. Amer. Chem. Soc.*, **90**, 513 (1968).

(19) S. J. Cristol and R. L. Snell, *ibid.*, **76**, 5000 (1954); *ibid.*, **80**, 1950 (1958); W. G. Dauben and R. L. Cargill, *Tetrahedron*, **15**, 197 (1961); C. F. Wilcox, S. Winskin, and W. G. McMillan, *J. Amer. Chem. Soc.*, **82**, 5450 (1960); H. G. Richey and N. C. Buckley, *ibid.*, **85**, 3057 (1963); P. R. Story and S. R. Fahrenholtz, *ibid.*, **86**, 527 (1964); P. G. Gassman, D. H. Aue, and D. S. Patton, *ibid.*, **86**, 4211 (1964); H. Tanida, Y. Hata, Y. Matsui, and I. Tanada, *J. Org. Chem.*, **30**, 2259 (1965); K. E. Wilzbach and L. Kaplan, *J. Amer. Chem. Soc.*, **87**, 4004 (1965); *ibid.*, **90**, 5868 (1968).

(20) M. A. Battiste and M. E. Burns, *Tetrahedron Lett.*, 523 (1966); R. M. Dodson and A. G. Zielske, *Chem. Commun.*, 353 (1965); M. S. Newman and G. Kangers, *J. Org. Chem.*, **30**, 3295 (1965).

(21) W. A. Ayer and G. G. Iverach, *Tetrahedron Lett.*, 19 (1960); A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.*, 959 (1956).

(22) P. J. Collins and W. H. F. Sasse, *Tetrahedron Lett.*, 1689 (1968).

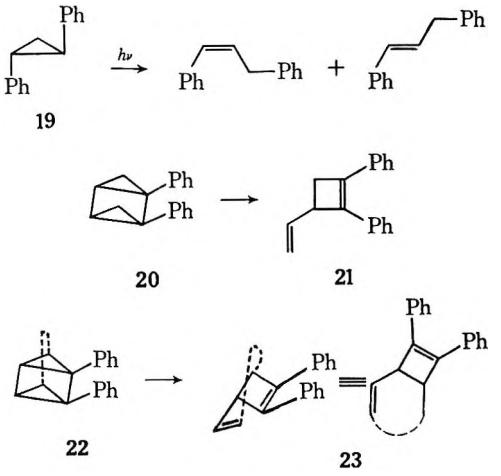
(23) "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967.

(24) S. P. Pappas, B. C. Pappas, and N. A. Portnoy, *J. Org. Chem.*, **34**, 520 (1969). G. R. Evanega and D. L. Fabiny, *Tetrahedron Lett.*, 2241 (1968).

(25) G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Close, *J. Amer. Chem. Soc.*, **87**, 1410 (1965).

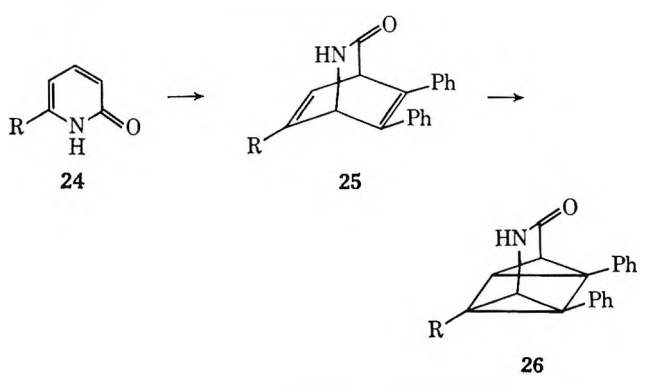
(26) H. Kristinsson and G. W. Griffin, *Tetrahedron Lett.*, 3259 (1966).

fer as well as isomerization. More suitable analogies of the type **20** to **21** and **22** to **23** do not appear to be



known. The isomerization of **8** to **16** may be envisioned to proceed by a concerted three-bond fission and recombination or may occur in a stepwise manner involving the intermediate shown in Scheme II. This photoisomerization has been found to be a general process and a number of pentacyclic lactams have been converted in a similar manner to the corresponding cyclobutenopyridones (Experimental Section).

Several attempts to induce photocycloaddition of diphenylacetylene to monocyclic pyridones **24** (R = H) and **24** (R = Me) resulted in trace amounts of 1:1 adducts which revealed through their mass, spectra to be possibly **25** and/or **26**. However, the quantities



were too minute for meaningful characterization and further studies in this respect as well as those relating to the multiplicity of the reactive species are planned. Meanwhile, the synthetic utility of this photocycloaddition process for preparing unusual heterocyclic caged systems need not await its in-depth understanding.

Experimental Section

All irradiations involving addition of diphenylacetylene to cycloalkano[*e*]-2-pyridones were carried out under nitrogen in Pyrex containers. Two types of light sources were used: (a) an assembly of sixteen external low pressure 8 Wmercury resonance lamps (Sylvania F8Ts/BLB) in an air cooled Rayonet Srinivasan-Griffin photochemical reactor manufactured by the Southern New England Ultraviolet Company, Middletown, Connecticut (the wavelength of this light source is a tits maximum[27] intensity at 3500 Å); (b) an internal water-cooled Hanovia high pressure quartz mercury vapor lamp, Type S, No. 654A36, 200 W with an arc length of 4.5 in., manufactured by Englehard Hanovia, Inc., Newark, N. J.

Isomerization of the pentacyclic lactams (**8**) leading to the cyclobutene derivatives (**16**) were carried out under nitrogen in quartz vessels with an assembly of sixteen external low pressure 8W mercury resonance lamps (Sylvania G8 T5) in the air-cooled Rayonet reactor. About 90% of the light intensity of this source is at 2537 Å. In all cases the solutions were degassed either by the freeze–thaw technique or by passing in pure nitrogen for at least 30 min.

Thin layer and preparative layer chromatography were done on silica gel G (PF_{254}), Brinkmann Company, Long Island, N. Y. All melting points were determined on a Fisher-Johns melting point apparatus, and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Medizinisch-Chemisches Institut und Pregl Laboratorium, Graz, Austria. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6E or the Varian instruments. Infrared and ultraviolet spectra were taken on Perkin-Elmer 257 and 450 instruments respectively.

Cycloalkano[*e*]-2-pyridones (4).—The cycloalkanopyridones were all prepared by the method of Meyers and Garcia[11] except for 6 g which was obtained using the method of Sakurai and Midorikawa.[28]

1-Methyl-5,6,7,8-tetrahydro-2-quinolone (6a).—A solution of 5,6,7,8-tetrahydro-2-quinolone (3.73 g, 25 mmol) and sodium hydride (1.04 g, 25 mmol, 58% oil dispersion) in 450 ml dry xylene was heated to reflux under nitrogen for 20 hr. The solution was allowed to cool under a stream of nitrogen and 14.2 g (100 mmol, 4 equiv) of methyl iodide was added dropwise with stirring. The reaction mixture was refluxed for another 6 hr and the hot xylene solution filtered to remove precipitated sodium iodide. The solvent was then removed under reduced pressure to give a yellow oil which was crystallized from ethyl acetate–hexane to give 2.44 g (59%) of 1-methyl-5,6,7,8-tetrahydro-2-quinolone (**6a**): mp 215–217°; ir 1660, 1582, 1550 cm^{-1}; nmr ($CDCl_3$) 1.5–2.1 (m, 4, methylene H), 2.3–2.8 (m, 4, allylic H), 3.43 (w, 3, N–CH_3), 6.33 (d, J = 9 Hz, 1, 3 H), 7.02 δ (J = 9 Hz, 1, 4 H).

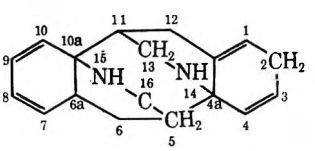
Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.56; H, 7.97; N, 8.64.

1,3,4,7,8,9,10,11-Octahydro-2H,5H-4a,11:10a,5-bis(iminomethano)dibenzo[*a*,*e*]cyclooctene-13,16-dione (7).[29]—A solution of 5,6,7,8-tetrahydro-2-quinolone (6) (500 mg, 3.4 mmol) in 20

(28) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jap.*, **41**, 165 (1968).

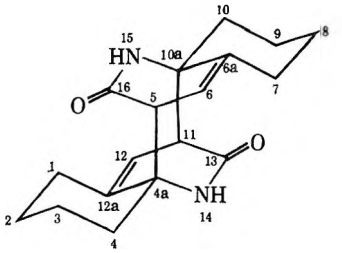
(29) The nomenclature utilized for the compounds described herein has been kindly suggested by Dr. Kurt L. Loening of Chemical Abstract Service, Columbus, Ohio, for which we are grateful.

The fundamental ring system in the proposed structure for the dimer of 5,6,7,8-tetrahydro-2-quinolone (**32**) is oriented, numbered, and, named as follows.



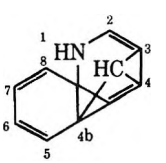
2H,5H-4a,11:10a,5-bis(iminomethano)dibenzo[*a*,*e*]cyclooctene

Thus, the nomenclature for the dimer is as follows.



1,3,4,7,8,9,10,11-octahydro-2H,5H-4a,11:10a,5-bis(iminomethano)dibenzo[*a*,*e*]cyclooctene-13,16-dione

The fundamental ring system in pentacyclic lactams **8a–g** is oriented, numbered, and named as follows.



1H-3,4,4b-methenobenzo[1,3]-cyclopropa[1,2-*b*]pyridine

(27) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966).

ml of methanol was irradiated under N_2 for 80 hr at 3500 Å to give 300 mg (60%) of the solid dimer. Higher yields of dimer could be obtained by irradiating in more concentrated solution for longer periods of time. The dimer was washed with methanol and dried at room temperature: mp 205–206°; mixture melting point with authentic 5,6,7,8-tetrahydro-2-quinolone **6** was undepressed; ir (Nujol) 1653, 1625 cm^{-1}; nmr (TFA) identical to nmr (TFA) of 5,6,7,8-tetrahydro-2-quinolone (**6**, R = H).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.49; H, 7.38; N, 9.39. Found: C, 72.21; H, 7.38; N, 9.15.

Calcd *m/e* for $C_{18}H_{22}N_2O_2$: 298. Found: 149.

Attempted Methylation of the Dimer 7.—The dimer (200 mg, 0.34 mmol) was stirred with an equivalent of sodium hydride in 100 ml anhydrous tetrahydrofuran under nitrogen in an oil bath maintained at 50°. After 0.5 hr a small portion of the solution was withdrawn and diluted with 95% ethanol for ultraviolet examination. The spectrum revealed (318 mμ, ε 6500) that reversal to the pyridone **6** had taken place.

Irradiation of 1-Methyl-5,6,7,8-tetrahydro-2-quinolone (6a) at 3500 Å.—A solution of 1-methyl-5,6,7,8-tetrahydro-2-quinolone (1.0 g, 6.1 mmol) in 10 ml methanol was irradiated under nitrogen at 3500 Å and the solution monitored periodically. No dimer separated during the irradiation which lasted one week. The methanol was removed *in vacuo* and examination of the residue revealed unchanged starting material.

Hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8). A. From Irradiation at 3500 Å.—A solution of 1.0 g (6.7 mmol) 5,6,7,8-tetrahydro-2-quinolone **6** and 2.5 g (14.0 mmol) diphenylacetylene in 8 ml anhydrous methanol and 5 ml *n*-hexane in a 25 × 200 mm Pyrex tube was stoppered with a rubber serum cap, securely held with copper wire. The air in the tube was then replaced by pure nitrogen using the freeze-thaw technique. The vessel was suspended from a clamp by a copper wire into an air cooled photochemical reactor (Rayonet) equipped with sixteen low pressure 8W lamps emitting light at 3500 Å. After overnight irradiation crystals of the dimer of the pyridone (**7**) began to deposit along the sides of the tube. The irradiation was continued for one week (188 hr). The separated solid was removed by filtration, the residue was washed first with anhydrous methanol and then with anhydrous ether, and the washings were combined with the filtrate. The amount of the separated solid dimer was 610 mg (61%). The combined filtrate and washings were concentrated under reduced pressure and the residue was dissolved in minimum amount of methylene chloride. The mixture was separated by preparative layer chromatography on five 20 × 40 cm plates coated to 1.5 mm thickness using ether eluent. The bands corresponding to the product with R_f (ether) = 0.27 were cut from each plate, combined and put in a 500-ml erlenmeyer flask containing 300 ml anhydrous ether. The flask was then stoppered with a cork and the silica stirred vigorosuly by means of a magnetic stirrer for 0.5 hr. It was then filtered through a sintered glass funnel and the silica thoroughly washed with anhydrous ether. The washings were combined and ether removed under reduced pressure to give 270 mg (12.5%, based on pyridone **6**) of the pentacyclic lactam, **8**. The product was homogeneous on a thin layer chromatogram. Crystallization from benzene–petroleum ether gave colorless needles: mp 203–205°; ir ($CHCl_3$) 1690 (–CONH–), 3410 cm^{-1} (–NH–); nmr ($CDCl_3$) 1.5–2.4 (m, 8, methylene H); 2.55 (d, J = 3 Hz, 1, Ha); 3.60 (doublet of doublets, J = 1, 3 Hz, 1, H_b); 6.9–7.5 (m, 10, aromatic H); 7.61 δ (broad singlet, 1, NH). Upon treatment with deuterium oxide, the signal at 7.61 ppm due to NH disappeared and the doublet of doublets at 3.60 ppm collapsed to a true doublet (J = 3 Hz). A 100-MHz spectrum ($CDCl_3$) showed the doublet of doublets sharply resolved. Irradiation of the NH signal at 7.61 ppm again resulted in collapse of doublet of doublets at 3.60 ppm to a true doublet (J = 3 Hz).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.48; N, 4.28. Found: C, 84.62; H, 6.58; N, 4.37.

Calcd *m/e* for $C_{23}H_{21}NO$: 327. Found: 327.

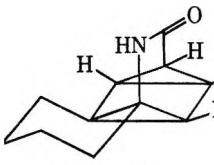
Fragments peaks at *m/e* 149 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

In a subsequent experiment low boiling petroleum ether was used as the irradiation solvent in place of *n*-hexane without significant change. Another run using 3.5 g (19.6 mmol) diphenylacetylene and 500 ml methanol (no *n*-hexane or petroleum ether) gave 450 mg (20.5%) of **8**. Thus, the yield of the cycloadduct, **8**, increases if a larger excess of diphenylacetylene is used and irradiations are performed for longer periods.

B. Using a Hanovia 200-W High Pressure Lamp.—A solution of 1.0 g (6.7 mmol) of pyridone (**6**) and 5.0 g (28.1 mmol) diphenylacetylene in 100 ml of hexane–methanol (6:4) in a Pyrex vessel was irradiated under nitrogen using an internal water cooled, high pressure 200-W Hanovia lamp for 36 hr. Work-up of the mixture produced 500 mg of the dimer and 350 mg (16%) of lactam, **8**. The product was identical in every respect with that obtained at 3500 Å.

Reversal of Hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8) to Its Components. A. In Base.—A solution of 50 mg (0.15 mmol) of **8** in 2 ml methanol and 2 ml 20% aqueous potassium hydroxide was heated to

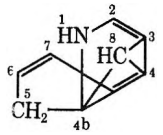
Thus, the nomenclature for the pentacyclic lactams is as follows, with the methyl substituents appropriately included as needed.



hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one

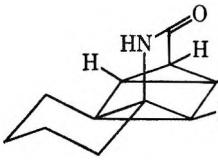
8

The fundamental ring system in the pentacyclic lactams **6f** and **6g** is oriented, numbered, and named as follows.



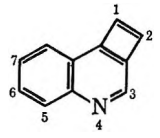
5H-3,4,4b-metheno-1H-cyclopenta-[1,3]cyclopropa[1,2-*b*]pyridine

Thus, the nomenclature of the above-mentioned pentacyclic lactams is given below.



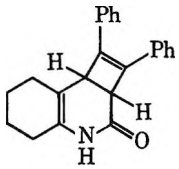
tetrahydro-4,4a-diphenyl-5H-3,4,4b-metheno-1H-cyclopenta[1,3]-cyclopropa[1,2-*b*]pyridin-2(3H)-one

The fundamental ring system in the cyclobutene derivatives **16a–e** is oriented, numbered, and named as follows.



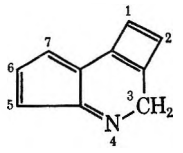
cyclobuta[*c*]quinoline

Thus, the nomenclature of the above-mentioned cyclobutene derivatives is as follows.



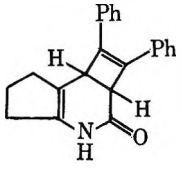
4,5,6,7,8,8b-hexahydro-1,2-diphenyl-cyclobuta[c]quinolin-3(2aH)-one

The fundamental ring system in the cyclobutene derivatives **16f,g** is oriented, numbered, and named as follows.



3H-cyclobuta[*d*]cyclopenta[*b*]pyridine

Thus, the nomenclature of the cyclobutene derivatives is as follows.



2a,4,5,6,7,7b-hexahydro-1,2-diphenyl-3H-cyclobuta[*a*]cyclopenta[*d*]cyclopenta[*b*]pyridin-3-one

reflux under nitrogen for 8 hr. Examination of the reaction contents by tlc indicated that a considerable amount of diphenylacetylene had formed.

B. **In Acid.**—A solution of 50 mg (0.15 mmol) of compound 8 in 2 ml methanol and 2 ml 6 *N* hydrochloric acid was refluxed under nitrogen for 4 hr and an aliquot removed for tlc examination. Visualization of the plates indicated an abundant quantity of diphenylacetylene.

Thermal Stability of Hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8).—A solution of 50 mg (0.15 mmol) of **8** in 15 ml dry benzene was heated to reflux under nitrogen; aliquots were removed at the end of 6, 24, 48, 72, and 96 hr. Thin layer examination exhibited one spot due to **8** and there was no evidence of any new products. Heating was discontinued and benzene removed, first on rotavapor and then on a vacuum pump. To the residue, 15 ml toluene was added and solution refluxed for 20 hr under nitrogen. A tlc check revealed that no new products had formed and only one homogeneous spot due to **8** was present.

Hexahydro-1-methyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8a). A. From 1-methyl-5,6,7,8-tetrahydro-2-quinolone and Diphenylacetylene.—A solution of 1.0 g (6.1 mmol) of 1-methyl-5,6,7,8-tetrahydro-2-quinolone **6a** and 2.5 g (14.0 mmol) of diphenylacetylene in 8 ml ethanol and 6 ml of *n*-hexane was irradiated in a Pyrex tube under nitrogen at 3500Å for one week (188 hr). During this period no solid dimer appeared. The solution was evaporated to dryness under reduced pressure and the residue dissolved in methylene chloride. The mixture was separated *via* preparative layer chromatography to give 170 mg (8.2%) of lactam **8a**, R_f (ether) = 0.43. The product was crystallized from benzene–petroleum ether to give colorless needles: mp 166–169°; ir ($CHCl_3$) 1675 cm^{-1} (–$CONCH_3$–), the band at 3400 cm^{-1} (NH) was absent; nmr ($CDCl_3$) 1.1–2.5 (m, 8, methylene H), 2.61 (d, J = 3 Hz, 1, H_a), 3.03 (s, 3, N–CH_3), 3.61 (d, J = 3 Hz, 1, H_b), 6.85–7.1 δ (m, 10, aromatic H).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.78; H, 7.02; N, 3.78.

Calcd *m/e* for $C_{24}H_{23}NO$: 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

B. **From Hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8) (Reaction with CH_3I).**—**8** (109 mg, 0.33 mmol) in 15 ml of dry benzene was treated with 18 mg of sodium hydride, previously washed with anhydrous benzene, and the solution was allowed to reflux for 10 hr. The reaction mixture, after cooling under a stream of N_2, was treated with 188 mg (2.54 mmol, 8.0 equiv) of methyl iodide and the solution refluxed for another 4 hr. The solution was filtered through a sintered-glass funnel with the aid of *filter gel* and the residue was washed with benzene. The filtrate and the washings were combined and concentrated under reduced pressure. The residue was dissolved in methylene chloride and purified *via* preparative layer chromatogaphy on one 20 × 20 cm plate coated to 1.5 mm thickness to give 102 mg (90%) of **8a**. Crystallization from benzene–petroleum ether furnished colorless needles identical in all respects with the product obtained by irradiation of 1-methyl-5,6,7,8-tetrahydro-2-quinolone and diphenylacetylene at 3500 Å. A small amount of diphenylacetylene was also formed during the alkylation reaction, confirmed by comparison with an authentic sample (tlc).

Hexahydro-3-methyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8b).—Pure, dry nitrogen was bubbled through a solution of 1.5 g (9.2 mmol) of 3-methyl-5,6,7,8-tetrahydro-2-quinolone (**6b**) and 7.5 g (42 mmol) diphenylacetylene in 80 ml methanol and 80 ml anhydrous ether for 40 min. The solution was then irradiated (Hanovia) for 48 hr. There was no separation of a solid dimer. The reaction was worked up by preparative layer chromatography (ether eluent) to give 647 mg (20.6%) of desired product **8b**. Crystallization from benzene petroleum ether afforded colorless needles: R_f (ether) = 0.46; mp 228–230°; ir ($CHCl_3$) 1708 (–CONH–), 3408 cm^{-1} (–NH–); nmr ($CDCl_3$) 1.0–2.3 (m, methylene H), 1.33 (s, CH_3) (total area = 11 protons), 2.39 (s, 1, H_a), 6.85–7.5 (m, 10, aromatic H), 7.7 δ (broad singlet, 1, NH).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.70; H, 7.00; N, 4.04.

Calcd *m/e* for $C_{24}H_{23}NO$: 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

Hexahydro-9-methyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8c).—Irradiation of a solution of 1.5 g (9.2 mmol) of 4-methyl-5,6,7,8-tetrahydro-2-quinolone (**6c**) and 7.5 g (42.0 mmol) of diphenylacetylene in 160 ml methanol–ether (1:1) (Hanovia) yielded 425 mg (28.3%) of the dimer. After preparative layer chromatography, 694 mg (22.1%) of the lactam, **8c**, was isolated. The product was crystallized from benzene–petroleum ether to obtain colorless needles: R_f (ether) = 0.40; ir ($CHCl_3$) 1690 (CONH), 3416 cm^{-1} (NH); nmr ($CDCl_3$) 1.1–2.4 (m, methylene H), 1.34 (s, CH_3) (total area = 11 protons), 3.51 (diffuse singlet, 1, H_b); 6.9–7.5 (m, 10, aromatic H), 8.61 δ (broad singlet, 1, NH) (mp 189–190°).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.66; H, 6.94; N, 4.00.

Calcd *m/e* for $C_{24}H_{23}NO$: 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

Tetrahydro-4,4a-diphenyl-5H-3,4,4b-metheno-1H-cyclopenta[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8f).—A solution of 1.35 g (10.0 mmol) of cyclopentano [*e*]-2-pyridone (**6f**) and 7.5 g (42.0 mmol) of diphenylacetylene in 80 ml methanol and 80 ml anhydrous ether was irradiated for 48 hr (Hanovia) to give 865 mg (63.6%) of the dimer and, after preparative layer chromatographic separation, 402 mg (12.8%) of the pentacyclic lactam, **8f** [R_f (ether) = 0.30]. The product was crystallized from benzene–petroleum ether to give colorless needles: mp 158–159°; ir ($CHCl_3$) 1693 (NH–C=O), 3410 cm^{-1} (NH); nmr ($CDCl_3$) 1.5–2.5 (m, 6, methylene H), 2.99 (d, J = 3 Hz, 1, H_a), 3.89 (diffuse doublet, J = 3 Hz, 1, H_b), 6.65–7.5 (m, 10, aromatic H), 8.0 δ (broad singlet, 1, NH).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.32; H, 6.11; N, 4.47. Found: C, 84.41; H, 6.24; N, 4.33.

Calcd *m/e* for $C_{22}H_{19}NO$: 313. Found: 313.

Fragment peaks at *m/e* 135 (pyridone) and *m/e* 178 (diphenylacetylene) were also present.

Tetrahydro-8-methyl-4,4a-diphenyl-5H-3,4,4b-metheno-1H-cyclopenta[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8g).—A solution of 1.371 g (9.2 mmol) of 4-methyl-cyclopentano[*e*]-2-pyridone (6 g) and 7.5 g (42.0 mmol) of diphenylacetylene in 160 ml methanol–ether (1:1) was irradiated under nitrogen (Hanovia) for 48 hr to obtain 347 mg (25.3%) of dimer and 1.480 g (49.0%) of the lactam, **8g** (R_f ether = 0.29). Crystallization from benzene–petroleum ether furnished colorless needles: mp 185–186°; ir ($CHCl_3$) 1690 (NHC=O), 3413 cm^{-1} (NH); nmr ($CDCl_3$) 1.5–2.5 (m, methylene H), 1.6 (s, CH_3) (total area = 9 protons), 3.75 (diffuse singlet, 1, H_b), 6.8–7.5 (m, 10, aromatic H), 7.75 δ (broad singlet, 1, NH). Upon treatment with deuterium oxide the signal at 7.75 ppm vanished and the diffuse singlet at 3.75 ppm due to H_b collapsed to a sharp singlet.

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.44; H, 6.55; N, 4.25.

Calcd *m/e* 327. Found: 327.

Hexahydro-1,3-dimethyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]-cyclopropa[1,2-*b*]pyridin-2(3H)-one (8d).—A solution of 512.0 mg (1.5 mmol) of pentacyclic lactam (**8b**) and 190 mg (4.5 mmol) of 58% oil dispersion of sodium hydride in 50 ml benzene was refluxed under nitrogen for 8 hr. Methyl iodide was then added and the solution refluxed again for 6 hr. The isolation procedure followed was similar to that used for the preparation of **8a** from **8**. Purification by preparative layer chromatography gave 455.0 mg (86%) of the desired product, **8d**. Crystallization from benzene–petroleum ether afforded colorless needles: mp 228–230°; ir ($CHCl_3$) 1670 cm^{-1} ($CONCH_3$); nmr ($CDCl_3$) 1.0–2.65 (m, methylene H), 1.28 (s, C–CH_3), 2.44 (s, H_a), 3.07 (s, 3, N–CH_3), 6.7–7.5 δ (m, 10, aromatic H).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 4.50. Found: C, 84.55; H, 7.19; N, 4.38.

Calcd *m/e* 355. Found: 355.

Hexahydro-1,9-dimethyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (8e).—The procedure followed was similar to that described in the preceding experiment. The product was isolated using preparative layer chromatography producing 460 mg (87%) of desired lactam, **8e**. Crystallization from benzene–petroleum ether gave colorless needles: R_f (ether) = 0.51; mp 158–159°; ir ($CHCl_3$) 1669 cm^{-1} ($CONCH_3$); nmr ($CDCl_3$) 1.1–2.4 (m, methylene H), 1.37 (s, C–CH_3), 2.97 (s, 3, N–CH_3), 3.48 (s, 1, H_b), 6.8–7.5 δ (m, 10, aromatic H).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 4.50. Found: C, 84.63; H, 7.12; N, 4.49.

Calcd *m/e* 355. Found: 355.

5,6,7,8-Tetrahydro-N-methyl-3,4-diphenyl-2-naphthamide (11, R = H).—A solution of 100 mg (0.29 mmol) of the pentacyclic lactam **8a** in 4 ml methanol and 4 ml 6 *N* hydrochloric acid was refluxed under nitrogen for 16 hr. A thin layer check indicated complete disappearance of starting material and appearance of a new, faster moving product [R_f (ether) = 0.61]. Refluxing was discontinued and the solution taken to dryness under reduced pressure by repeatedly adding benzene and evaporating. Purification *via* preparative layer chromatography on a 20 × 20 cm plate coated to 1.5 mm thickness gave 58 mg (58%) of **11**. The analytical sample was obtained by crystallization from benzene–petroleum ether as colorless needles: mp 199–202°; ir ($CHCl_3$) 1648 (–CONH–), 3440 cm^{-1} (–NH–); nmr ($CDCl_3$) 1.5–1.9 (m, 4, methylene H), 2.3–2.8 (m, 4, benzylic H), 2.5 (d, J = 5 Hz, 3, N–CH_3), 5.12 (broad singlet, 1, NH), 7.10–7.6 δ (m, 11, aromatic H). Upon treatment with deuterium oxide the signal at 5.12 vanished and the doublet at 2.5 collapsed to a singlet. Furthermore, irradiation of the NH signal at 5.12 ppm lead to the collapse of the doublet at 2.5 ppm to a singlet: uv (cyclohexane) λ_{max} 230 mμ.

Calcd *m/e* for $C_{24}H_{23}NO$: 341. Found: (70 eV) 341.

Calcd *precise m/e* for $C_{24}H_{23}NO$: 341.17796. Found: 341.17756.

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.22; H, 6.40.

5,6,7,8-Tetrahydro-N,1-dimethyl-3,4-diphenyl-2-naphthamide (11, R = Me). A. From 8e.—The procedure followed was similar to that used for the preparation of **11** (R = H). A solution of 97 mg (0.27 mmol) of the pentacyclic lactam, **8e**, in 3 ml methanol and 3 ml 6 *N* hydrochloric acid was refluxed under nitrogen for 12 hr. Work-up of the reaction mixture *via* preparative layer chromatography afforded 45 mg (47%) of the desired product, **11** (R = Me). Crystallization from benzene–petroleum ether gave colorless needles: R_f (ether) = 0.82; mp 233–234°; ir ($CHCl_3$) 1653 (CONH), 3440 cm^{-1} (NH); nmr ($CDCl_3$) 1.2–1.9 (m, methylene H), 1.98 (s, C–CH_3), 2.2–2.8 (m, benzylic H), 2.51 (d, J = 5 Hz, N–CH_3), 5.25 (broad singlet, 1, NH), 7.0–7.7 δ (m, 10, aromatic H).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09. Found: C, 84.31; H, 7.26.

Calcd *m/e* 355. Found: 355.

In addition to **11**, 35 mg (36%) of an unidentified product (R_f ether = 0.67) and a small amount of diphenylacetylene was also detected by tlc.

B. From 8d.—The procedure followed was similar to the procedure employed for the preparation of **11** (R = H). A solution of 97 mg (0.27 mmol) of pentacyclic lactam, **8d**, in 6 ml methanol and 3 ml 6 *N* hydrochloric acid was refluxed in an oil bath under nitrogen and the reaction monitored by tlc. It was found that even after heating for 82 hr, some **8d** was still present. The reaction mixture was worked up as usual to give 27 mg (28%) of **11** (R = Me). Crystallization from benzene–petroleum ether gave colorless needles, mp 233–234°. A mixture mp with the product obtained from **8e** was undepressed, and the two infrared spectra were superimposable. An abundant amount of diphenylacetylene was also formed in the reaction indicating reversal of the product to pyridone.

4,5,6,7,8,8b-Hexahydro-1,2-diphenylcyclobuta[*c*]quinolin-3(2aH)-one (16). A. From Irradiation of 8 at 2537 Å.—A solution of 290 mg (0.89 mmol) hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (**8**) in 60 ml benzene was irradiated in a quartz tube under nitrogen at 2537Å in an air cooled Rayonet reactor. Irradiation was stopped after 3.75 hr and the product worked up by preparative layer chromatography to give 135 mg (47%; 60% based on unrecovered pentacyclic lactam **8**) of the cyclobutene derivative, **16**. Crystallization from benzene–petroleum ether furnished colorless needles (R_f ether = 0.68): mp 167–169°; ir ($CHCl_3$) 1655 (C=C–NH·CO), 3990 cm^{-1} (NH); nmr ($CDCl_3$) 1.2–2.4 (m, 8, methylene H), 3.74 (diffuse doublet, J = 5 Hz, 1, H_a), 4.02 (d, J = 5 Hz, 1, H_b), 7.1–8.0 δ (m, 11, aromatic H and NH). Upon treatment with deuterium oxide the NH proton exchanged and signals at 7.1–8.0 ppm integrated to 10 protons only: uv max (EtOH) 226 (log ε 4.36), 266 (4.14), 288 mμ (sh) (4.08).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.48; N, 4.28. Found: C, 84.50; H, 6.31; N, 4.25.

Calcd *m/e* 327. Found: 327.

Fragment peaks at *m, e* 149 (pyridone) and *m, e* 178 (diphenylacetylene) were also seen. The minor product in this reaction was obtained in trace amounts and was not characterized further.

B. From Pyridone 6 and Diphenylacetylene.—Irradiation of a mixture of 1.0 g (6.7 mmol) 5,6,7,8-tetrahydro-2-quinolone and 2.5 g (14.0 mmol) diphenylacetylene as described previously, afforded (tlc) 35 mg (1.5%) of cyclobutene derivative (**16**). The product was crystallized from benzene–petroleum ether and was identical with that obtained by irradiation of hexahydro-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa[1,2-*b*]pyridin-2(3H)-one (**8**) at 2537 Å.

4,5,6,7,8,8b-Hexahydro-4-methyl-1,2-diphenylcyclobuta[*c*]-quinolin-3(2aH)-one (16a). A. From Irradiation at 2537 Å.—Irradiation of a solution of 300 mg (0.88 mmol) of hexahydro-1-methyl-4,4a-diphenyl-1H-3,4,4b-methenobenzo[1,3]cyclopropa-[1,2-*b*]pyridin-2(3H)-one (**8a**) in 60 ml benzene in a quartz tube under nitrogen at 2537 Å for 10 hr followed by work-up *via* preparative layer chromatography afforded 110 mg (37%) of the cyclobutene derivative **16a** (R_f ether = 0.78). Crystallization from benzene–petroleum ether furnished colorless needles: mp 120–122°; ir ($CHCl_3$) 1635 cm^{-1} (–N–C=O); nmr ($CDCl_3$) 1.2–2.4 (m, 8, methylene H), 3.12 (s, 3, N–CH_3), 3.63 (diffuse doublet, half band width ≅ 5 Hz, J = 5 Hz, 1, H_a), 4.04 (d, J = 5 Hz, 1, H_b), 7.1–8.0 δ (m, 10, aromatic H); spin decoupling of the signals at 2.22 led to the collapse of diffuse doublet at 3.63 ppm to a true doublet, J = 5 Hz; uv max (EtOH) 226 (log ε 4.32), 268 (4.11), 292 sh (432).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.69; H, 6.99.

Calcd *m/e* 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

B. From Pyridone 6a and Diphenylacetylene.—Irradiation of a mixture of 1.0 g (6.1 mmol) of pyridone **6a** and 2.5 g (14.0 mmol) of diphenylacetylene as described previously, gave the cyclobutene derivative, **16a**, in trace amounts as seen *via* tlc. The amount was too small to isolate. Comparison (tlc) of this product with that obtained from A confirmed their identity.

4,5,6,7,8,8b-Hexahydro-2a-methyl-1,2-diphenylcyclobuta[*c*]-quinolin-3(2aH)-one (16b). A. From Irradiation at 2537 Å.—A solution of 110 mg (0.32 mmol) of **8b** in 25 ml dry benzene was irradiated at 2537Å for 6 hr and the product **16b** isolated *via* preparative layer chromatography in 64% yield (R_f ether = 0.80). Crystallization from benzene–petroleum ether gave colorless needles: mp 234–236° dec; ir ($CHCl_3$) 1655 (C=C–NH–C=O), 3388 cm^{-1} (NH); nmr ($CDCl_3$) 1.2–2.5 (m, methylene H), 1.67 (s, C–CH_3) (total area = 11 protons), 3.33 (diffuse singlet, 1, H_a), 7.15–8.0 δ (m, 11, aromatic H and NH); uv max (EtOH) 228 (log ε 4.59), 287 mμ (4.22).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.55; H, 6.84.

Calcd *m/e* 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetyl) were also observed.

B. From Pyridone 6b and Diphenylacetylene.—Irradiation of a mixture of 1.5 g (9.2 mmol) of pyridone **6b** and 7.5 g (42.0 mmol) of diphenylacetylene with a 200-W high pressure Hanovia lamp as described before furnished 200 mg (6.6%) of the cyclobutene derivative. The product was identical with that obtained by 2537-Å irradiation of the pentacyclic lactam, **8b**, as determined by mixture melting point, ir, and nmr.

4,5,6,7,8,8b-Hexahydro-8b-methyl-1,2-diphenylcyclobuta[c]quinolin-3(2aH)-one (16c). A.—A solution of 100 mg (0.29 mmol) of **8c** in 20 ml of benzene was irradiated for 5.5 hr at 2537 Å; the product (**16c**) was isolated *via* preparative layer chromatography (R_f ether = 0.84) in 62% yield (62 mg). Crystallization from benzene–petroleum ether gave colorless needles: mp 205–207° dec; ir ($CHCl_3$) 1660 (C=C·NH·C=O), 3388 cm^{-1} (NH); nmr ($CDCl_3$) 1.2–2.3 (m, methylene H), 1.5 (s, CH_3) total area = 11 protons), 3.58 (s, 1, H_b), 7.05–7.9 δ (m, 11, aromatic H and NH); uv max (EtOH) 230 (sh) (log ε 4.39), 260 mμ (4.19).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.67; H, 7.07.

Calcd *m/e* 341. Found: 341.

Fragment peaks at *m/e* 163 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

B. From Pyridone 6c and Diphenylacetylene.—Irradiation of a mixture of 1.5 g (9.2 mmol) of pyridone **6c** and 7.5 g (42.0 mmol) of diphenylacetylene as described previously, gave 210 mg (6.7%) of the cyclobutene derivative, **16c**. The product was

identical with that obtained by 2537-Å photolysis of the pentacyclic lactam, 8c.

2a,4,5,6,7,7b-Hexahydro-1,2-diphenyl-3H-cyclobuta[*d*]cyclopenta[*b*]pyridin-3-one (16f).—Irradiation of a mixture of 1.359 g (10.0 mmol) of the pyridone 6f and 7.5 g (42.0 mmol) of diphenylacetylene as described above gave, in addition to **8f**, 275 mg (8.7%) of cyclobutene derivative, **16f** (R_f ether = 0.65). The product was crystallized from benzene–petroleum ether producing colorless needles: mp 184–186° dec; ir ($CHCl_3$) 1663 (C=C·NH·C=O), 3398 cm^{-1} (NH); nmr ($CDCl_3$) 1.6–2.6 (m, 6, methylene H), 3.88 (diffuse doublet J = 6 Hz, 1, H_a), 4.02 (d, J = 5 Hz, 1, H_b), 7.0–8.0 δ (m, 11, aromatic H and NH); uv max (EtOH) 224 (log ε 4.45), 277 mμ (4.08).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11. Found: C, 84.45; H, 6.36.

Calcd *m/e* 313. Found: 313.

Fragment peaks at *m/e* 135 (pyridone) and *m/e* 178 (diphenylacetylene were also observed. No attempt was made to obtain this product from the photoisomerization of **8f**.

2a,4,5,6,7,7b-Hexahydro-7b-methyl-1,2-diphenyl-3H-cyclobuta[*d*]cyclopenta[*b*]pyridin-3-one (16g).—Irradiation of a mixture of 1.371 g (9.2 mmol) of 4-methylcyclopentano-[*e*]-2-pyridone (6g) and 7.5 g (42.0 mmol) of diphenylacetylene as described before gave, in addition to other products, 400 mg (13.3%) of the cyclobutene derivative (16g) (R_f ether = 0.75). Crystallization from benzene–petroleum ether furnished colorless needles: mp 202–203°; ir ($CHCl_3$) 1661 (C=C·NH·C=O), 3398 cm^{-1} (NH); nmr ($CDCl_3$) 1.3–2.7 (m, methylene H), 1.5 (s, CH_3), 3.58 (s, 1, H_b), 7.0–7.85 (m, 10, aromatic H), 8.05 δ (broad singlet, 1, NH); uv max (EtOH) 225 (log ε 4.37), 263 mμ (4.17).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46. Found: C, 84.51; H, 6.60.

Calcd *m/e* 327. Found: 327.

Fragment peaks at *m/e* 149 (pyridone) and *m/e* 178 (diphenylacetylene) were also observed.

Stability of 8 at 3500 Å.—A solution of 10 mg (0.03 mmol) of pentacyclic lactam, **8**, in 20 ml of methanol was irradiated under nitrogen at 3500 Å and the reaction monitored by tlc at various intervals. After 100 hr no spot corresponding to the cyclobutenopyridone, **16**, was detected.

Photoisomerization of 8 to 16 in Methanol–Ether at 2537 Å.—A solution of 10 mg (0.03 mmol) of the pentacyclic lactam (**8**) in 2 ml of methanol and 2 ml of anhydrous ether was irradiated at 2537 Å and the reaction followed by tlc. After 12 hr, it was found that isomerization to the cyclobutenopyridone, **16**, had taken place.

Irradiation of the Pyridone (6) and Diphenylacetylene in Methanol–Ether at 2537 Å.—A solution of 300 mg (2.0 mmol) of 5,6,7,8-tetrahydro-2-quinolone (**6**) and 750 mg (4.2 mmol) of diphenylacetylene in 8 ml of MeOH and 8 ml of Et_2O was irradiated at 2537 Å for 12 hr. A tlc examination revealed that a minute trace of the pentacyclic lactam, (**8**), was present but no spot due to cyclobutenopyridone (**16**), could be detected.

Irradiation of the Pyridone (6) and Diphenylacetylene in Benzene at 2537 Å.—Irradiation of a solution of 100 mg (0.67 mmol) of **6** and 119.3 mg (0.67 mmol) of diphenylacetylene in 10 ml of benzene at 2537 Å for 4 hr followed by an examination by tlc revealed that a trace of cyclobutenopyridone, **16**, was present but no spot corresponding to the pentacyclic lactam, **8**, was visible.

Photostability of 16 at 2537 Å.—A solution of 13 mg (0.04 mmol) of cyclobutenopyridone (**16**) in 3 ml of benzene was irradiated at 2537 Å and the reaction checked by tlc after 6 and 17 hr. It was found that some decomposition had taken place as shown by streaking on the plate but the predominant spot was due to unchanged **16**.

Photostability of 16 at 3500 Å.—A solution of 27 mg (0.08 mmol) of cyclobutenopyridone (**16**) in 15 ml of methanol was irradiated for 16 hr and the reaction followed by tlc. It was found that some decomposition had taken place but no spots corresponding to new products were seen on the tlc plate.

Registry No.—Diphenylacetylene, 501-65-5; **6a**, 25183-42-0; **7**, 25183-43-1; **8**, 20670-50-2; **8a**, 20199-81-9; **8b**, 25183-46-4; **8c**, 25183-47-5; **8d**, 25183-48-6; **8e**, 25183-49-7; **8f**, 25183-50-0; **8g**, 25183-51-1; **11**, R = H, 19734-36-2; **11**, R = Me, 25183-53-3; **16**, 20177-91-7; **16a**, 20177-92-8; **16b**, 25183-56-6; **16c**, 25183-57-7; **16f**, 25183-58-8; **16g**, 25184-11-6.

Alkylation Reactions of 2-Fluoro-2,2-dinitroethanol[1]

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2-Fluoro-2,2-dinitroethanol in aqueous alkali reacted with dimethyl sulfate, allyl bromide, acetic anhydride, ethyl chloroformate, and oxalyl chloride yielding 2-fluoro-2,2-dinitroethyl methyl ether, allyl 2-fluoro-2,2-dinitroethyl ether, 2-fluoro-2,2-dinitroethyl acetate, ethyl 2-fluoro-2,2-dinitroethyl carbonate, and 2-fluoro-2,2-dinitroethyl oxalyl chloride, respectively. Ethylene oxide, propylene oxide, epihalohydrins, and butadiene dioxide yielded 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether, 2-fluoro-2,2-dinitroethyl 2-hydroxylpropyl ether, 2-fluoro-2,2-dinitroethyl glycidyl ether, and 4-(2-fluoro-2,2-dinitroethoxy)-3-hydroxybutene 1,2-oxide, respectively. Pyridine-catalyzed reactions of 2-fluoro-2,2-dinitroethanol with thionyl chloride and sulfuryl chloride gave bis(2-fluoro-2,2-dinitroethyl) sulfite and 2-fluoro-2,2-dinitroethyl chloride, respectively. Tris(2-fluoro-2,2-dinitroethyl) borate was obtained in the ester-exchange reaction. Reactions of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether, 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether, and 2-fluoro-2,2-dinitroethyl oxalyl chloride were investigated.

Although the synthesis of 2-fluoro-2,2-dinitroethanol was only recently reported,[2,3] the reactions of this unusual polynitro alcohol have been already explored by several groups of investigators.[2-6] 2-Fluoro-2,2-dinitroethanol undergoes deformylation in aqueous alkaline solutions in a manner similar to other 2,2-dinitro alcohols,[7] but unlike the other polynitro alcohols 2-fluoro-2,2-dinitroethanol in basic medium may also exist in equilibrium with its alkoxide ions. The dissociation to alkoxide ions, attributed to the reported

$$FC(NO_2)_2CH_2OH \overset{OH^-}{\rightleftharpoons} FC(NO_2)_2CH_2O^- \rightleftharpoons FC(NO_2)_2^- + CH_2O$$

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(7) For a review, see P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **64**, 19 (1964).

destabilization of nitronate anion by α fluorines,[8] was recently demonstrated in the Michael reaction of 2-fluoro-2,2-dinitroethanol with ethyl propiolate[6] where, in addition to 3-fluoro-3,3-dinitrocrotonate, the "normal" Michael adduct, β-(2-fluoro-2,2-dinitroethoxy)-acrylate was also obtained. This finding suggested that the observed alkoxide reaction may not be limited to the α,β unsaturated carbonyl compounds, but may represent an example of much broader class of nucleophilic reactions of 2-fluoro-2,2-dinitroethoxide anions. With this anticipation in mind, alkali-catalyzed reactions of 2-fluoro-2,2-dinitroethanol with a number of electrophilic reagents were examined and the results are presented in this paper.

Aqueous alkaline 2-fluoro-2,2-dinitroethanol was treated with dimethyl sulfate and allyl bromide at ambient temperature to give 2-fluoro-2,2-dinitroethyl methyl ether[9] (75% yield) and allyl 2-fluoro-2,2-dinitroethyl ether (30% yield), respectively, as shown.

$$FC(NO_2)_2CH_2OH + (CH_3)_2SO_4 \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCH_3$$

$$FC(NO_2)_2CH_2OH + CH_2{=}CHCH_2Br \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCH_2CH{=}CH_2$$

The Williamson reactions of simple alcohols with dialkyl sulfates or alkyl halides are usually carried out in nonaqueous media under more rigorous reaction conditions.[10] The Williamson reactions of 2,2-dinitro alcohols were not investigated because in alkaline solution these polynitro alcohols undergo deformylation to nitronate salts.[7] Several known polynitro ethers were synthesized indirectly. Thus, 2,2-dinitropropyl ethyl ether was obtained by addition of ethanol to 2-nitropropene, followed by the oxidative nitration of the adduct.[11]

In connection with characterization of polynitro ethers, we synthesized 2,2-dinitropropyl methyl ether by heating 2,2-dinitropropanol with dimethyl sulfate. 2,2-Dinitropropyl methyl sulfate was also obtained.

$$CH_3C(NO_2)_2CH_2OH + (CH_3)_2SO_4 \xrightarrow{95^\circ} CH_3C(NO_2)_2CH_2OCH_3 + CH_3OSO_2OCH_2C(NO_2)_2CH_3$$

This reaction seems to be of general utility in the synthesis of "mixed" nitroalkyl ethers. Thus, 2,2-dinitropropanediol reacted with dimethyl sulfate to give 1,3-dimethoxy-2,2-dinitropropane and 3-methoxy-2,2-dinitropropyl methyl sulfate.

$$(NO_2)_2C(CH_2OH)_2 + (CH_3)_2SO_4 \longrightarrow (NO_2)_2C(CH_2OCH_3)_2 + CH_3OCH_2C(NO_2)_2CH_2OSO_2OCH_3$$

On the other hand, attempts to synthesize 2-fluoro-2,2-dinitroethyl ethers from 2-fluoro-2,2-dinitroethanol were unsuccessful under these reaction conditions.

Acetic anhydride and ethyl chloroformate reacted with aqueous alkaline 2-fluoro-2,2-dinitroethanol to give 2-fluoro-2,2-dinitroethyl acetate[5] and ethyl 2-fluoro-2,2-dinitroethyl carbonate, respectively, in 70–80% yields.

$$FC(NO_2)_2CH_2OH + Ac_2O \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCOCH_3$$

$$FC(NO_2)_2CH_2OH + ClCO_2Et \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCO_2C_2H_5$$

Pyridine-catalyzed reaction of 2-fluoro-2,2-dinitroethanol with oxalyl chloride yielded, depending on the stoichiometry of reagents, bis(2-fluoro-2,2-dinitroethyl) oxalate[12] and 2-fluoro-2,2-dinitroethyl oxalyl chloride. The bis ester was still the major product at a 1:1 ratio of the reagents but 2-fluoro-2,2-dinitroethyl oxalyl chloride was obtained in 20% yield. The Curtius reaction of this ester chloride gave carbo(2-fluoro-2,2-dinitroethoxy) isocyanate as is depicted below.

$$FC(NO_2)_2CH_2O_2CCOCl + NaN_3 \xrightarrow[C_2H_4Cl_2]{H_2O} [FC(NO_2)_2CH_2O_2CCON_3] \xrightarrow{\Delta} FC(NO_2)_2CH_2O_2CNCO$$

The isocyanate polymerized readily at room temperature and its elemental analysis was not obtained.[13] The freshly prepared compound exhibited the characteristic NCO infrared absorption peak and reacted with 2-fluoro-2,2-dinitroethanol to give bis(2-fluoro-2,2-dinitroethyl) iminodicarboxylate, which was characterized by elemental analysis and proton nmr spectrum.

$$FC(NO_2)_2CH_2O_2CNCO + HOCH_2CF(NO_2)_2 \longrightarrow NH[CO_2CH_2CF(NO_2)_2]_2$$

Simple carboalkoxy isocyanates could not be synthesized *via* the Curtius reaction[14] and this example seems to represent the first case of this rearrangement.

The above alkylation reactions suggested that in a manner similar to that of simple alkoxides[15] 2-fluoro-2,2-dinitroethoxide may react with 1,2-epoxides to give the corresponding 2-fluoro-2,2-dinitroethyl 2-hydroxyalkyl ethers. This was found to be the case. Ethylene oxide and propylene oxide reacted with 2-fluoro-2,2-

$$FC(NO_2)_2CH_2OH + \underset{CH_2-CHR}{\overset{O}{\diagup\diagdown}} \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCH_2CH(OH)R$$

R = H or CH_3

(8) H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966).

(9) 2-Fluoro-2,2-dinitroethyl methyl ether was synthesized by Adolph and Kamlet by reacting 2-fluoro-2,2-dinitroethanol with diazomethane,[3] and in the fluorination of 2,2-dinitroethyl methyl ether.[3]

(10) For a review of Williamson reactions, see Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, Vol. VI [3], Georg Thieme Verlag, Stuttgart, 1955, pp 24–33.

(11) H. Schechter, *et al.*, "Research in Nitromonomers and their Applications to Solid Smokeless Propellants," Ohio State University Research Foundation, Report No. 10, March 25, 1954. Available through the Defense Documentation Center, Cameron Station, Alexandria, Va.

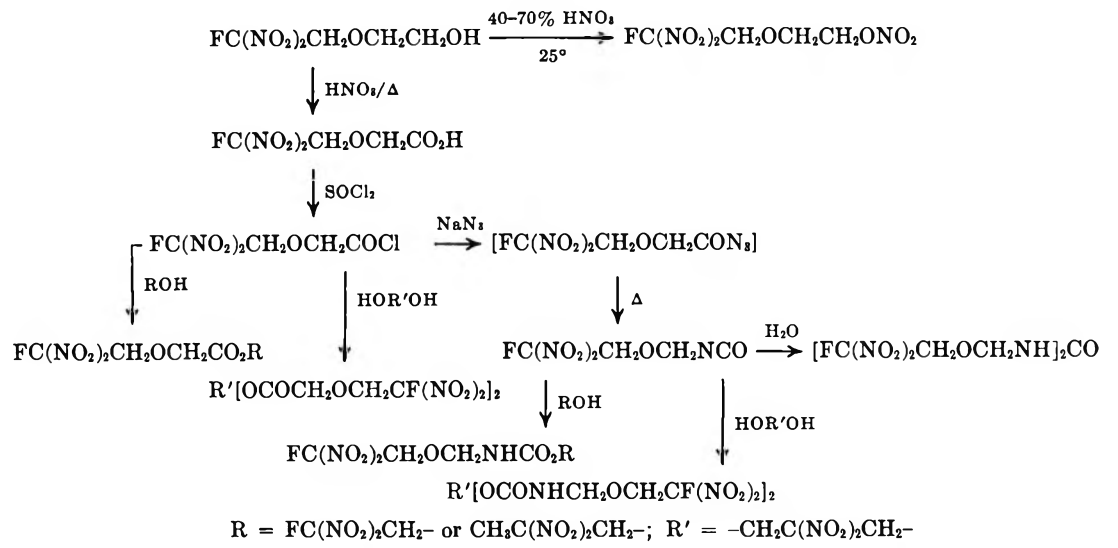
(12) Bis(2-fluoro-2,2-dinitroethyl) oxalate was first synthesized by Dr. M. B. Frankel, Rocketdyne Corp., Canoga Park, Calif. (private communication) whose priority in this regard we herewith acknowledge.

(13) On storage at ambient temperature, the originally mobile liquid turned progressively more viscous and solidified. The resulting solid analyzed for $C_4H_2N_8FO_7$. The material was not characterized but based on the related reaction of ethyl chloroformate with potassium cyanide [O. Diels and K. Jacoby, *Ber.*, **41**, 2393 (1908)], it appears to be tris[carbo(2-fluoro-2,2-dinitroethoxy)]isocyonuric acid.

(14) P. A. S. Smith, *Org. Reactions*, **3**, 337 (1946).

(15) For a general discussion of epoxide–alkoxide reactions, see (a) S. Winstein and R. B. Henderson, *Heterocycl Compounds*, **1**, 47 (1950); (b) G. Dittus in Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, Vol. VI [3], Georg Thieme Verlag, Stuttgart, 1965, pp 40 and 447.

SCHEME I

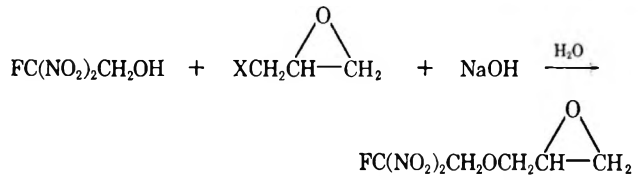


R = $FC(NO_2)_2CH_2-$ or $CH_3C(NO_2)_2CH_2-$; R' = $-CH_2C(NO_2)_2CH_2-$

dinitroethanol in aqueous sodium hydroxide to give 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl and 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ethers, respectively, in 40 to 60% yields.

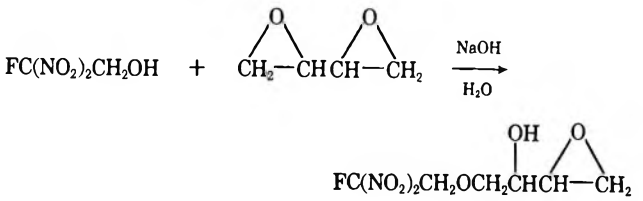
The product yields were not optimized but a significant increase in yields resulted when excess of an epoxide was used, the concentration of reagents was increased, and the reaction temperature was kept low (0–5°). 2-Fluoro-2,2-dinitroethyl 2-hydroxypropyl ether was also obtained in 12% yield in stannic chloride-catalyzed reaction of 2-fluoro-2,2-dinitroethanol with propylene oxide.

2-Fluoro-2,2-dinitroethanol reacted with epichlorohydrin or epibromohydrin in aqueous sodium hydroxide to give 2-fluoro-2,2-dinitroethyl glycidyl ether in 15 to 30% yields.



At least stoichiometric amounts of sodium hydroxide were required in these reactions to effect the cyclization of halohydrin intermediates.

The reaction of butadiene dioxide with 2-fluoro-2,2-dinitroethane in aqueous sodium hydroxide yielded 4-(2-fluoro-2,2-dinitroethoxy)-3-hydroxybutene 1,2-oxide, identified by elemental analysis and nmr spectra.



The proton nmr spectrum of the distillation residue remaining in the purification of the 1:1 alkylation product suggested that the 1:2 adduct, 1,4-bis(2-fluoro-2,2-dinitroethoxy)-2,3-butanediol, was also produced in the above reaction but the elemental analysis of the material was only in a fair agreement with this structure.

2-Fluoro-2,2-dinitroethyl 2-hydroxyethyl ether and 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether were found to be useful starting materials in the synthesis of other 2-fluoro-2,2-dinitroethoxy derivatives and their reactions were investigated.

2-Fluoro-2,2-dinitroethyl 2-hydroxyethyl ether was oxidized with 70% nitric acid to give 2-fluoro-2,2-dinitroethoxyacetic acid in 91% yield. The acid was converted to 2-fluoro-2,2-dinitroethoxyacetyl chloride with thionyl chloride. The Curtius reaction of the acid chloride gave 2-fluoro-2,2-dinitroethoxymethyl isocyanate. 2-Fluoro-2,2-dinitroethoxyacetyl chloride was treated with 2-fluoro-2,2-dinitroethanol, 2,2-dinitropropanol, and 2,2-dinitropropanediol to give the corresponding esters quantitatively. 2-Fluoro-2,2-dinitroethoxymethyl isocyanate also reacted with the above nitro alcohols to give the corresponding N-(2-fluoro-2,2-dinitroethoxymethyl)carbamic acid esters. N,N'-Bis[(2-fluoro-2,2-dinitroethoxy)methyl]urea was obtained by reacting the isocyanate with water. Several attempts to oxidize 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether to the corresponding aldehyde with dilute nitric acid under mild conditions failed; small amounts of 2-fluoro-2,2-dinitroethoxyethyl nitrate were obtained. The reactions of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether are summarized in Scheme I. All the compounds are new and were characterized by their elemental analyses and their infrared and nmr spectra.

The reactions of 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether were explored to a lesser degree than those of 2-fluoro-2,2-dinitroethyl 2-hydroxylpropyl ether. The compound was oxidized with 70% nitric acid to give 2-fluoro-2,2-dinitroethoxyacetic acid in 40% yield. Oxidation with chromic acid in acetone yielded 2-fluoro-2,2-dinitroethoxyacetone in 95% yield. The ketone was treated with hydroxylamine to give the corresponding oxime, which was nitrated and the resulting nitro-nitroso intermediate oxidized to 2-fluoro-2,2-dinitroethyl 2,2-dinitropropyl ether, following the procedure of Bull, *et al.*[16] The ether was contaminated with 2-

(16) J. R. Bull, Sir E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965).

fluoro-2,2-dinitroethoxyacetone and some difficulties were encountered with its purification. The reactions of 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether are summarized below.

$$FC(NO_2)_2CH_2OCH_2CO_2H \text{ and/or } FC(NO_2)_2CH_2OCH_2CH_2ONO_2$$
$$\uparrow 70\%\ HNO_3$$
$$FC(NO_2)_2CH_2OCH_2CH(OH)CH_3$$
$$\downarrow CrO_3/\text{acetone}$$
$$FC(NO_2)_2CH_2OCH_2COCH_3$$
$$\downarrow NH_2OH\cdot HCl\text{–}NaOAc$$
$$FC(NO_2)_2CH_2OCH_2C(=NOH)CH_3$$
$$\text{1. } HNO_3 \downarrow \text{2. } H_2O_2$$
$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2CH_3$$

In addition to the reactions of 2-fluoro-2,2-dinitroethanol in aqueous alkali, several related reactions of the alcohol were carried out in the presence of pyridine.[17] Under these conditions, the alcohol reacted with thionyl chloride to give bis(2-fluoro-2,2-dinitroethyl) sulfite[18] (80–85% yield) and a small amount (5–7% yield) of 2-fluoro-2,2-dinitroethyl chloride as is shown below.

$$2FC(NO_2)_2CH_2OH + SOCl_2 + 2C_5H_5N \xrightarrow{CH_2Cl_2} [FC(NO_2)_2CH_2O]_2SO + FC(NO_2)_2CH_2Cl$$

2-Fluoro-2,2-dinitroethyl chloride was obtained in 75% yield in the pyridine-catalyzed reaction of the alcohol with sulfuryl chloride.

Tris(2-fluoro-2,2-dinitroethyl) borate was obtained quantitatively in the ester-exchange reaction between triethyl borate and 2-fluoro-2,2-dinitroethanol.

$$B(OC_2H_5)_3 + 3FC(NO_2)_2CH_2OH \xrightarrow{90^\circ} B[OCH_2CF(NO_2)_2]_3 + 3C_2H_5OH$$

2-Fluoro-2,2-dinitroethyl nitrate was obtained in 75% yield in the reaction of 2-fluoro-2,2-dinitroethanol with a sulfuric–nitric acid mixture.

$$FC(NO_2)_2CH_2OH + HNO_3\text{–}H_2SO_4 \longrightarrow FC(NO_2)_2CH_2ONO_2$$

The compound has been recently synthesized by Eremenko and Natsibullin[4] in 30% yield.

Experimental Section

Caution.—2-Fluoro-2,2-dinitroethanol is a *severe* skin irritant. Safety shielding should be used in work with fluorodinitro compounds.

2-Fluoro-2,2-dinitroethyl Methyl Ether.[2,3]—To a stirred solution of 2.0 g (0.05 mol) of sodium hydroxide and 6.24 g (0.04 mol) of 2-fluoro-2,2-dinitroethanol in 55 ml of water was added dropwise at 25° over a period of 10 min 5.1 g (0.04 mol) of dimethyl sulfate. After 45 min the reaction mixture was extracted with 35 ml of methylene chloride and distilled to give 5.1 g of 2-fluoro-2,2-dinitroethyl methyl ether (75% yield), bp 27° (0.1 mm) [lit.[2] bp 47–48° (4 mm)], $n^{25}D$ 1.4045.

Anal. Calcd for $C_3H_5N_2FO_5$: C, 21.4; H, 3.0; N, 16.7; F, 11.3. Found: C, 21.2; H, 2.7; N, 16.2; F, 10.6.

Proton nmr ($CDCl_3$): δ 4.60 (d, J_{HF} = 18 Hz, CH_2O) and 3.61 (s, CH_3). Fluorine nmr: ϕ 110.9 (s).

(17) 2-Fluoro-2,2-dinitroethanol forms a sparingly water soluble 1:1 complex with pyridine from which the alcohol can be recovered upon acidification or by removing pyridine at reduced pressure. The complex was examined by nmr but the proton and ^{19}F spectra did not provide any information regarding its structure.

(18) Bis(2-fluoro-2,2-dinitroethyl) sulfite was reported by K. Baum, *J. Amer. Chem. Soc.*, **91**, 4594 (1969), as a side reaction product in the reaction of sulfur tetrafluoride with 2-fluoro-2,2-dinitroethanol.

Allyl 2-Fluoro-2,2-dinitroethyl Ether.—A mixture of 1.6 g (0.04 mol) of sodium hydroxide in 30 ml of water, 4.62 g (0.04 mol) of 2-fluoro-2,2-dinitroethanol and 4.85 g (0.04 mol) of allyl bromide was stirred at 25° for 3 hr.

The product was extracted with 30 ml of methylene chloride and distilled to give 2.5 g of alkyl 2-fluoro-2,2-dinotroethyl ether (34% yield), bp 31–32° (0.2 mm).

Anal. Calcd for $C_5H_7N_2FO_5$: C, 30.9; H, 3.6; N, 14.4; F, 9.8. Found: C, 30.6; H, 3.4; N, 13.9; F, 9.9.

Proton nmr ($CDCl_3$): δ 5.56–6.20 (d, d, t, J_{cis} = 9 Hz, J_{trans} = 17.5 Hz, J_{allyl} = 5.5 Hz, CH), 5.06–5.51 (m, CH_2=), 4.15 (d, J_{HH} = 5.5 Hz, CH_2), and 4.58 (d, J_{HF} = 18 Hz, OCH_2CF). Fluorine nmr: ϕ 111.0 (t, J_{HF} = 17.3 Hz).

2,2-Dinitropropyl Methyl Ether.—A mixture of 20 g (0.16 mol) of dimethyl sulfate and 10.0 g (0.067 mol) of 2,2-dinitropropanol was heated at 95–100° for 10 hr and distilled to give 18 g of colorless liquid, bp 30–90° (0.1 mm), and a residue amounting to *ca.* 10 g. The distillate, containing mainly dimethyl sulfate, was stirred with 100 cc of 25% aqueous sodium hydroxide at 25° for 16 hr. An insoluble liquid was extracted with 25 ml of methylene chloride, and distilled to give 2.5 g of 2,2-dinitropropyl methyl ether, bp 35° (0.1 mm), $n^{25}D$ 1.4295.

Anal. Calcd for $C_4H_8N_2O_5$: C, 29.3; H, 4.9; N, 17.1. Found: C, 29.0; H, 4.8; N, 17.5.

Proton nmr (CCl_4): δ 4.13 [s, $OCH_2C(NO_2)_2$], 3.39 (s, OCH_3), and 2.13 (s, CH_3).

2,2-Dinitropropyl Methyl Sulfate.—The distillation residue above was washed with 100 ml of water and an insoluble liquid was distilled in a molecular still at 100° (25 μ) to give 1.5 g of colorless oil, $n^{25}D$ 1.4470.

Anal. Calcd for $C_4H_8N_2SO_8$: C, 19.7; H, 3.3; N, 11.5. Found: C, 20.0; H, 3.3; N, 11.8.

Proton nmr (CCl_4): δ 4.85 (s, 2), 3.92 (s, 3), and 2.25 (s, 3).

1,3-Dimethoxy-2,2-dinitropropane.—A solution of 5.0 g (0.03 mol) of 2,2-dinitropropanediol in 24 g (0.19 mol) if dimethyl sulfate was heated at 90–95° for 7 hr and distilled at 50–90° (0.1 mm) to give 19 g of a colorless liquid (mainly dimethyl sulfate) and a residue amounting to 9.0 g. The distillate was stirred with 200 ml of 10% aqueous sodium hydroxide at 25° for 16 hr. An insoluble liquid was extracted with 15 ml of methylene chloride and distilled to give 0.7 g of 1,3-dimethoxy-2,2-dinitropropane, bp 38° (0.05 mm), $n^{25}D$ 1.4302.

Anal. Calcd for $C_5H_{10}N_2O_6$: C, 30.9; H, 5.2; N, 14.4. Found: C, 30.7; H, 5.1; N, 14.6.

Proton nmr (CCl_4): δ 3.47 (s, 3) and 4.28 (s, 2).

Methyl 3-Methoxy-2,2-dinitropropyl Sulfate.—The distillation residue above was stirred with 100 ml of water. The product was extracted with 30 ml of methylene chloride and distilled in a molecular still at 100–102° (25 μ) to give 0.9 g of colorless liquid, $n^{25}D$ 1.4460.

Anal. Calcd for $C_5H_{10}N_2SO_9$: C, 21.9; H, 3.7; N, 10.2. Found: C: 22.2; H, 3.7; N, 11.0.

2-Fluoro-2,2-dinitroethyl Acetate.—To a stirred solution of 4.4 g (0.11 mol) of sodium hydroxide and 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 150 ml of water was added dropwise (10 min) with cooling at 0–2° 10.2 g (0.1 mol) of acetic anhydride. The reaction mixture was stirred for 1.5 hr, the product extracted with 50 ml of methylene chloride and distilled to give 16.4 g (83% yield) of 2-fluoro-2,2-dinitroethyl acetate, bp 91° (50 mm), $n^{21}D$ 1.4198 [lit.[4] bp 90–90.5° (50 mm), $n^{20}D$ 1.4200].

2-Fluoro-2,2-dinitroethyl Ethyl Carbonate.—To a stirred solution of 4.4 g (0.11 mol) of sodium hydroxide and 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 75 ml of water was added at 0–2° with cooling over a period of 15 min 10.8 g (0.1 mol) of ethyl chloroformate. After 45 min the product was extracted with 50 ml of methylene chloride and distilled to give 18.2 g (80% yield) of 2-fluoro-2,2-dinitroethyl ethyl carbonate, bp 53–54° (0.1 mm), $n^{23}D$ 1.4215.

Anal. Calcd for $C_5H_7N_2FO_7$: C, 26.6; H, 3.1; N, 12.4; F, 8.4. Found: C, 26.3; H, 3.2; N, 13.1; F, 8.5.

Proton nmr (CCl_4): δ 1.33 (t, CH_2), 4.23 (q, J = 7.1 Hz, CH_2), and 5.17 (d, J_{HF} = 15.7 Hz, CH_2). Fluorine nmr: ϕ 111.3 (s).

2-Fluoro-2,2-dinitroethyl Oxalyl Chloride.—To a stirred solution of 12.7 g (0.1 mol) of oxalyl chloride in 75 ml of diethyl ether was added at 5–10° with cooling over a period of 15 min a solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 7.9 g (0.1 mol) of pyridine in 75 ml of diethyl ether. The reaction mixture was filtered and the filter cake was washed with three 25-ml portions of diethyl ether. The combined filtrate and washings were

distilled to give 4.5 g of 2-fluoro-2,2-dinitroethyl oxalyl chloride, bp 66–67° (0.1 mm).

Anal. Calcd for $C_4H_2N_2FClO_7$: C, 19.6; H, 0.8; N, 11.5; F, 7.8. Found: C, 20.0; H, 0.8; N, 11.3; F, 7.4.

Carbo(2-fluoro-2,2-dinitroethoxy) Isocyanate.—A solution of 2.45 g (0.01 mol) of 2-fluoro-2,2-dinitroethyl oxalyl chloride in 25 ml of ethylene chloride was added dropwise over a period of 8 min at 12–15° to a stirred solution of 0.8 g (0.012 mol) of sodium azide in 15 ml of water and the mixture was stirred for 15 min. The ethylene chloride solution was washed with 30 ml of ice water, dried over anhydrous sodium sulfate, and filtered. The filtrate was warmed at 50° for 45 min in a distillation apparatus protected from the atmospheric moisture and concentrated at 25 mm. The pale yellow liquid was dried at 35° (0.1 mm); weight 2.0 g. The infrared spectrum of the freshly prepared material showed intense absorption peaks at 4.5 and 6.25 μ, attributed to –NCO and $-NO_2$ groups, respectively.

Soon after its preparation (20–30 min), the clear liquid started to turn turbid and on standing in a closed vial at room temperature for several days it solidified into a white solid.

2-Fluoro-2,2-dinitroethyl Iminodicarboxylate.—To a solution of 1.0 g of freshly prepared carbo(2-fluoro-2,2-dinitroethoxy) isocyanate and 0.75 g of 2-fluoro-2,2-dinitroethanol in 15 ml of ethylene chloride was added a catalytic amount of ferric acetylacetonate. After 18 hr a white crystalline solid was filtered, washed with two 1-ml portions of ethylene chloride and dried; wt 1.0 g, mp 182–183°.

Anal. Calcd for $C_6H_5N_5F_2O_{12}$: C, 19.1; H, 1.3; N, 18.6; F, 10.1. Found: C, 18.8; H, 1.3; N, 17.8; F, 10.4.

Proton nmr (d_6-acetone): δ 10.11 (s, 1, NH) and 5.58 (d, 4, J_{HF} = 16 Hz, CH_2).

2-Fluoro-2,2-dinitroethyl 2-Hydroxyethyl Ether.—To a stirred solution of 4.0 g (0.1 mol) of sodium hydroxide in 90 ml of water at 0–5° was added 15.5 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 5.5 g (0.125 mol) of ethylene oxide. After standing for 16 hr at 0° the reaction mixture was extracted with three 25-ml portions of methylene chloride and the combined extracts were distilled to give 5.4 g (27% yield) of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether, bp 74–75° (50 μ), $n^{23}D$ 1.4370.

Anal. Calcd for $C_4H_7N_2FO_6$: C, 24.5; H, 3.6; N, 14.1; F, 9.6. Found: C, 24.3; H, 3.6; N, 13.8; F, 9.5.

The infrared spectrum showed absorption peaks at (μ) 3.0 (s), 3.44 (m); 3.50 (sh); 6.27 (s); 6.86 (m); 7.43 (m); 7.62 (s); 8.15 (w); 8.83 (s); 9.40 (s); 11.83 (s); and 12.20 (s).

Proton nmr ($CDCl_3$): δ 4.77 [d, J_{HF} = 18 Hz, $OCH_2CF(NO_2)_2$], 3.82 (s, CH_2), and 3.25 (s, OH). Fluorine nmr ϕ 111.0 (t, J_{HF} = 18 Hz).

Higher yields (68%) and conversion (57%) were observed in a large-scale run using 185 g (1.2 mol) of 2-fluoro-2,2-dinitroethanol, 30 g (0.75 mol) of sodium hydroxide and 125 g (2.86 mols) of ethylene oxide in 750 ml of water. *p*-Toluenesulfonate, bp 160–163° (25 μ) (molecular still), $n^{23}D$ 1.5035, was obtained quantitatively by treating the hydroxy ether with *p*-toluenesulfonyl chloride in methylene chloride–pyridine solution.

Anal. Calcd for $C_{11}H_{13}N_2FSO_8$: C, 37.5; H, 3.7; N, 8.0; F, 5.4. Found: C, 37.7; H, 3.6; N, 7.6; F, 5.5.

2-Fluoro-2,2-dinitroethyl 2-Hydroxypropyl Ether.—To a solution of 2.2 g (0.055 mol) of sodium hydroxide in 70 ml of water at 0° was added 9.24 g (0.06 mol) of 2-fluoro-2,2-dinitroethanol and 3.5 g (0.06 mol) of propylene oxide. The reaction mixture was allowed to stand at 0° for 18 hr, extracted with three 30-ml portions of diethyl ether, and the combined etheral extracts were distilled to give 3.1 g of colorless liquid (25 % yield), bp 62° (0.05 mm), $n^{23}D$ 1.4325.

Anal. Calcd for $C_5H_9N_2FO_6$: C, 28.3; H, 4.3; N, 13.2; F, 9.0. Found: C, 28.0; H, 4.1; N, 13.0; F, 9.3.

Proton nmr ($CDCl_3$): δ 4.75 [d, J_{HF} = 18 Hz, $OCH_2CF(NO_2)_2$], 4.00 (d, q, CH), and 3.6 (s, OCH_2 and OH; AB pattern after D_2O exchange). Fluorine nmr: ϕ 110.8 (t, J_{HF} = 17.5 Hz).

The yield of the product increased to 45 and 63%, respectively, when a 2:1 and a 4:1 molar ratio of propylene oxide to 2-fluoro-2,2-dinitroethanol were employed in the above reaction.

An acid-catalyzed reaction was carried out as follows. To a solution 9.24 g (0.06 mol) of 2-fluoro-2,2-dinitroethanol and 4.0 g (0.068 mol) of propylene oxide in 50 ml of methylene chloride was added 3 drops of stannic chloride and the reaction mixture was allowed to stand at 25° for 18 hr. The solution was washed with 50 ml of water, dried, and distilled to give 1.5 g (12% yield) of 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether, identified by its infrared spectrum.

p-Toluenesulfonate, bp 150–153° (25 μ) (molecular still), $n^{23}D$ 1.4975, was obtained quantitatively in the same manner as that of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether (see above).

Anal. Calcd for $C_{12}H_{15}N_2FSO_8$: C, 39.4; H, 4.1; N, 7.6; F, 5.2. Found: C, 39.5; H, 4.1; N, 7.2; F, 5.3.

2-Fluoro-2,2-dinitroethyl Glycidyl Ether.—Epichlorohydrin, 3.7 g (0.04 mol), and 6.24 g (0.04 mol) of 2-fluoro-2,2-dinitroethanol was added at 0° to a stirred solution of 2.5 g of sodium hydroxide in 75 ml of water. After standing at 0–3° for 48 hr the reaction mixture was extracted with 30 ml of methylene chloride and the extract was distilled to give 2.6 g (31% yield) of 2-fluoro-2,2-dinitroethyl glycidyl ether, bp 70–71° (0.1 mm), $n^{23}D$ 1.4362.

Anal. Calcd for $C_5H_7N_2FO_6$: C, 28.6; H, 3.3; N, 13.3; F, 9.0. Found: C, 28.4; H, 3.2; N, 12.8; F, 8.8.

Proton nmr (CCl_4): δ 4.71 [d, J_{HF} = 18 Hz, $OCH_2CF(NO_2)_2$], 4.1 and 3.5 (d, d, OCH_2), 3.11 (m, CH), and 3.7 and 3.5 (d, d, ring CH_2). Fluorine nmr: ϕ 111.9 (t, J_{HF} = 18 Hz).

2-Fluoro-2,2-dinitroethyl glycidyl ether was obtained in 15% yield when epibromohydrin instead of epichlorohydrin was used in the above reaction.

4-(2-Fluoro-2,2-dinitroethoxy)-3-hydroxybutene 1,2-Oxide.—To a solution of 30.8 g (0.2 mol) of 2-fluoro-2,2-dinitroethanol and 8.6 g (0.1 mol) of butadiene dioxide in 150 ml of water at 0° was added a solution of 8.0 g (0.2 mol) of sodium hydroxide in 75 ml of water. After standing at 0° for 5 days, the product was extracted with 75 ml of methylene chloride and dried to give 19 g of viscous oil. A 1.5 g aliquot of the material was distilled at 120–125° (10 μ) (molecular still) to give 0.9 g of colorless oil.

Anal. Calcd for $C_6H_9FN_2O_7$: C, 30.0; H, 3.8; N, 11.7; F, 7.0. Found: C, 29.7; H, 3.8; N, 11.9; F, 7.4.

Proton nmr ($CDCl_3$): δ 4.70 [d, J_{HF} = 18 Hz, $OCH_2CF(NO_2)_2$], 3.75 (m, CH_2 and CH), 2.71 (ABM pattern, ring protons), and 3.12 (s, OH; confirmed by D_2O exchange).

2-Fluoro-2,2-dinitroethoxyacetic Acid.—2-Fluoro-2,2-dinitroethyl 2-hydroxyethyl ether, 3.1 g (0.02 mol), was added dropwise with stirring at 25° to 6.5 ml of 70% nitric acid and the solution was allowed to stand at 25° for 18 hr. The mixture was heated at 65–70° for 3 hr, evaporated to dryness at reduced pressure (3–5 mm), and a yellow solid was crystallized from methylene chloride to give 3.1 g (91% yield) of 2-fluoro-2,2-dinitroethoxyacetic acid, white crystalline solid, mp 69–70°.

Anal. Calcd for $C_4H_5N_2FO_7$: C, 22.6; H, 2.3; N, 13.2; F, 9.0. Found: C, 22.5; H, 2.1; N, 12.9; F, 8.9.

Proton nmr (d_6-acetone): δ 10.29 (s, CO_2H), 5.00 [d, J_{HF} = 17.2 Hz, $OCH_2CF(NO_2)_2$], and 4.37 (s, CH_3).

2-Fluoro-2,2-dinitroethoxyacetic acid was also obtained in the oxidation of 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether as follows. A solution of the ether, 4.3 g, in 20 ml of 70% nitric acid was allowed to stand at 25° for 18 hr and then was heated at 55–60° for 2 hr. The mixture was evaporated to dryness at reduced pressure, and the product was recrystallized from methylene chloride to give 1.5 g of the acid, 40% yield, mp 68–69°.

2-Fluoro-2,2-dinitroethoxyacetyl Chloride.—To a solution of 10.6 g (0.05 mol) of 2-fluoro-2,2-dinitroethoxyacetic acid and 8.0 g (0.067 mol) of thionyl chloride in 30 ml of ethylene chloride was added 2 drops of pyridine and the reaction mixture was warmed at 65–70° until the evolution of hydrogen chloride and sulfur dioxide ceased (30 min). The solution was distilled to give 11.6 g (quantitative yield) 2-fluoro-2,2-dinitroethoxyacetyl chloride, bp 67–68° (0.1 mm), $n^{23}D$ 1.4505.

Anal. Calcd for $C_4H_4N_2ClFO_6$: C, 20.8; H, 1.7; N, 12.2; F, 8.3. Found: C, 20.6; H, 2.1; N, 11.6; F, 8.5.

2-Fluoro-2,2-dinitroethoxymethyl Isocyanate.—To a stirred solution of 7.8 g (0.12 mol) of sodium azide in 50 ml of water and 150 ml of ethylene chloride at 15–16° was added dropwise over a period of 10 min 23 g (0.1 mol) of 2-fluoro-2,2-dinitroethoxyacetyl chloride. The reaction mixture was stirred at 10–12° for 35 min, phases separated, and the ethylene chloride solution was dried over anhydrous sodium sulfate and filtered. The filtrate was placed in a 250 ml round-bottomed flash equipped with a reflux condenser protected from the atmospheric moisture by a drying tube, and heated at 60–65° until the evolution of nitrogen ceased (45 min). The solution was distilled to give 20.7 g (100% yield) of 2-fluoro-2,2-dinitroethoxymethyl isocyanate, bp 55–56° (50 μ), $n^{23}D$ 1.4420.

Anal. Calcd for $C_4H_4N_3FO_6$: C, 23.0; H, 1.9; N, 20.1; F, 9.0. Found: C, 22.7; H, 1.9; N, 19.9; F, 8.7.

Proton nmr ($CDCl_3$): δ 4.93 (s, CH_2NCO) and 4.71 (d, J_{HF} = 17.3 Hz, CH_2). Fluorine nmr: ϕ 110.3 (t, J_{HF} = 16.5 Hz).

2-Fluoro-2,2-dinitroethyl 2-Fluoro-2,2-dinitroethoxyacetate.—To a stirred solution of 3.45 g (0.015 mol) of 2-fluoro-2,2-dinitroethoxymethyl chloride and 2.31 g (0.015 mol) of 2-fluoro-2,2-dinitroethanol in 15 ml of methylene chloride was added dropwise over a period of 5 min at 25–28° a solution of 1.2 g (0.015 mol) of pyridine in 15 ml of methylene chloride. After 20 min, the solution was washed with 70 ml of 3% sulfuric acid and distilled in a molecular still at 110–115° (25 μ) to give 5.2 g (100 % yield) of a colorless liquid, $n^{23}D$ 1.4485.

Anal. Calcd for $C_6H_6N_4F_2O_{11}$: C, 20.7; H, 1.7; N, 16.1; F, 10.9. Found: C, 20.5; H, 1.7; N, 15.9; F, 10.8.

Proton nmr ($CDCl_3$): δ 5.31 (d, 1, J_{HF} = 16 = 16 Hz), 4.73 (d, 1, J_{HF} = 17 Hz), and 4.40 (s, 1). Fluorine nmr: ϕ 110.1 (t, J_{HF} = 15 Hz) and ϕ 111.1 (t, J_{HF} = 17 Hz).

2,2-Dinitropropyl 2-Fluoro-2,2-dinitroethoxyacetate.—2,2-Dinitropropyl 2-fluoro-2,2-dinitroethoxyacetate, bp 138–143° (25 μ) (molecular still), $n^{24}D$ 1.4645, was obtained quantitatively in the reaction of 2,2-dinitropropanol and 2-fluoro-2,2-dinitroethoxyacetyl chloride following the above described procedure.

Anal. Calcd for $C_7H_9N_4FO_{11}$: C, 24.4; H, 2.6; N, 16.3; F, 5.5. Found: C, 24.4; H, 2.6; N, 15.8; F, 5.6.

Proton nmr ($CDCl_3$): δ 5.00 (s, OCH_2CO), 4.73 [d, J_{HF} = 17.5 Hz, $OCH_2CF(NO_2)_2$], 4.33 [s, $OCH_2C(NO_2)_2$–], and 2.23 (s, CH_3). Fluorine nmr: ϕ 111.2 (t, J_{HF} = 17.4 Hz).

Bis(2-fluoro-2,2-dinitroethoxyacetate) of 2,2-Dinitropropanediol.—Bis(2-fluoro-2,2-dinitroethoxyacetate) of 2,2-dinitropropanediol was obtained quantitatively in the reaction of 2,2-dinitropropanediol with 2 mol of 2-fluoro-2,2-dinitroethoxyacetyl chloride following the above procedure. The viscous oil, degassed at 100° (0.1 mm), was not further purified.

Anal. Calcd for $C_{11}H_{12}N_6F_2O_{18}$: C, 23.8; H, 2.2; N, 15.2; F, 6.9. Found: C, 23.6; H, 2.1; N, 14.7; F, 6.9.

Proton nmr ($CDCl_3$–d_6-acetone): 5.12 (s, 1, $COCH_2O$), 4.78 [d, 1, J_{HF} = 17 Hz, $OCH_2CF(NO_2)_2$], and 4.38 (s, 1, CH_2). Fluorine nmr: ϕ 111.2 (t, J_{HF} = 16.2 Hz).

2-Fluoro-2,2-dinitroethyl 2-Fluoro-2,2-dinitroethoxymethylcarbamate.—To a solution of 2.1 g (0.01 mol) of 2-fluoro-2,2-dinitroethoxymethyl isocyanate and 1.65 g (0.011 mol) of 2-fluoro-2,2-dinitroethanol in 20 ml of methylene chloride at 25° was added a catalytic amount of ferric acetylacetonate (FeAA). The reaction mixture was kept at 35° for 20 min and distilled in a molecular still at 155–160° (25 μ) to give 3.5 g of viscous colorless oil, $n^{26}D$ 1.4585.

Anal. Calcd for $C_6H_7N_5F_2O_{11}$: C, 19.8; H, 1.9; N, 19.3; F, 10.5. Found: C, 19.6; H, 1.8; N, 19.3; F, 10.2.

The infrared spectrum showed major absorption peaks at 2.90, 5.72, 6.25, 7.62, 8.10, 8.95, 11.79, 12.52, and 13.02 μ.

Proton nmr ($CDCl_3$): δ 6.25 (t, J = 7.5 Hz, NH), 5.30 (d, J_{HF} = 16 Hz), 4.72 [d, J_{HF} = 17.8 Hz, $OCH_2CF(NO_2)_2$], and 4.83, (d, J = 7.5 Hz, NCH_2). Fluorine nmr: ϕ 110.5 (t, J_{HF} = 15.6 Hz) and ϕ 111.0 (t, J_{HF} = 17.4 Hz).

Bis(2-fluoro-2,2-dinitroethoxymethylcarbamate) of 2,2-Dinitropropanediol.—Bis(2-fluoro-2,2-dinitroethoxymethylcarbamate)of 2,2-dinitropropanediol was obtained quantitatively in the reaction of 2,2-dinitropropanediol with 2 mol of 2-fluoro-2,2-dinitroethoxymethyl isocyanate following the above procedure. The material, a viscous oil, was purified only by drying at 100° (0.1 mm).

Anal. Calcd for $C_{11}H_{14}N_8F_2O_{18}$: C, 22.6; H, 2.4; N, 19.2; F, 6.5. Found: C, 22.4; H, 2.3; N, 19.0; F, 6.4.

The infrared spectrum showed the following major absorption peaks 2.93, 5.76, 6.30, 7.68, 8.20, 9.35, 11.82, and 12.56 μ.

Proton nmr (d_6-acetone): δ 7.90 (t, J = 7.3 Hz, NH), 5.22 [s, $CH_2C(NO_2)_2CH_2$], 4.97 [d, J_{HF} = 18 Hz, $OCH_2CF(N)_2)_2$], and 4.92 (d, J_{NH-CH_2} = 7 Hz, NCH_2). Fluorine nmr: ϕ 110.8 (t, J_{HF} = 17.7 Hz).

N,N'-Bis(2-fluoro-2,2-dinitroethoxymethyl)urea.—A suspension of 0.7 g of 2-fluoro-2,2-dinitroethoxymethyl isocyanate in 5 ml of water was stirred at 25–30° for 45 min. The product, a viscous oil, extracted with 10 ml of methylene chloride, was purified only by drying at 100° (0.1 mm), wt 0.6 g, $n^{23}D$ 1.4703.

Anal. Calcd for $C_7H_{10}N_6F_2O_{11}$: C, 21.4; H, 2.6; N, 21.4; F, 9.8. Found: C, 21.1; H, 2.4; N, 20.6; F, 9.9.

2-(2-Fluoro-2,2-dinitroethoxy)ethyl Nitrate.—A solution of 4.0 g of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether in 10 ml of 70% nitric acid was allowed to stand at 25° for 16 hr. The product was added to 50 ml of ice water and extracted with 30 ml of methylene chloride to give 2.5 g of semisolid. The material was treated with 50 ml of 10% aqueous sodium bicarbonate and extracted with 10 ml of methylene chloride to give 0.5 g of a colorless liquid. [The amount of the material was too small to determine the boiling point, estimated bp 85–90° (0.1 mm)].

Anal. Calcd for $C_4H_6N_3FO_8$: C, 19.8; H, 2.5; N, 17.3; F, 7.8. Found: C, 19.8; H, 2.6; N, 16.8; F, 7.8.

Proton nmr ($CDCl_3$): δ 4.67 [d, J_{HF} = 18 Hz, $OCH_2CF(NO_2)_2$] and 3.9–4.6 (AA'BB' pattern, CH_2).

2-Fluoro-2,2-dinitroethoxyacetone.—Sulfuric–chromic acid solution was prepared by adding 8.7 ml of concentrated sulfuric acid to a solution of 10.0 g of chromium trioxide in 19 ml of water following the procedure of Eisenbraun.[19] The chromic acid solution was added dropwise, over a period of 1 hr, at 25–28° to a stirred solution of 15.9 g (0.075 mol) of 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether in 190 ml of acetone until the color of Cr^{6+} persisted (only *ca* 2/3 of the chromic acid solution was required). The reaction mixture was stirred at 25° for 1.5 hr and the excess Cr^{6+} was destroyed with few drops of 2-propanol. The mixture was filtered and the filter cake was washed with two 35-ml portions of acetone. The combined filtrate and washings were stirred with 10 g of sodium bicarbonate for 25 min, filtered, and concentrated to *ca.* 40 ml. Extraction with 45 ml of methylene chloride and distillation gave 14.5 g (92% yield) of 2-fluoro-2,2-dinitroethoxyacetone, bp 70° (0.05 mm), $n^{23}D$ 1.4335.

Anal. Calcd for $C_5H_7N_2FO_6$: C, 28.6; H, 3.3; N, 13.3; F, 9.0. Found: C, 28.4; H, 3.4; N, 13.2; F, 9.1.

Proton nmr (CCl_4): δ 2.12 (s, CH_3), 4.35 (s, CH_2CO), and 4.74 [d, J_{HF} = 17.4 Hz, $OCH_2CF(NO_2)_2$]. Fluorine nmr: ϕ 109.3 (t, J_{HF} = 17.3 Hz).

2-Fluoro-2,2-dinitroethoxyacetone Oxime.—A mixture of 2.3 g (0.033 mol) of hydroxylamine hydrochloride, 2.1 g (0.01 mol) of 2-fluoro-2,2-dinitroethoxyacetone, and 4.53 g (0.033 mol) of sodium acetate trihydrate in 85 ml of absolute ethanol was refluxed for 45 min, and then *ca.* 70 ml of ethanol was removed at 25° (25 mm). The residue was added to 100 ml of ice water and the product was extracted with 40 ml of methylene chloride and dried at 100° (0.1 mm) to give 2.15 g (95.5% yield) of colorless liquid which was not further purified.

Anal. Calcd for $C_5H_8N_3FO_6$: C, 26.7; H, 3.6; N, 18.7; F, 8.4. Found: C, 26.5; H, 3.4; N, 18.5; F, 8.3.

Proton nmr (CCl_4): δ 4.52 [d, J_{HF} = 17.0 Hz, $OCH_2CF(NO_2)_2$], 4.20 (s, CH_2), 1.91 (s, CH_3), and δ 9.75 (s, NOH). Fluorine nmr: ϕ 108.7 (t, J_{HF} = 17.0 Hz).

2,2-Dinitropropyl 2-Fluoro-2,2-dinitroethyl Ether.—To a stirred solution of 0.9 g of 2-fluoro-2,2-dinitroethoxyacetone oxime in 25 ml of methylene chloride was added dropwise over a period of 10 min at 0–3° with cooling 5 ml of 100% nitric acid. The deep blue solution was stirred for 45 min and then to it was added dropwise (5 min) 4 ml of 32% hydrogen peroxide. After 15 min, the pale yellow solution was washed with two 25-ml portions of ice water. The methylene chloride solution was distilled in a molecular still at 75° (10 μ) to give 0.45 of colorless liquid. The proton nmr spectrum showed that the distillate was contaminated with 2-fluoro-2,2-dinitroethoxyacetone (13%), which could not be removed by fractionation. An analytical sample of the ether was obtained by washing the mixture with carbon tetrachloride, where the ketone is much more soluble than the ether.

Anal. Calcd for $C_5H_7N_4FO_9$: C, 21.0; H, 2.4; N, 19.6; F, 6.6. Found: C, 21.0; H, 2.4; N, 18.6; F, 6.6.

Proton nmr (d_6-acetone–$CDCl_3$): δ 4.95 [d, J_{HF} = 16.8 Hz, $OCH_2CF(NO_2)_2$], 4.65 (s, CH_2) and 2.20 (s, CH_3). Fluorine nmr: ϕ 109.2 (t, J_{HF} = 17.1 Hz).

Bis(2-fluoro-2,2-dinitroethyl) Sulfite.[18]—A solution of 3.6 g (0.03 mol) of thionyl chloride in 20 ml of methylene chloride was added at 25–28° to a stirred solution of 9.26 g (0.06 mol) of 2-fluoro-2,2-dinitroethanol and 5.0 g (0.063 mol) of pyridine in 50 ml of methylene chloride. After standing at 25° for 16 hr, the product was washed with 100 ml of cold 2% sulfuric acid and distilled to give 6.8 g (70% yield) of bis(2-fluoro-2,2-dinitroethyl) sulfite, bp 100–105° (25 μ) (moleclar still), $n^{23}D$ 1.4607.

Anal. Calcd for $C_4H_4N_4F_2SO_{11}$: C, 13.6; H, 1.1; N, 15.8; F, 10.7. Found: C, 13.4; H, 1.0; N, 15.2; F, 10.6.

Proton nmr ($CDCl_3$): a pair of very closely spaced doublets centered at 307 Hz. Fluorine nmr: ϕ 110.0 (t, J_{HF} = 16.2 Hz).

Fractionation of methylene chloride removed in the purification of the sulfite gave 0.5 g of 2-fluoro-2,2-dinitroethyl chloride, identified by comparing its infrared spectrum with that of an authentic sample (see below).

(19) E. J. Eisenbraun, *Org. Syn.*, **45**, 28 (1965).

2-Fluoro-2,2-dinitroethyl Chloride.—To a stirred solution of 6.24 g (0.04 mol) of 2-fluoro-2,2-dinitroethanol and 3.95 g (0.04 mol) of pyridine in 50 ml of methylene chloride was added dropwise at 0–5° with cooling 2.7 g (0.02 mol) of sulfuryl chloride. No visible reaction. After 45 min, the reaction mixture was warmed to 25° and was allowed to stand for 7 days. The solution was washed with 200 ml of ice-cold 1% sulfuric acid and distilled to give 3.4 g of 2-fluoro-2,2-dinitroethyl chloride, bp 22–23° (0.2 mm), n^{23}D 1.4270.

Anal. Calcd for $C_2H_2N_2ClFO_4$: C, 13.9; H, 1.2; N, 16.2; F, 11.0. Found: C, 13.8; H, 1.0; N, 15.4; F, 11.1.

Differential thermal analysis showed an endotherm at 156°, the boiling point of the compound.

Proton nmr (CCl_4): δ 4.60 (d, J_{HF} = 16.1 Hz). Fluorine nmr: ϕ 108.2 (s, broad).

Tris(2-fluoro-2,2-dinitroethyl) Borate.—A mixture of 10.8 g (0.07 mol) of 2-fluoro-2,2-dinitroethanol and 2.92 g (0.02 mol) of triethyl borate was heated in a distillation apparatus protected from the atmospheric moisture at 95° for 3 hr, and then ethanol was distilled at reduced pressure. The remaining solid was recrystallized from methylene chloride to give 8.9 g of white crystalline solid which hydrolyzed slowly when exposed to the moist air.

Anal. Calcd for $C_6H_6N_6BF_3O_{15}$: C, 15.3; H, 1.3; N, 17.9; F, 12.1. Found: C, 15.0; H, 1.3; N, 16.9; F, 11.7.

Proton nmr (CH_3CN): δ 4.96 (d, J_{HF} = 16.5 Hz). Fluorine nmr: ϕ 111.9 (t, J_{HF} = 16.2 Hz).

2-Fluoro-2,2-dinitroethyl Nitrate.—To a stirred mixture of 12 ml of 100% nitric acid and 12 ml of concentrated sulfuric acid was added dropwise (5 min) at 0–5° 7.7 g of 2-fluoro-2,2-dinitroethanol. The reaction mixture was stirred for 15 min, added to 100 g of crushed ice, a water-insoluble liquid separated, and washed with 50 m of water, wt 7.5 g (75% yield), bp 62–63° (5 mm), n^{23}D 1.4377 [lit.[4] bp 62–62.5° (5–6 mm), n^{20}D 1.4372].

Registry No.—2-Fluoro-2,2-dinitroethanol, 17003-75-7; allyl 2-fluoro-2,2-dinitroethyl ether, 25171-99-7; 2,2-dinitropropyl methyl ether, 5917-65-7; 2,2-dinitropropyl methyl sulfate, 25172-01-4; 1,3-dimethoxy-2,2-dinitropropane, 25172-02-5; methyl 3-methoxy-2,2-dinitropropyl sulfate, 25172-03-6; 2-fluoro-2,2-dinitroethyl ethyl carbonate, 25172-14-9; 2-fluoro-2,2-dinitroethyl oxalyl chloride, 25172-15-0; 2-fluoro-2,2-dinitroethyl iminodicarboxylate, 25172-16-1; 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether, 25172-17-2; 2-fluoro-2,2-dinitroethanol *p*-toluenesulfonate, 25172-18-3; 2-fluoro-2,2-dinitroethyl 2-hydroxypropyl ether, 25172-19-4; 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether *p*-toluenesulfonate, 25172-20-7; 2-fluoro-2,2-dinitroethyl glycidyl ether, 25184-14-9; 4-(2-fluoro-2,2-dinitroethoxy)-3-hydroxybutene 1,2-oxide, 25172-21-8; 2-fluoro-2,2-dinitroethoxyacetic acid, 25172-22-9; 2-fluoro-2,2-dinitroethoxyacetyl chloride, 25172-23-0; 2-fluoro-2,2-dinitroethyoxymethylisocyanate, 25172-24-1; 2-fluoro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethoxyacetate, 25172-25-2; 2,2-dinitropropyl 2-fluoro-2,2-dinitroethoxyacetate, 25172-26-3; bis(2-fluoro-2,2-dinitroethoxyacetate), 25172-27-4; 2-fluoro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethoxymethylcarbamate, 25172-28-5; bis(2-fluoro-2,2-dinitroethoxymethylcarbamate), 25172-29-6; N,N′-bis(2-fluoro-2,2-dinitroethoxymethyl)urea, 25172-30-9, 2-(2-fluoro-2,2-dinitroethoxy)ethyl nitrate, 25172-31-0; 2-fluoro-2,2-dinitroethoxyacetone, 25172-32-1; 2-fluoro-2,2-dinitroethoxyacetone oxime, 25172-33-2; 2,2-dinitropropyl 2-fluoro-2,2-dinitroethyl ether, 25172-34-3; bis(2-fluoro-2,2-dinitroethyl) sulfite, 24590-46-3; 2-fluoro-2,2-dinitroethyl chloride, 25172-36-5; tris(2-fluoro-2,2-dinitroethyl) borate, 25172-37-6.

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Disproportionation of 3,3-Difluorotetrachloropropene. Application of the Hard and Soft Acids and Bases Principle to Organic Halogen Compounds[1]

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Product distributions from the reaction of 3,3-difluorotetrachloropropene (**1a**) at 50° with aluminum chloride and bromide, titanium tetrachloride, and antimony pentachloride were determined. The aluminum and titanium halides were converted to the fluorides by the reaction; the aluminum fluoride so formed was shown to catalyze the disproportionation of **1a**. 1-Bromo-1,2-dichloro-3,3,3-trifluoropropene (**8**) was formed in the reaction with aluminum bromide and was also independently synthesized. Formation of **8** is rationalized in terms of the hard and soft acids and bases (HSAB) concept; numerous examples from the literature are similarly interpreted. The reactions of $AlCl_3$ with 3-fluoropentachloropropene, 3,3,3-trifluorotrichloropropene, and 1,1-difluorotetrachloroethane were also investigated.

The disproportionation of polyhalogenated aliphatic fluorides has long been recognized, and is of commercial significance, particularly in the case of the fluorochloromethanes, as demonstrated by the profusion of patents in this area. It is also well known that aluminum chloride, a catalyst frequently employed in the disproportionation of fluorochloro compounds, is unsuitable for use in Friedel–Crafts alkylations involving aliphatic fluorides, because of its tendency to abstract organically bound fluorine. Information in the literature which contributes to the general understanding of these processes is meager, however, and little, if any, attempt has been made in the past to determine the extent to which the two occur simultaneously.

The question of the relative effectiveness of various Lewis acids in these two reactions also exists. In the disproportionation of 3,3-difluorotetrachloropropene (**1a**), it is reported that catalytic activity decreases in the sequence[3] antimony pentachloride > titanium tetrachloride > aluminum bromide, aluminum chloride > ferric chloride. The order of activity was determined by the length of time required to produce a

(1) Taken in part from the Ph.D. Thesis of G. C. B., The University of Iowa, Iowa City, Iowa, 1970.

(2) Shell Foundation Fellow, 1965–1966.

(3) M. Prober, *J. Amer. Chem. Soc.*, **76**, 4189 (1954).

TABLE I

REACTION OF PERHALO OLEFINS WITH METAL HALIDES AT 50°

Reactants					Products				
Expt	mmol	Olefin	mmol	Metal halide	Time, hr	TFP, mmol	DFP, mmol	MFP, mmol	HCP, mmol	Fluorine balance, mmol
1	100	1a	10.0	$AlCl_3$	12	48.0	9.4	8.7	33.9	−28.5
2	100	1a	10.0	$SbCl_5$	12	8.5	86.7	4.8	0.0	3.7
3[a]	100	1a	10.0	$SbCl_5$	36	16.3	70.4	9.0	1.1	1.3
4	100	1a	9.8	$TiCl_4$	12	3.0	68.4	12.6	16.0	−41.6
5[b]	100	1a	10.0	$AlBr_3$	12	45.2	3.1	4.7	28.5	−28.6[c]
6	105	1a	9.9	$FeCl_3$	12	0.0	100.0	0.0	0.0	0.0
7	100	1a	10.0	AlF_3	12	0.0	100.0	0.0	0.0	0.0
8[d]	20	1a	2.0	BBr_3	12	0.0	19.9+	0.0	0.0	
9[e]	100	7a	10.0	$AlCl_3$	12	90.0	4.0	1.0	5.0	−21.0
10	100	3a	10.0	$AlCl_3$	12.5	14.8	12.1	16.3	56.8	−14.9[f]

[a] Unknown material eluted after 5a, ~3.2 mmol. [b] A total of ~17.9 mmol of unknown products was formed. See text. [c] Fluorine content of 8 and 9 included. [d] A trace (0.1 mmol or less) of material was eluted after 1a. [e] Approximate values; a base-line shift occurred during each analysis of this mixture. [f] Initial fluorine content, 100 mmol.

detectable quantity of the lower boiling 3,3,3-trifluorotrichloropropene (7). Formation of this material was indicated by a drop in the reflux temperature at the head of a fractionating column over a flask of the reactants. Stoichiometrically, the disproportionation may be formulated as below.

$$2CCl_2{=}CClCClF_2 \longrightarrow CCl_2{=}CClCF_3 + CCl_2{=}CClCCl_2F \quad (1)$$
$$2CCl_2{=}CClCCl_2F \longrightarrow CCl_2{=}CClCCl_3 + CCl_2{=}CClCClF_2$$

In the light of other work,[4] the aluminum halides appear too late in the above series of metal halides; further, the method[3] described provides no information about the extent of substitution. Such information would be of interest since, in the case of aluminum halides, substitution would produce aluminum fluoride, which can be a suitable catalyst for both the disproportionation[5] and fluorination[6] of fluorochloroalkanes in the vapor phase. Catalysts of this sort can be prepared by the gas phase reaction of hydrogen fluoride with aluminum chloride,[5] or fluorochloroethanes with alumina at elevated temperatures.[7] The generation *in situ* of catalytically active aluminum fluoride in the reaction of **1a** at reflux temperature or below seems possible. For these reasons a careful reexamination of this reaction was undertaken.

Results and Discussion

When **1a** was prepared by the usual Swarts reaction of hexachloropropene with antimony trifluoride it contained a significant amount (*ca.* 5%) of 2,3,3-trichloroacrylyl fluoride.

It was first thought that **1a** so prepared was contaminated with antimony salts.[8] The recommended treatment with quinoline[8] failed to remove the contaminant, however, as did extraction with ten portions of 1 *N* hydrochloric acid which surely would have removed dissolved antimony salts from such a nonpolar medium.[9] Careful analysis by gas–liquid partition chromatography (glpc) on a silicone rubber column indicated a minor component eluted close to **1a**. The impurity was isolated and characterized as 2,3,3-trichloroacrylyl fluoride; it was conveniently removed from **1a** by treatment with ammonia.

The acid fluoride is believed to have arisen from the reaction of antimony oxide contained in the antimony trifluoride according to reaction 2.

$$3CCl_2{=}CClCCl_3 + Sb_2O_3 \xrightarrow{SbCl_3} 3CCl_2{=}CClCOCl + 2SbCl_3 \quad (2)$$
$$3CCl_2{=}CClCOCl + SbF_3 \longrightarrow 3CCl_2{=}CClCOF + SbCl_3$$

The reaction formulated has a well-known parallel in Knox and Tyree's method of preparation[10] of anhydrous inorganic halides by the reaction of carbon tetrachloride with a metal oxide. Indeed, **5a** has been substituted for carbon tetrachloride in such reactions,[11] although no reaction is reported to occur with antimony pentoxide.[12] It would seem probable that the metal halide would catalyze this exchange by polarization of the carbon–chlorine bond, and perhaps also by formation of an oxychloride soluble in the halide reaction mixture. Similar reactions of organic halides with sulfur oxides in the presence of antimony halides have been reported.[13]

Substitution.—Product distributions in Table I from the various reaction mixtures were obtained by glpc; the organic fluorine balance was calculated from the glpc data as the difference in total organic fluorine content (as mmol F^-) between starting olefin and products, *i.e.*, 3(7) − 2(**1a**) + **3a** − initial fluorine content.

Examination of Table I shows that both aluminum chloride and titanium tetrachloride are converted to the corresponding fluorides in reaction with **1a**, whereas antimony pentachloride does not undergo such substitution. In the case of **1a** and aluminum chloride,

(4) D. J. Burton, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1961.

(5) (a) C. B. Miller, U. S. Patent 2,637,748 (1953); *Chem. Abstr.*, **48**, 2755 (1954). C. B. Miller and J. D. Calfee, U. S. Patent 2,676,996 (1954); *Chem. Abstr.*, **49**, 1770 (1955). (b) H. Agahigian and C. Woolf, German Patent 1,139,831 (1962); *Chem. Abstr.*, **58**, 10075 (1963).

(6) C Woolf and C. B. Miller, U. S. Patent 2,673,139 (1954); *Chem. Abstr.*, **48**, 10261 (1954). J. D. Calfee and C. B. Miller, U. S. Patent 2,681,267 (1954); *Chem. Abstr.*, **48**, 10958 (1954). C. B. Miller and J. D. Calfee, U. S. Patent 2,748,177 (1956); *Chem. Abstr.*, **51**, 455 (1957).

(7) (a) M. Hauptschein and A. H. Fainberg, U. S. Patent 3,138,559 (1964); *Chem. Abstr.*, **61**, 8188 (1964). (b) British Patent 921,796 (1963); *Chem. Abstr.*, **59**, 9788 (1963).

(8) W. T. Miller, Jr., and A. H. Fainberg, *J. Amer. Chem. Soc.*, **79**, 4164 (1957).

(9) G. H. Morrison and H. Freiser, "Solvent Extraction in Analytical Chemistry," Wiley, New York, N. Y., 1957, p 127.

(10) K. Knox, S. Y. Tyree, Jr., R. D. Srivastana, V. Norman, J. Y. Bassett, Jr., and J. H. Holloway, *J. Amer. Chem. Soc.*, **79**, 3358 (1957).

(11) A. B. Bardawil, F. N. Collier, Jr., and S. Y. Tyree, Jr., *J. Less-Common Metals*, **9**, 20 (1965).

(12) W. Porterfield, Ph.D. Thesis, University of North Carolina, Chapel Hill, N. C., 1962.

(13) (a) R. F. Sweeney, B. Veldhuis, E. E. Gilbert, L. G. Anello, R. J. DuBois, and W. J. Cunningham, *J. Org. Chem.*, **31**, 3174 (1966). (b) The reaction of 1,1-dichloroethane with sulfur dioxide in the presence of antimony pentafluoride is mentioned by G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Amer. Chem. Soc.*, **90**, 2587 (1968).

precipitation of chloride ion in the aqueous hydrolysate showed substitution to be essentially complete after 1 hr. Thus disproportionation which occurred after that time was almost certainly catalyzed by aluminum fluoride.

These results may be explained in terms of Pearson's concept of hard and soft acids and bases (HSAB).[14] Since aluminum and titanium cations are hard,[14a] they will combine preferentially with hard anions, *i.e.*, fluoride ion. The difference in activity of these two Lewis acids points out the difference between acid *strength* and acid hardness. Although both aluminum chloride and titanium tetrachloride are hard, and both chlorides are apparently *strong* acids since substitution requires carbon–fluorine bond cleavage, there is a marked difference in strength between the resulting aluminum and titanium fluorides. Whereas aluminum fluoride produces considerable disproportionation, as evidenced by the amount of **7** formed, relatively little **7** is produced in the reaction catalyzed by titanium, and the products are predominantly those resulting from substitution, *i.e.*, **3a** and **5a**.

Antimony pentachloride presents a different situation. Apparently it is not a particularly hard acid, since it preferentially combines the softer chloride ion (relative to F^-). This idea is supported by the fluorination of organic chlorine compounds by antimony pentafluoride.[15] Antimony pentachloride produces substantial disproportionation, however, and must therefore be a *strong* Lewis acid. The absence of hexachloropropene in the 12-hr reaction is attributed to consumption of this compound by side reactions with antimony salts. The reaction of water with the solid hexachloropropene–antimony pentachloride complex is reported to lead to hydrolysis of **5a**, whereas hydrolysis of the complex of aluminum chloride with **5a** regenerates hexachloropropene.[16]

The hydrolysis may be envisioned as proceeding by attack of water on the metal to displace chloride ion to yield **5a**, an intermediate metal oxychloride, and hydrogen chloride. In the case of antimony, reaction between hexachloropropene (or the pentachloroallyl cation) and antimony oxychloride (or oxide) would give 2,3,3-trichloroacrylyl chloride in a manner analogous to reaction 2 above.[17]

This reaction may be viewed as a competition between Sb^{5+} and $-C^+Cl_2$ for the hard oxide ion; formation of the acyl halide indicates that $-C^+Cl_2$ is harder. The resemblance to fluorination of the $-CCl_3$ group by antimony trifluoride, in which $-C^+Cl_2$ and Sb^{3+} compete for the hard F^-, may be noted. The unknown material formed in the 36-hr reaction is believed to be octachloropropane formed by the reduction of the antimony to the trichloride. Similar reductions have been previously reported.[11,12]

Since boron halides are usually considered to be hard, reaction of boron tribromide with **1a** might be expected to give boron trifluoride and organic bromide compounds. Essentially no reaction occurs, however, which implies that boron tribromide is a relatively weak Lewis acid; this point is discussed more fully in the following section.

That substitution occurs with aluminum bromide is obvious from the formation of bromopropenes. The amount and order of elution of the unknown products for a typical experiment were 7.8% after **7**, 0.5% after **1a**, 0.4% after **3a**, 9.2% after **5a**. The formation of a bromopropene having a retention time less than **1a** was perplexing, since these materials elute in order of boiling point on a silicone rubber column, and substitution of bromine for either chlorine or fluorine would result in an increased boiling point. Small amounts of the bromopropenes eluted immediately after **7** and **1a** were isolated. The infrared spectrum of each showed the presence of the trifluoromethyl group, as well as unsaturation. The spectra, particularly that of the lower boiling component, were quite similar to the spectrum of **7**, except that the bands were shifted to longer wavelength, which is characteristic of substitution of bromine for chlorine in such systems.[18] The two compounds were thus assigned the structures $CF_3CCl{=}CClBr$ and $CF_3CCl{=}CBr_2$. The infrared spectrum and glpc retention time of 1-bromo-1,2-dichloro-3,3,3-trifluoropropene (**8**), synthesized by an independent route, were identical with that of the unknown eluted between **7** and **1a**. The evidence available does not exclude the possibility that materials isolated from the reaction of aluminum bromide with **1a** may contain bromine in the 2 position; substitution in the 2 position seems unlikely, however.

Disproportionation.—From the preceding discussion and the data in Table I, it is apparent that the order of activity in the disproportionation of **1a** is aluminum chloride, aluminum bromide (aluminum fluoride) > antimony pentachloride > titanium tetrachloride (titanium tetrafluoride) > boron tribromide, ferric chloride, commercial aluminum fluoride (inactive). That the aluminum halides (excluding commercial aluminum fluoride) are clearly more active than the others listed is further shown by the fact that aluminum chloride with 1,1-difluorotetrachloroethane gave both disproportionation and substitution reactions. The rapidity and extent of these reactions were very similar to those of **1a** with aluminum chloride; this result was unexpected since it was thought that resonance stabilization of **2** would make the reaction of **1a** more facile. The difference in reactivity between **1a** and the ethane was obvious in the case of antimony pentachloride and titanium tetrachloride, since 1,1-difluorotetrachloroethane did not undergo reaction in their presence at 50°

The activity sequence above may be viewed as a qualitative scale of Lewis acidity. The positions of aluminum and antimony halides is consistent with the finding[16] that the 1:1 complex of **5a** and aluminum chloride exists as the pentachloroallyl cation (**4**) in methylene chloride solution, whereas with antimony pentachloride **5a** in solution is largely uncomplexed. Further, it is reported[19] that no complex formation

(14) (a) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963). (b) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

(15) R. A. Davis, U. S. Patent 3,201,483 (1965); *Chem. Abstr.*, **63**, 13074 (1965).

(16) R. West and P. T. Kwitowski, *J. Amer. Chem. Soc.*, **88**, 5280 (1966).

(17) (a) The hydrolysis of 2-fluorotrichlorocyclopropene to 2,3-dichloroacrylyl fluoride with antimony pentachloride and moisture is reported in ref (18b). (b) The presence of benzoyl chloride in the product mixture from the reaction of $C_6H_5CF_2Cl$ with antimony pentachloride followed by hydrolysis is mentioned in ref 1.

(18) (a) R. West and P. T. Kwitowski, *J. Amer. Chem. Soc.*, **90**, 4697 (1968); (b) S. W. Tobey and R. West, *ibid.*, **88**, 2481 (1966).

(19) R. West, A. Sado, and S. W. Tobey, *ibid.*, **88**, 2488 (1966).

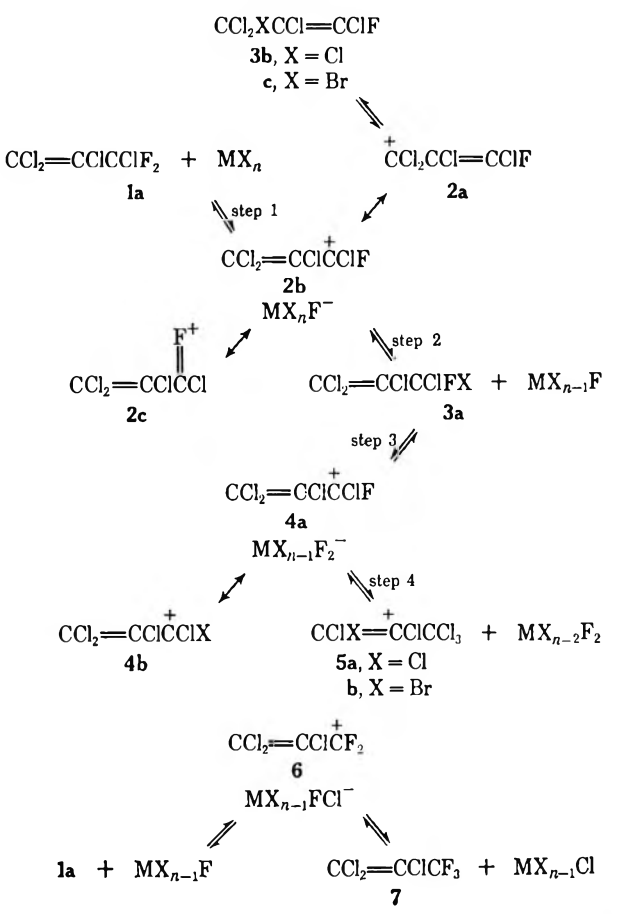
occurs between tetrachlorocyclopropene and the boron halides (or antimony trichloride), although the trichlorocyclopropenium cation was formed upon reaction with the chlorides of Al^{III}, Sb^{V}, and Fe^{III}.

Several reasons might account for this conflict with the literature activity sequence. An obvious difference between the previous study and this one is that of temperature, 128 and 50°, respectively. Although it is unlikely that this difference would alter the order of the activity sequence, it might account for the discrepancy in the case of ferric chloride.

Stirring was found to have a profound effect on the rate of disproportionation of **1a** with aluminum halides. With vigorous stirring the salt was soon dispersed as fine particles, whereas a gummy mass resulted from inefficient stirring. The surface area of the salt would be markedly different in the two cases, and would be expected to be of major importance in a heterogeneous reaction of this sort. Although mixtures were efficiently stirred in the present work, stirring is not mentioned in the previous report.

Mechanism.—A straightforward pathway for these reactions is outlined in Scheme I. A similar mechanism

SCHEME I



has been postulated for the vapor-phase disproportionation of dichlorofluoromethane on the basis of a kinetic study.[20] The formation of cation intermediates such as **2**, **4**, and **6** seems reasonable in view of the characterization of **4** as the tetrachloroaluminate and hexachloroantimonate salts.[16] Additional evidence of such cations is indicated by exchange of chlorine in the 1 and 3 positions of **5a** in the presence of aluminum chloride,[21] and the observation by nmr of 1,2,3-trichloropropenium tetrachloroaluminate in methylene chloride,[22] and of a variety of allylic and halogen containing cations.[23]

With titanium and aluminum chlorides, the substitution process illustrated in steps 2 and 4 would continue until the metal is completely fluorinated, and the formation of the metal fluoride would be expected to provide a driving force for step 1. The position of equilibrium for step 1 in the reaction of antimony pentachloride, however, apparently lies well to the left. Step 3 could of course involve MX_n instead of $MX_{n-1}F$.

Resonance stabilization of cations by donation from fluorine[24] should be significant, and thus canonical form **2c** would be more important than **2a**. This reasoning is consistent with the report[3] that the disproportionation of **1a** with antimony pentachloride does not give 1-fluoropropenes, and that only the allylic chlorofluoro group was involved in the reaction. Hence, it would seem that only **3a** would be formed. A similar argument would hold in the case of **6**.

This mechanism seems fully adequate for the reactions of antimony pentachloride, titanium tetrachloride, and aluminum chloride; unfortunately, it does not readily account for the formation of $CF_3CCl{=}CClBr$ (**8**) and $CF_3CCl{=}CBr_2$ (**9**) from the reaction of aluminum bromide. Stepwise substitution of **1a** would lead first to $CFClBrCCl{=}CCl_2$, and then to $CClBr{=}CCl\text{-}CCl_2Br$ (**10**) and $CClBr_2CCl{=}CCl_2$ (**11**). It seems unrealistic to rationalize the formation of a substantial amount of **8** in terms of a random halogen exchange that would lead to the complete allylic fluorination of **10**. Such a process might seem plausible if **8** were present as only a trace amount, as is **9**, but that is not the case. An intermediate 1-bromo-3-fluoropropene such as **12** appears to be necessary to a plausible rationalization of the formation of **8**, since such an intermediate would readily disproportionate to **8**. An intermediate of this sort probably would not arise by Scheme I in quantities consistent with the final concentration of **8**, since an allylic shift to give a 1-bromo compound would not be expected to occur until removal of fluorine from the molecule were complete (step 4, X = Br).

Further, **12** must arise by yet another allylic shift in **3c**. Such rearrangements would be expected intuitively to be controlled by thermodynamic rather than kinetic factors, so that further rearrangement of **3c** would seem to conflict with any rationalization for its formation. However, **12** appears to be essential to a reasonable mechanism which gives rise to **8** *via* the reaction below; this process would require **12a** to be formed

$$3CClBr{=}CClCFClX \longrightarrow 8 + CClBr{=}CClCCl_2X + CClBr{=}CClCClX_2$$

12a, X = Cl
b, X = Br

(20) E. Cavaterra, V. Fattore, and N. Giordano, *J. Catal.*, **8**, 137 (1967).

(21) F. Boberg, K. Kirchoff, and G. R. Schultze, *J. Label. Compounds*, **3**, 293 (1967); *Chem. Abstr.*, **68**, 95052 (1968).

(22) K. Kirchoff, F. Boberg, and D. Friedman, *Tetrahedron Lett.*, **25**, 2935 (1968); *Chem. Abstr.*, **69**, 76354 (1968).

(23) (a) G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Amer. Chem. Soc.*, **90**, 2587 (1968); (b) G. A. Olah and J. M. Bollinger, *ibid.*, **90**, 947 (1968); G. A. Olah and Paul E. Petersen, *ibid.*, **90**, 4675 (1968).

(24) J. Hine, *ibid.*, **85**, 3239 (1963); J. Hine and F. E. Rogers, *ibid.*, **90**, 6701 (1968).

in at least 75% yield in order to give the quantity of **8** found experimentally. A 1-bromo-3,3-difluoropropene such as **13** formed in half that yield would give the amount of **8** found.

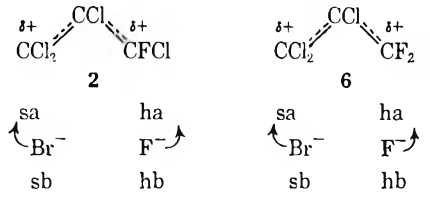
$$3CClBr{=}CClCF_2X \longrightarrow 2CClBr{=}CClCF_3 + CClBr{=}CClCX_3$$

13a, X = Cl
b, X = Br

Most of the theoretical considerations which conflict with the formation of **12** apply to **13** as well; another more serious objection may be raised against postulation of this intermediate, however. Since the data in Table I indicate that conversion of aluminum bromide to the fluoride is complete, and since the analogous reaction with aluminum chloride is essentially complete in 1 hr, direct conversion to the fluoride would be more attractive from the standpoint of both thermodynamics and simplicity. Complete halogen exchange between aluminum bromide and perchloroolefins does occur,[18] however, and it is likely that the activation energy for the bromine–chlorine exchange would be lower than that of bromine for fluorine.

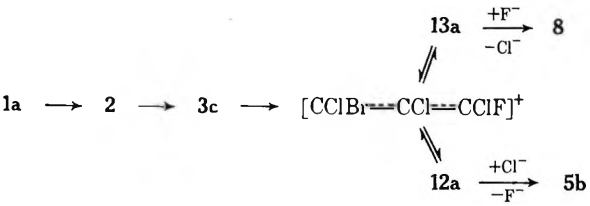
The exclusive initial coordination of fluorine by aluminum chloride has been demonstrated[25] in the rearrangement of $CF_2ClCFCl_2$; radioactive chlorine from the aluminum chloride was not contained by the rearranged CF_3CCl_3. This point is discussed more fully below.

From the involuted deduction above it is apparent that need exists for a simple, generally applicable concept which will account for the unexpected formation of **8**. In fact, the principle of hard and soft acids and bases (HSAB) advanced by Pearson[14] provides an explanation for the formation of **8**.



Intermediate ion **2** is seen as an ambident electrophile, in which $-C^+Cl_2$ is the softer electrophilic center. Thus, whenever opportunity exists, attack by F^-, a hard base (hb), will occur at the harder $-C^+FCl$, whereas Br^-, a soft base, will preferentially attack the *gem*-dichloro group. The most likely rationalization for the formation of **8** then would be the rapid initial reaction of aluminum bromide with **1a** to give **2** which is attacked by bromide yielding **3c**. This compound reacts further as shown in Scheme II. Ion **6** would not

SCHEME II



be expected to play a significant role in the formation of **8** because initial attack of aluminum bromide would be expected to occur on fluorine.

Since **2** is attacked at $-C^+Cl_2$ by the soft Br^-, and at $-C^+FCl$ by the hard F^-, one might wonder whether the borderline base Cl^- would show a clear preference for one of these electrophilic centers. That is, might not attack of Cl^- on **2** lead to **3b** just as attack by Br^- yields **3c**? Examination of the infrared spectra of the product mixtures from the reaction of **1a** with Al^{III}, Ti^{IV}, and Sb^V chlorides, and from the reaction of aluminum chloride with **7**, failed to show the characteristic fluoroalkene absorption in the 1800–1600-cm^{-1} region. No rearranged olefins such as **3b** have been reported[3,8,26] in the reactions or preparation of **1a**.

HSAB and Other Systems.—In support of this mechanism predicted by the HSAB principle, it may be seen that many examples from the literature, which have been incompletely understood in the past, are more fully explained by this concept. Several similar allylic rearrangements have been reported; rationalization for many of these is lacking, although, as it will be shown, a consistent explanation is provided by HSAB theory.

The fluorination of 1,1,2,3,3-pentachloropropene (**14**) with antimony trifluoride[27] gives the three products indicated below, each in about 25% yield. When anti-

$$\underset{\mathbf{14}}{CCl_2{=}CClCHCl_2} + SbF_3 \longrightarrow CCl_2{=}CClCHF_2 + CHCl{=}CClCClF_2 + CHCl{=}CClCF_3$$
15 **16** **17**

mony pentachloride was added as a catalyst, the rearranged product **17** was formed in 92% yield. These results could be rationalized by the isomerization of **14** to the 1-hydro olefin by antimony pentachloride, except that **14** was unchanged upon treatment of antimony pentachloride alone. Clearly both antimony salts are necessary for the exclusive formation of **17**, although the reason for this requirement is not apparent. The equation below provides an understanding from HSAB concepts.

$$\mathbf{14} \underset{+Cl^-}{\overset{-Cl^-}{\rightleftharpoons}} [CCl_2C{=}CCl{=}CClH]^+ \underset{-F^-}{\overset{+F^-}{\rightleftharpoons}} CCl_2FCCl{=}CClH$$
ha **18** sa **19**

Abstraction of chloride ion by antimony halide gives the ion **18**, as proposed by Whalley and Davis.[27] The $-C^+CCl_2$ group is a harder acid than $-C^+ClH$, owing to replacement of the soft base H^- in the latter by the harder Cl^-. Comparison of the two nucleophiles shows that F^- is harder than Cl^-, so that the former preferentially attacks the harder electrophilic center to give **19**. Further reaction of **19** forms another ambident ion which is attacked by F^- at the harder end, *i.e.*, $-C^+ClF$.

The addition of pentavalent antimony allows formation of a relatively long-lived ion so that the product reflects equilibration between the 1 and 3 positions; this does not occur with antimony trifluoride alone because it is a relatively weak Lewis acid. The fact that **14** is not isomerized by antimony pentachloride alone demonstrates that the limit of the symbiotic effect[14b]

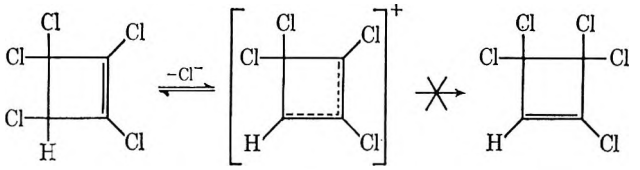
(25) W. T. Miller, Jr., E. W. Fager, and P. H. Griswald, *J. Amer. Chem. Soc.*, **72**, 705 (1950).

(26) A. L. Henne, A. M. Whalley, and J. K. Stevenson, *ibid.*, **63**, 3478 (1941).

(27) A. M. Whalley and H. W. Davis, *ibid.*, **70**, 1026 (1948).

has been reached. That is, the tendency of carbon in $-CCl_2^+$ to surround itself with chlorine atoms to form the $-CCl_3$ group is counteracted by steric effects. The facile rearrangements of 3,3,3-trichloropropene and 2,-3,3,3-tetrachloropropene to 1,1,3-trichloropropene and 1,1,2,3-tetrachloropropene, respectively, reported by Haszeldine follow this pattern, although the suggestion that 3,3-dichloro-3-fluoropropene rearranges to 1,1-difluoro-3-chloropropene seems open to question.[28]

Another similar example is the reaction of 2-chloro-3,3,4,4-tetrafluorocyclobutene with aluminum chloride[29] to give the 3-H isomer **20**. Although **22** should be favored because of the symbiotic effect, the steric interaction of the adjacent *gem*-dichloro groups apparently precludes the formation of **22**.

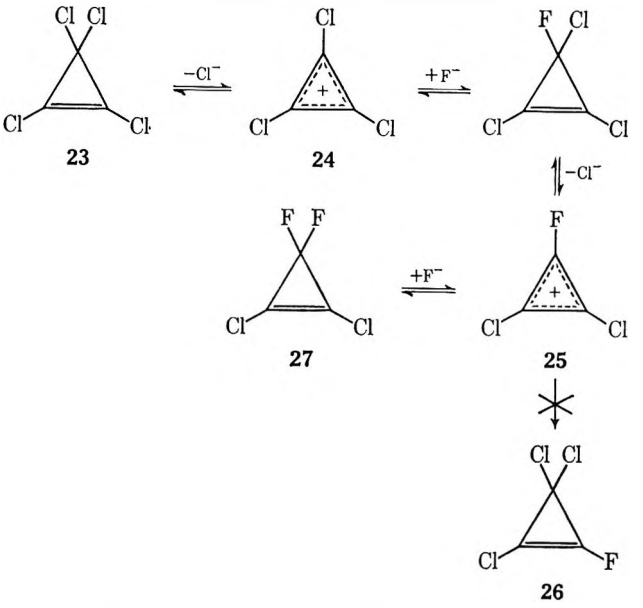


20 **24** **22**

Hine[24] has pointed out the profound effect of clustering of like atoms about the same carbon atom (the symbiotic effect in HSAB terminology) on the behavior of organic fluorine or oxygen compounds and has interpreted this effect in terms of double bond–no bond resonance. From the examples cited above it may be seen that such an effect is usually of less importance than steric factors in the case of allylic chlorine compounds.

It is for this reason that **3b** and **1b** are not formed in readily detectable amounts in the reactions of **1a**, although by naive application of this HSAB concept one would expect these isomeric materials to be formed. It has been pointed out[24] that operation of double bond–no bond resonance (or the symbiotic effect) by halogens other than fluorine would not be likely. It may be seen then that neither approach is wholly successful in the rationalization of the reactions of **1a** since the formation of **8** may not be explained completely in terms of double bond–no bond resonance, and the formation of rearranged products **3b** and **1b** would be predicted by the HSAB concept of symbiosis. The rationalization presented in Scheme II is a fusion of the two approaches: the HSAB concept explains the formation of **12b**; and the concept of double bond–no bond resonance accounts for rearrangement of this compound to **12a**, since structures having the fluorine atom on a saturated carbon atom would be expected to provide more effective double bond–no bond resonance. It should be mentioned that in the absence of the concept of symbiosis, prediction of the position of attack of Cl^- on **2** from the HSAB principle would be difficult, since Cl^- is a borderline base and the difference in hardness between the two electrophilic centers would not be great.

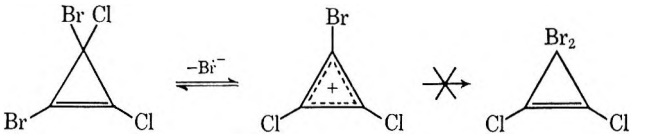
The utility of HSAB concepts, however, is demonstrated in the reaction of tetrachlorocyclopropene with antimony trifluoride.[18b] The substitution would be predicted to cease after the introduction of the second fluorine atom since attack by fluoride ion on intermediate **25** would occur preferentially at the harder $>C^+F$ group. Further reaction would require removal of F^- from **27** which only regenerates **25**. That **26** is not formed by attack of Cl^- on **25** must again be attrib-



23 **24** **27** **25** **26**

uted to more effective double bond–no bond resonance by fluorine at a saturated carbon atom. Tobey and West rationalized the behavior of **23** in this reaction in terms of double bond–no bond resonance.[18b]

That reaction of **23** with boron tribromide does not cease after formation of the dibromide, but instead gives tetrabromocyclopropene,[18b] may be attributed in part to steric factors. Although attack by Br^- to give

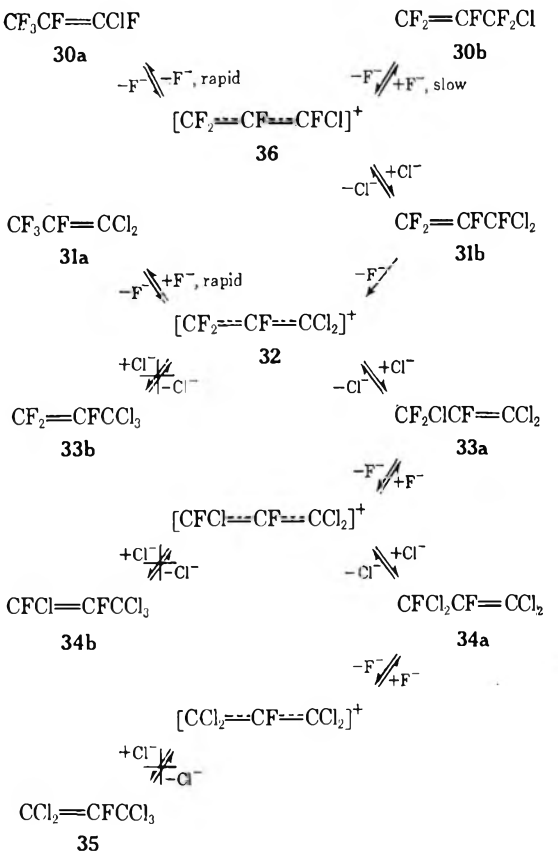


a *gem*-dibromo group would be favored by the symbiotic effect, this tendency is counteracted by steric interactions so that **29** is formed. Successive reaction of this sort leads to the fully substituted product. This argument would also apply to the reaction of hexachlorocyclopentadiene with boron tribromide.[18a] Another factor which probably comes into play in the reactions of **24** is discussed later.

The reaction of hexafluoropropene with aluminum chloride has been studied by Park, Hopwood, and Lacher who reported the following products in addition to starting material:[30] $CF_3CF{=}CFCl$ (**30a**), $CF_3CF{=}CCl_2$ (**31a**), $CF_2ClCF{=}CCl_2$ (**33a**), $CFCl_2CF{=}CCl_2$ (**34a**), $CCl_3CF{=}CCl_2$ (**35**). The **31a** and **35** were formed in much larger amounts than the others. Comparison of the mechanism postulated by these investigators with Scheme III, which represents the pathway derived from HSAB concepts for the conversion of the initially formed **30b** to **35**, reveals several significant differences. Whereas the former accounts for the formation of **31a** by rearrangement of $CF_2ClCF{=}CFCl$ through an unspecified route, Scheme III shows **31a**, as well as **30a**, to arise quite naturally from combination of the extremely hard acid $-C^+F_2$ with the hard F^- from a fluoroaluminate ion.

(28) R. N. Haszeldine, *J. Chem. Soc.*, 3371 (1953).
(29) K. V. Scherer and T. J. Meyers, *ibid.*, **90**, 6253 (1968).
(30) J. D. Park, S. L. Hopwood, and J. R. Lacher, *J. Org. Chem.*, **23**, 1169 (1958).

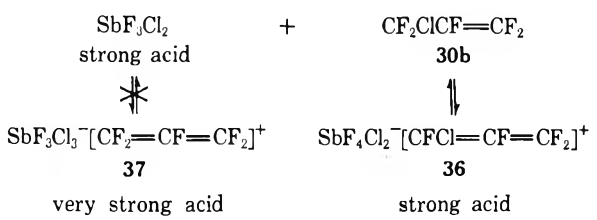
SCHEME III



The resistance of these two materials to further substitution by Cl^- originates from the kinetics of the reaction, since the step which leads to each is an impasse in the substitution process. The olefins **33b**, **34b**, and **35** were not reported. The apparent reason for the difficulty in the replacement of the fluorine in **35** is that the fluorine is not in an allylic or potential allylic position, although this fact apparently was not fully appreciated in the past.[30]

The allylic rearrangement of $CF_2{=}CFCF_2Cl$ (**30b**) reported by Henne and Newby[31] brings up an important aspect of these reactions which has not been fully discussed. This compound was converted in 82% yield to the isomeric **30a** upon attempted fluorination with SbF_3Cl_2 and antimony trifluoride. Under similar conditions **31b** was also converted to **30a**.

It may be seen that these results are readily interpreted in terms of formation of the common intermediate **36**. The formation of **36** from **30b** seems inconsistent with previous examples, since antimony would be expected to preferentially abstract the softer base Cl^-. However, removal of Cl^- from **30b** would generate the very *strong* acid **37**, which is apparently a *stronger* acid



than SbF_3Cl_2 and, in this case, the considerations of acid strength take precedent over those of hardness and softness. In the case of **31b**, SbF_3Cl_2 is a sufficiently strong acid, so that ion formation is determined as expected by hardness and softness considerations. It should also be remembered in this regard that F^- is a *stronger* base toward the proton than are the other halide ions.

HSAB and Saturated Compounds.—The effect of acid strength discussed above may be seen more clearly in the fluorination of aliphatic compounds with antimony salts. The reaction of hexachloroethane with antimony trifluoride[32] containing 10% SbF_3Cl_2 gives products containing the $-CCl_2F$ group, whereas reaction with SbF_3Cl_2 proceeds to the $-CClF_2$ group. Conversion of $-CCl_3$ to $-CCl_2F$ results not only in a harder group, but one which is a *stronger* acid as well. For this reason, reaction occurs in an alternate stepwise fashion, and ceases with the formation of the $-CClF_2$ group. That is, $CF_2Cl^+CF_2$ is a *stronger* acid than SbF_3Cl_2, just as $CF_2{=}CF^+CF_2$ is. The reaction of hexachloropropene proceeds to $CF_3CCl{=}CCl_2$ (**7**) with antimony trifluoride alone,[26] because removal of Cl^- from $CF_2ClCCl{=}CCl_2$ gives $[CF_2{=}CCl{=}CCl_2]^+$ (**6**), which is a weaker acid than either $[CF_2{=}CF{=}CF_2]^+$ (**37**) or $CF_2Cl^+CF_2$.

$$SbF_3 + CCl_3CCl_3 \xrightarrow[10\%\ SbF_3Cl_2]{} CCl_3CCl_2F + CCl_2FCCl_2F + SbCl_3$$
s h ss h h s s

$$SbF_3Cl_2 + CCl_3CCl_3 \longrightarrow CCl_2FCClF_2 + CClF_2CClF_2$$

That antimony pentachloride is ineffective as a catalyst for the disproportionation of saturated fluorochlorocarbons, as we have found with CF_2ClCCl_3, and as reported with CCl_3F and CCl_2FCCl_2F,[3] is consistent with this argument. These findings indicate that $SbCl_5$ is a weaker acid than SbF_3Cl_2, since the latter is strong enough to remove Cl^- from CCl_2FCCl_2F and CCl_2FCClF_2. The reactivity toward fluorination by antimony compounds suggests that the acid strength of various ions toward Cl^- in these reactions decreases in the order $C^+F_2CX_3$, $[CF_2{=}CX{=}CF_2]^+ > C^+FClCX_3$, $[CFCl{=}CX{=}CF_2]^+ > C^+Cl_2CX_3$, $[CCl_2{=}CX{=}CF_2]^+ > [CCl_2{=}CX{=}CClF]^+ > [CCl_2{=}CX{=}CCl_2]^+$; X = F, Cl; $-CX_3 = -CF_2Cl, -CFCl_2, -CCl_3$.

It may be noted from this arrangement that the softer, less acidic end of the ambident ions determines their acidity, and that the effect of the $-CF{=}CF_2$ group is approximately the same as that of a $-CF_2Cl$ or $-CFCl_2$ groups. The $-CCl{=}CCl_2$ group reduces the acid strength of an ion considerably, although an analogous group is not evident from this series. The parallel between these carbonium ion acidities and the reactivity of the parent compound toward disproportionation is readily apparent.

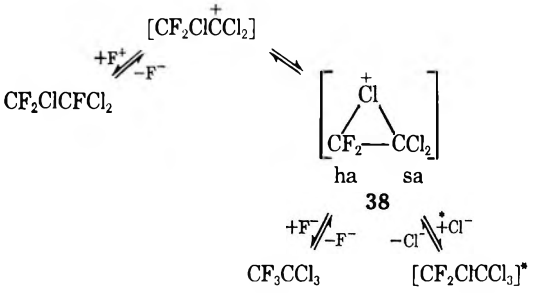
It should be pointed out that members of the ethane series are unstable toward intramolecular rearrangement of the sort described by Miller.[25,33] As mentioned above, radioactive chlorine from aluminum chloride was not incorporated by $CF_2ClCFCl_2$ during rearrange-

(31) (a) A. L. Henne and T. H. Newby, *J. Amer. Chem. Soc.*, **70**, 130 (1948). (b) Rearrangement of **30b** (or **30a**) to **31a** and hexafluoropropene at 400° over active aluminum fluoride is claimed by ref 3b.

(32) E. G. Lock, W. R. Brode, and A. L. Henne, *ibid.*, **56**, 1726 (1934).

(33) W. T. Miller, Jr., U. S. Patent Application 47,553; *Chem. Abstr.*, **47**, 4895 (1953); W. T. Miller, Jr., and E. W. Fager, U. S. Patent 2,598,411 (1952).

ment.[25] This fact strongly suggests the following mechanism for this reaction. Formation of halonium ions resembling **38** has been demonstrated by spectral

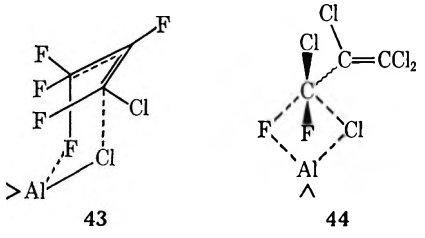


and chemical means,[34] and intermediacy of such an ion in this case seems likely. Absence of this rearrangement during fluorination with SbF_3Cl_2 may be attributed to insufficient acid strength of SbF_3Cl_2, which would lead to a short-lived ion.

Another aspect of the acidity series should be mentioned. Since the trichlorovinyl group has such a pronounced effect on the acid strength of the cation, and because the π electrons of the trichlorovinyl group would increase the polarizability of the ion, it seems reasonable that the relative hardness of the ion would be altered. It seems likely, then, that the hardness of the $-C^+FCl$ group of $[CFCl{=}{=}CCl{=}{=}CCl_2]^+$ (**2**) might be reduced to a borderline classification. This softening effect would mitigate the symbiotic effect in the attack of Cl^- on **2**.

A similar effect would operate on cation **24**, which contains the dichlorovinyl group. This effect, coupled with steric factors, would tend to prevent the formation of **26**. Fluorination of this compound by a process of the sort observed in the reaction of hexachloroethane with SbF_3 might be expected to give complete substitution. For such a process to occur, however, a short-lived ion must be formed; this could hardly be the case with **24**, because it is probably an even weaker acid than **4**. Reaction of **24** with SbF_3 should give long-lived ions which would allow selective attack by nucleophiles.

Other Mechanistic Considerations.—The transition state in the substitution reactions involving rearrangement might well take the form of a six-centered configuration such as **43**, which represents the conversion of



43 44

30a to **31b**. It may be seen that such an arrangement would not allow full overlap of p orbitals, although coplanarity of the *gem*-dihalo groups of the free ion would cause considerable steric interaction, particularly when chloro groups are involved.

In this regard, the ^{36}Cl exchange between the 1 and 3 positions of hexachloropropene and $Al_2{}^{36}Cl_6$ in solution may be mentioned;[21] reaction through a transition state similar to **43** would seem to provide a reasonable rationalization. It is interesting to note that ^{36}Cl exchange at the 2 position of **5a** is reported[21] to occur on solid aluminum chloride; this finding is consistent with the reaction of **35** with aluminum chloride[30] to give **5a**, although this reaction apparently only occurs under vigorous conditions.[30,35]

Although association of complex metal halide and carbonium ions to give a transition state similar to **43** would be required for reaction determined by HSAB considerations, *e.g.*, conversion of **1a** to **3c**, a non-HSAB reaction involving a four-centered transition state such as **44** would account for disproportionation and substitution reactions occurring without rearrangement, *e.g.*, **1a** to **7** and **3a**.

The nature of the metal halide would doubtless have a marked effect on the course of reaction; that is, reaction which occurs in solution could well follow a path different from that which occurs on the surface of a solid. That the aluminum fluoride formed in these reactions is an active catalyst may be attributed to a large number of lattice defects, which would result from the precipitation of aluminum fluoride from such a nonpolar medium. Such defects are usually well correlated with catalyst activity.[5,6,7,36]

Synthesis of 1-Bromo-1,2-dichloro-3,3,3-trifluoropropene (8).—The route devised to this compound was preparation of 1,2-dichloro-3,3,3-trifluoropropene (**17**), and bromination of this compound followed by its dehydrobromination. The reaction of **7** with zinc in formamide is reported[37] to give **17**. When this procedure was followed, the lower boiling isomer of **17** predominated. Separation of this material from 1,1-dichloro-3,3,3-trifluoropropene was not practicable, however, and the amount of the higher boiling isomer was too small to be useful.

Reduction of **7** with sodium borohydride was therefore undertaken. This reaction provided predominantly the high-boiling isomer of **17** which was readily purified. The proton nuclear magnetic resonance spectra of these compounds show a quartet (J_{HF} = 1.2 Hz) at δ 7.13 for the lower boiling compound and a broadened peak ($J_{HF} \leq 0.2$ Hz) at δ 6.65 for the higher boiling isomer. Other investigations[38] have shown J_{HF} to be greater in the case of the *cis* isomer. On this basis, we believe the higher boiling compound to be *trans*-1,2-dichloro-3,3,3-trifluoropropene and the lower boiling material to be the *cis* isomer, although this assignment conflicts with a previous one,[37] and with the usual relationship of boiling points of *cis–trans* isomers.

Bromination of **17**, followed by treatment with aqueous sodium hydroxide gave **8** whose retention time and infrared spectrum matched those of material isolated from the reaction of **1a** with aluminum bromide.

(34) (a) G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, **90**, 6082 (1968); (b) G. A. Olah and J. M. Bollinger, *ibid.*, **89**, 4744 (1967).

(35) R. N. Sterlin, V. A. Siderov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otd Khim. Nauk*, 62 (1959); *Chem. Abstr.*, **53**, 14916 (1959).

(36) J. M. Thomas and W. J. Thomas, "Introduction to the Principles of Heterogeneous Catalysis," Academic Press, New York, N. Y., 1967.

(37) W. G. Finnegan and W. P. Norris, *J. Org. Chem.*, **28**, 1139 (1963).

(38) A. A. Bothner-By, S. Castellano, and H. Gunther, *J. Amer. Chem. Soc.*, **87**, 2439 (1965); J. B. Wilford and F. G. A. Stone, *Inorg. Chem.*, **4**, 93 (1965); W. R. Cullen, D. S. Dawson, and G. E. Styan, *Can. J. Chem.*, **43**, 3392 (1965); W. R. Cullen and W. R. Leeder, *Inorg. Chem.*, **5**, 1005 (1966); D. J. Burton, R. L. Johnson, and R. T. Bogan, *Can. J. Chem.*, **44**, 635 (1966).

Experimental Section

Apparatus.—Glpc data were obtained using an F & M Model 720 or Model 700 gas chromatograph equipped with thermal conductivity detectors. Analyses of products from reactions of 1a were carried out using 10% SE-30 0.25 in. × 2 ft stainless steel column (column A) with a flow rate of 40 ml min^{-1} at a temperature programmed from 100 to 170° at 15° min^{-1}. Preparative glpc was performed using an F & M Model 720 fitted with a 0.5-in.-o.d. column or a Model 770 with a 0.75-in.-o.d. column. The glpc data in Table I are percentages from internal normalization which have been corrected to mole percentages with calibration curves. The amount of 1a was then obtained by difference, and was in good agreement with the value obtained using *n*-decane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 21 or on a Perkin-Elmer Infracord. Melting points were determined using a modified Hershberg apparatus, and are corrected. Boiling points were determined during fractional distillation and are uncorrected. Transfers and weighings of anhydrous inorganic halides were accomplished in a drybox under an atmosphere of nitrogen.

Reactions between organic and inorganic halides were carried out in sealed ampoules which contained a magnetic stirring bar and were supported by a rack mounted over an air-driven magnetic stirrer. This entire apparatus was immersed in a well-stirred oil bath which was thermostated at 50 ± 0.5°.

Materials.—Aluminum chloride (J. T. Baker Chemical Co., 99.1% stated purity) was sublimed under vacuum and ground to a fine powder in an agate mortar in a drybox. Aluminum bromide (Fisher Scientific Co., 99%) was similarly ground. Boron tribromide (American Potash and Chemical) was treated with mercury and fractionally distilled under vacuum before use. Antimony pentachloride (Baker and Adamson Reagent), titanium tetrachloride (Matheson Coleman and Bell), aluminum fluoride (Matheson Coleman and Bell), antimony trifluoride (Ozark-Mahoning), 1,1-difluorotetrachloroethane (Hynes Chemical Co.), and sodium borohydride (Metal Hydrides Co.) were used directly.

Hexachloropropene (Eastern Chemical) was distilled under vacuum before use; glpc analysis of the distillate showed the presence of 5+% higher boiling impurities. Prolonged treatment of the distillate with concentrated aqueous potassium hydroxide reduced the amount of these contaminants to 0.5%. Preparative glpc (0.75 in. × 8 ft 10% SE-30) at 190° with a flow rate of 500 ml/min^{-1} nitrogen gave pure material: bp 92–93° (16 mm), lit.[3] bp 93.0–93.4° (16 mm), ir 1553 cm^{-1} (C=C).[39]

3,3-Difluorotetrachloropropene (1a).[4,8]—Antimony trifluoride (986 g, 5.5 mol) was placed in a 3-l. three-necked flask fitted with a mechanical stirrer, a pressure-equalized dropping funnel, and a column (40 cm × 19 mm od) which was connected in turn to an elbow, a water-cooled condenser, and a vacuum take-off adapter terminating in a 1-l. receiver. The funnel was charged with hexachloropropene (1494.0 g, 6.0 mol, 99.5%) which had been treated with potassium hydroxide. The system was evacuated to 140 mm by a water aspirator, and the flask was heated to 135° in an oil bath. The olefin was added over a period of 5 min.

When distillation under these conditions ceased, the distillate was poured into dilute hydrochloric acid, and the organic layer separated. The suspension of antimony salts was treated with an amount of 12 *N* hydrochloric acid just sufficient to dissolve the precipitate. The organic material freed by this treatment was combined with the first portion. The crude product was washed with three 250-ml portions 1 *N* hydrochloric acid and one 250-ml portion water; it weighed 954.7 g. Treatment with cold concentrated aqueous ammonia gave 18.7 g of 2,3,3-trichloroacrylamide. The olefin mixture was washed with water, dried (Na_2SO_4), and fractionated through a 30-cm glass helix packed column to give (a) 211 g, bp 89–125.7° (95% 1a, 5% 7); (b) 420.8 g, bp 125.7° (99.5% 1a), $n^{20}D$ 1.4572, ir 1592 cm^{-1} (C=C) (lit.[3] bp 128.3°, $n^{20}D$ 1.4575); (c) 96.0 g, mid-cut (22% 1a, 79% 3a); (d) 167.3 g, bp 169.7° (99.5+% 3a), $n^{20}D$ 1.5053, ir 1570 cm^{-1} (lit.[3] bp 170.1° $n^{20}D$ 1.5052), and (e) 15.7 g residue. These results (35% yield 1a, 13% yield 3a) are consistent with those obtained from several repetitions of this procedure.

2,3,3-Trichloroacrylyl Fluoride, CCl_2=CClCOF.—This material was isolated from fractions of 1a prepared as above except that the ammonia treatment was omitted. Preparative glpc (10% Fluorosilicone DCQF-1 0.5 in. × 10 ft) at 65° gave material which was pure by glpc, and which had the following properties: $n^{20}D$ 1.4841; ir 1810 cm^{-1} (C=O), 1550 cm^{-1} (C=C). The 1250–650-cm^{-1} region of the ir spectrum closely resembled that of 2,3,3-trichloroacrylic acid.

This compound has a pungent, irritating odor and has a markedly deleterious effect on the sense of smell. Full olfactory acuity may not be regained for a period of 48 hr or more after a brief exposure.

2,3,3-Trichloroacrylamide, CCl_2=CClCONH$_2$.—The solid obtained from the treatment of crude 1a with ammonia was collected on a filter and pressed dry. One recrystallization from 5:1 water–ethanol followed by vacuum drying gave fine white needles: mp 98.0° (lit.[40] mp 96–97°).

Anal. Calcd for $C_3H_2Cl_3NO$: C, 20.66; H, 1.16; N, 8.03. Found: C, 20.72; H, 1.30; N, 7.87.

2,3,3-Trichloroacrylic Acid.—A sample of hexachloropropene on prolonged exposure to the atmosphere was converted to large crystals which were acidic to litmus and congo red. One recrystallization from methanol–hexane (Skellysolve B) followed by air drying gave white crystals: mp 75–76° (lit.[41] mp 76, 74–75, 73, and 72.9°); ir (CCl_4) 2970–2550 (CO_2H), 1750, 1700 (C=O), 690 (C–Cl); ir (Nujol mull) 1720 (C=O), 1550 cm^{-1} (C=C).

Reaction of 1a with Metal Halides.—Inorganic halide (typically 0.010 mol) was transferred in a nitrogen-filled drybox to an ampule (20 mm o.d. × 150 mm with a neck 12 mm o.d. × 140 mm) which contained a Teflon-coated magnetic stirring bar (0.25 in. o.d. × 3/8 in.). Samples of aluminum chloride and bromide were weighed on tared 60-mm squares of aluminum foil, which assisted in dissipating static charges. Samples of antimony pentachloride, titanium tetrachloride, and boron tribromide were weighed by difference from excess liquid contained in a hypodermic syringe.

The ampoule was stoppered, removed from the drybox, and cooled in a Dry Ice bath. A gentle stream of nitrogen swept the ampoule during cooling. A weighed sample of 1a (typically 21.60 g, 0.100 mol) was added, and the ampoule was sealed. The reaction mixture was stirred and heated in the apparatus described. At the end of the time specified, the mixture was poured into approximately 20 ml water and was vigorously stirred. The organic layer was separated and washed with three 10-ml portions of 1 *N* hydrochloric acid and one 10-ml portion of water. The sample was dried (Na_2SO_4) and analyzed by glpc as described above.

The aluminum chloride became bright yellow on contact with 1a, but this color was soon replaced by a dull red-brown. After stirring a short time (*ca.* 0.5–1.0 hr), the solid was converted to very fine black particles which were dispersed almost to the top of the liquid. Aluminum bromide behaved similarly except that it was initially a deep red and had marked tendency to adhere to the ampoule and the stirring bar.

The titanium tetrachloride reaction mixture remained homogeneous for 20 min; at the end of this time a heavy brown suspension formed. The solid remained dispersed uniformly throughout the liquid for the remainder of the reaction; after a few hours, it had become a grassy-green color.

Reaction mixtures of 1a with antimony pentachloride and with boron tribromide remained homogeneous and without visible change.

Gravimetric Chloride Analysis.—Aluminum chloride and 1a were allowed to react for 1 hr as described above. The reaction mixture was then treated with 25 ml of distilled water, and the organic layer was separated and twice washed with 25-ml portions of water. The combined aqueous extracts were treated with 30 ml of a solution *ca.* 0.1 *M* in silver nitrate. The precipitate coagulated, collected in a dried and tared sintered-glass funnel, and washed with three portions (5–10 ml each) of 0.01 *N* nitric acid. It was dried to constant weight at 110–115°; the data are summarized below.

	1a, g	Al_2Cl_6, g	AgCl, g	Al_2Cl_6 remaining, %
Trial 1	21.60	1.3316	0.0423	0.99
Trial 2	21.60	1.3603	0.0614	1.40

(39) It may be noted that Sadtler's Standard Spectra (#4655) shows extraneous bands at 2950 and 1750 cm^{-1}, which are indicative of trichloroacrylic acid or its derivatives.

(40) "Beilstein's Handbuch," **H2**, 402.

(41) E. H. Huntress, "Organic Chlorine Compounds," Wiley, New York, N. Y., 1948, p 236.

Isolation of 1-Bromo-1,2-dichlorotrifluoropropene (8), CF_3-CCl=CClBr.—Compound **1a** (13.9 g, 0.0644 mol) was added to aluminum bromide (8.60 g, 0.322 mol) in a 50-ml flask surrounded by an ice–water bath. The mixture was then stirred and heated at 50 ± 5° under an atmosphere of nitrogen for 16 hr. The mixture was hyrolyzed, and the organic material washed with water and dried. The crude product, which contained *ca.* 7% of the first-eluted unknown compound, was subjected to simple distillation to remove high-boiling compounds.

The distillate was separated by preparative glpc (15% SE-30 0.5 in. × 10 ft) at 70° with a flow rate of 300 ml min^{-1}. The sample of the first-eluted unknown compound gave a single peak on column A: ir 1585 cm^{-1} (C=C), 1269, 1200, and 1156 cm^{-1} (CF_3), 999, 883, 798, 791, 688, 667 cm^{-1} (C–C, C–X).

Anal. Calcd for $C_3BrCl_2F_3$: C, 14.77; H, 0.00. Found: C, 15.40; H, 0.68.

A small sample of the second-eluted unknown compound was collected, and gave a single peak on column A: ir 1565 (C=C), 1258, 1193, and 1153 (CF_3), 986, 827, 776 cm^{-1} (C–C, C–X).

Preparation of 17.—Compound **7** (199.5 g, 1.0 mol) and 200 ml of diethylene glycol dimethyl ether (diglyme) were placed in a 2-l. three-necked flask fitted with a thermometer, a pressure-equalized dropping funnel, and a water-cooled condenser, which was in turn connected to a mercury–acetone bubbler. The solution was cooled to 0° in a 1-propanol–Dry Ice bath, and a solution of sodium borohydride (19.3 g, 0.50 mol 98% purity) and water (27.0 g, 1.5 mol) in 600 ml of diglyme was added over a period of 1 hr. Temperature during the addition was maintained at 10–15°.

The mixture was allowed to stir at room temperature for 36 hr after the addition was complete; it was then poured into 2 l. water with vigorous stirring. The organic layer was separated, washed with water, and dried. Fractionation through a 45-cm spinning-band annular still (Column A) gave (a) 14.4 g, bp 55.0–56.0°, *cis*- and *trans*-**17** containing a trace of 2-chloro-3,3,3-trifluoropropene; (b) 4.8 g, bp 56.0–60.5°, *cis* and *trans* **17**; and (c) 5.6 g, bp 60.5–61.5°, *trans* isomer of **17**, 99.5+% by glpc.

This procedure was repeated as above, except that the water was contained in the olefin solution. Analysis of the crude mixture by glpc on column B at 25° showed 2-chloro-3,3,3-trifluoropropene 4.3%, low-boiling **17** 7.2%, high-boiling **17** 27.4%, and starting olefin 60.8%. Fractionation through column A gave samples of each geometric isomer of 99.9% purity of *cis*-1,2-dichloro-3,3,3-trifluoropropene: bp 55.5° (750 mm), $n^{20}D$ 1.3672; nmr δ 7.13, J_{HF} = 1.2 Hz [lit.[37] bp 51–52° (702 mm), $n^{20}D$ 1.3638; nmr δ 7.08, J_{HF} = 1.1 Hz]; ir 1629 cm^{-1} (C=C), 1307, 1205–1160 cm^{-1} (CF_3); high-boiling **17**, bp 60.0° (742 mm), $n^{20}D$ 1.3768; nmr δ 6.65, $J_{HF} \leq 0.2$ Hz [lit.[37] bp 58° (702 mm), $n^{25}D$ 1.3795; nmr δ 6.65, J_{HF} = 0.2 Hz]. Recovery of starting olefin was 90.8 g.

Bromination of 17.—Bromine (10.1 g, 0.063 mol) and 1,2-dichloro-3,3,3-trifluoropropene (10.4 g, 0.063 mol 91% high-boiling isomer, 9% low-boiling isomer) were placed in a flask, which was equipped with a water-cooled condenser and a magnetic stirring bar. The mixture was irradiated by an ultraviolet lamp from a distance of 15 cm for 72 hr. Analysis by glpc on column A indicated the absence of starting olefin, although the color of bromine persisted in the reaction mixture. The crude 1,2-dibromo-1,2-dichloro-3,3,3-trifluoropropane (**45**) was washed with water and used without further purification.

Dehydrobromination of 45.—Dibromide **45** was treated with a solution of sodium hydroxide (2.90 g, 0.070 mol 97% purity) in 15 ml of water with vigorous stirring for 3 hr. The organic halide was separated, washed with water, and dried ($MgSO_4$). Fractionation through a 12 × 150 mm Vigreux gave 4.8 g **8**: bp 108.0° (740 mm), $n^{20}D$ 1.4402; ir 1582 cm^{-1} (C=C), 1267, 1196, 1156 cm^{-1} (CF_3), 998, 876, 796, 789, 689, 665 cm^{-1} (C–C, C–X); 99.9+% pure by glpc. A small fraction, 0.25 g, bp 108.0°, containing 1.5% low-boiling impurity was also obtained; the residue weighed 4.0 g.

Anal. Calcd for $C_3BrCl_2F_3$: C, 14.77; H, 0.00; Br, 32.77; Cl, 29.07; F, 23.37. Found: C, 15.16; H, 0.00; Br, 32.90; Cl, 27.63; F, 23.70.

Registry No.—**1a**, 431-50-5; **8**, 25055-21-4; *cis*-**17**, 25062-10-6; *trans*-**17**, 25062-11-7.

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Triarylphosphine-Catalyzed Dimerization of Acrylonitrile and Related Reactions

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In the triarylphosphine-catalyzed dimerization of acrylonitrile to 2-methyleneglutaronitrile (I) and 1,4-dicyano-1-butene (II), the importance of a proper balance between nucleophilicity of the phosphine catalyst and protolytic strength of the solvent is delineated. Best results (85% yield of a mixture of 68% I and 32% II at 36% conversion of acrylonitrile) are obtained with a tri(*p*-tolyl)phosphine catalyst in triethylsilanol solution at 160°. Reaction of methyl vinyl ketone with a triphenylphosphine catalyst in triethylsilanol solvent gives only one catalytic dimer, 3-methylene-2,6-heptanedione, in 78% yield. Treatment of equimolar amounts of acrylonitrile and ethyl acrylate with a tributylphosphine catalyst at 100° affords only one cross-condensation product, 2-carbethoxy-4-cyano-1-butene, despite the fact that two cross-condensates are possible.

Recently, Baizer, and Anderson[1] have described a novel triphenylphosphine-catalyzed dimerization of acrylonitrile to a mixture of 60% 2-methyleneglutaronitrile (I) and 40% 1,4-dicyano-1-butene (II). The reaction was carried out at 45° in the presence of a small amount of *t*-butyl alcohol and only a 9% conversion of acrylonitrile to dimers was observed after 198 hr. We discovered[2] this reaction independently and now describe our results which show the triarylphosphine-catalyzed dimerization to be of significantly greater value[3] for the synthesis of II than implied by Baizer and Anderson.

Both the conversion of acrylonitrile and the yields of I and II vary significantly with the reaction temperature, the nature of the triarylphosphine, and the solvent. The results in Table I show that in *t*-butyl alcohol solvent at 175°[4] with triphenylphosphine as a catalyst, only a 45% yield[5] of dimers (I + II) at 15% conversion of acrylonitrile is obtained. The principal by-products are an insoluble crystalline hexamer[6] (15–20%) and soluble polymer (25–30%). When tri(*p*-

(1) M. M. Baizer and J. D. Anderson, *J. Org. Chem.* **30**, 1357 (1965).

(2) J. D. McClure, U. S. Patent 3,225,083 (1965).

(3) The synthetic value of the tributylphosphine-catalyzed dimerization which produces I, exclusively, was emphasized by Baizer and Anderson.[1]

(4) At temperatures greater than 175°, the thermal dimerization to 1,2-dicyanocyclobutane becomes significant.

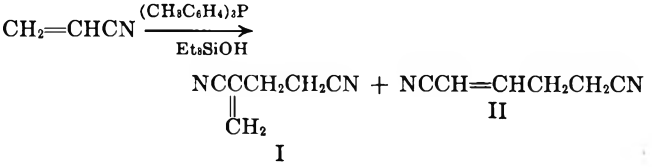
(5) Yields are based on converted acrylonitrile.

(6) N. Takashina and C. C. Price, *J. Amer. Chem. Soc.*, **84**, 489 (1962).

Table I
Triarylphosphine Catalyzed Dimerization of Acrylonitrile
(40 g of monomer)

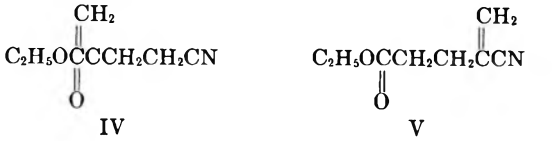
Catalyst (1 g)	Solvent	Temp, °C	Time, hr	% convn of acrylonitrile	% yield of dimer (I + II)	% II in dimer
$(C_6H_5)_3P$	Me_3COH (40 g)	175	8	15	45	39
$(CH_3C_6H_4)_3P$	Me_3COH (80 g)	160	8	30	65	30
$(C_6H_5)_3P$	Et_3SiOH (40 g)	175	8	16	75	40
$(CH_3C_6H_4)_3P$	Et_3SiOH (80 g)	160	11	36	85	32
$(CH_3C_6H_4)_3P$	Et_3SiOH (80 g)	160	4	15	90	38

tolyl)phosphine [$(CH_3C_6H_4)_3P$] is used as catalyst in place of triphenylphosphine at 160°, the acrylonitrile conversion is doubled to 30% and the yield of dimers is increased to 65%. However, the percentage of II in the dimer decreases from 39 to 30. When triethylsilanol[7] (Et_3SiOH) is used as solvent in place of *t*-butyl alcohol with triphenylphosphine as catalyst at 175°, the yield of dimers is increased from 45 to 75%. Finally, with triethylsilanol as the solvent and tri(*p*-tolyl)-phosphine as the catalyst at 160°, an 85% yield of dimers is realized at 36% conversion of acrylonitrile. The dimer composition is 32% II and 68% I. Thus, by



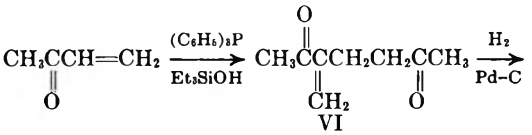
proper choice of triarylphosphine catalyst and solvent, a fourfold increase in acrylonitrile conversion over that reported by Baizer and Anderson[1] is attainable with only a slight decrease (from 40 to 32%) in the percentage of II in the dimer.

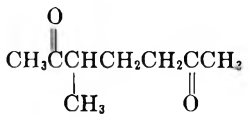
Baizer and Anderson[1] also reported that acrylonitrile is dimerized exclusively to 2-methyleneglutaronitrile (I) when treated with a tributylphosphine catalyst at 45°. Rauhut and Currier[8] had disclosed earlier that ethyl acrylate is converted to the dimer, diethyl 2-methyleneglutarate (III), when treated with the same catalyst. We have found that reaction of equimolar amounts of acrylonitrile and ethyl acrylate with a tributylphosphine catalyst at 100° in *t*-butyl alcohol solvent affords only one cross-condensation product (IV) in 48% yield (21% conversion of either reactant) despite the fact that two cross-condensates (IV and V) are possible. I (25% yield) and III (22% yield) are formed as by-products. That IV is a single (>97% pure) compound and not a mixture of products is evident from spectral studies and capillary (250 ft) gas–liquid chromatographic analysis.



High resolution infrared and mass spectroscopy[9] show unequivocally that the cross-condensate is 2-carbethoxy-4-cyano-1-butene (IV). In the ir spectrum the nitrile absorption at 2250 cm^{-1} is clearly in the range of a saturated alkyl nitrile (2260–2240 cm^{-1})[10] and outside the range of an α,β-unsaturated nitrile (2235–2215 cm^{-1})[10]. The ester carbonyl absorption at 1721 cm^{-1} is within the range of an α,β-unsaturated ester (1730–1717 cm^{-1})[10] and outside the range of a saturated ester (1750–1735 cm^{-1})[10]. The mass spectrum of the cross-condensate shows a molecular formula of $C_8H_{11}NO_2$. A principal fragment at m/q = 113, $C_6H_9O_2$, is consistent with structure IV but not with V. The expected cleavage of IV at the bond β to the nitrile group would produce a fragment of m/q = 113. No fragment of m/q = 101, $C_5H_9O_2$, which would be expected to result from cleavage of the bond β to the nitrile group of V was observed. To our knowledge, IV is a new compound.

We have also examined the catalytic reactions of methyl vinyl ketone with both trialkyl and triarylphosphines. Treatment of methyl vinyl ketone with a catalytic amount of tributylphosphine in dilute triethylsilanol or *t*-butyl alcohol solution affords only a solid polymer (mol wt 1300) even when carried out at 5–10°. However, when triphenylphosphine is used as the catalyst at 118° in triethylsilanol solvent, a single new[11] dimer is isolated in 78% yield at 60% conversion of ketone. With *t*-butyl alcohol as a solvent the yield of dimer is reduced to 60%. The dimer has been identified as 3-methylene-2,6-heptanedione (VI) by spectral means. Compound VI shows the following spectral





characteristics: ir, 5.83 μ (saturated ketone), 5.96 μ (α,β-unsaturated ketone), 6.15 μ (carbon–carbon double bond), 10.55 μ (carbon–carbon double bond conjugated with ketone); uv, λ_{max} 218 mμ (ϵ 9500); nmr, singlet at δ 2.12 ppm [3 H, $CH_3C(=O)CH_2$], singlet at 2.32 [3 H, $CH_3C(=O)-C=CH_2$], singlet at 2.55 (4 H, CH_2CH_2), two singlets at 5.85 and 6.10 (1 H each, $CH_2=C$). The presence of a CH_3 doublet at 1.10 ppm in the nmr spectrum of the hydrogenation product (VII) of VI eliminates the alternative structure, 3-octene-2,7-dione, from consideration. To our knowledge, VI has not been reported previously in the literature. In addition to VI, thermal dimer, 6-acetyl-5,6-dihydro-2-methylpyran[11] (7% yield), and an unknown product (3–4% yield) are isolated from the product mixture. The

(7) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 2282 (1946).

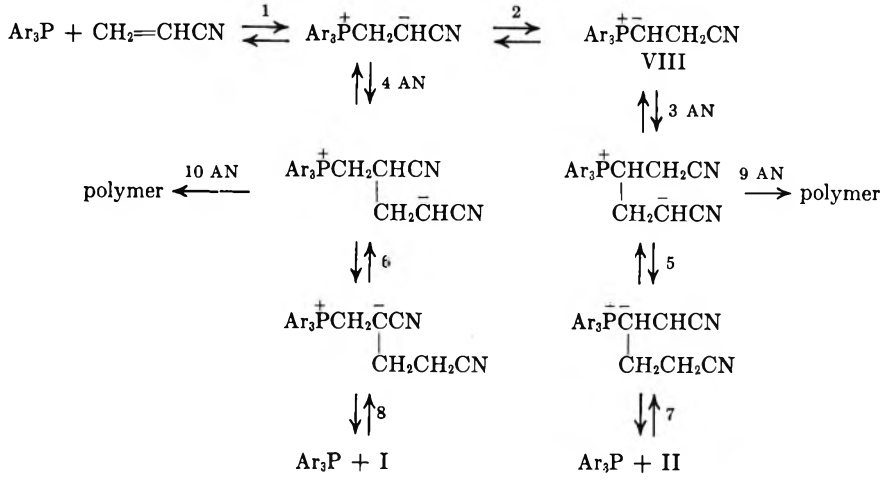
(8) M. Rauhut and H. Currier (to American Cyanamid), U. S. Patent 3,037,999 (1963).

(9) The nmr of IV which is not definitive is recorded in the Experimental Section.

(10) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 179, 263.

(11) Methyl vinyl ketone has been reported to undergo thermal dimerization at 150° to give 6-acetyl-5,6-dihydro-2-methylpyran: K. Alder, H. Offermanns, and E. Ruden, *Chem. Ber.*, **74B**, 905 (1941).

SCHEME I



infrared spectrum of the unknown compound shows that it is not 3-octene-2,7-dione.

Discussion

The mechanism of the triarylphosphine-catalyzed dimerization of acrylonitrile has been discussed by Baizer and Anderson[1] and is shown below in slightly modified form. Support for the presence of the phosphorus ylide intermediate (VIII) has been obtained by both Oda[12] and ourselves[13] through the isolation of Wittig-type reaction products when the dimerization is conducted in the presence of an aromatic[12,13] or aliphatic[13] aldehyde (Scheme I).

The improvement in conversion to dimer that is observed when tritolylphosphine is used in place of triphenylphosphine as catalyst is attributed to the slightly greater nucleophilicity of the methyl substituted phosphine (steps 1 and 2). It is important that the nucleophilicity of the triarylphosphine not be too great because then only a low (<10%) percentage of II in the dimer is observed. Thus, tri(*p*-anisyl)phosphine which is significantly more nucleophilic than triphenylphosphine gives dimer containing only 9% II.

The improvement in dimer yield that is observed when triethylsilanol is used as a replacement solvent for *t*-butyl alcohol is particularly noteworthy. The increased dimer yield is at the expense of decreased insoluble (hexamer) and soluble polymer formation. Triethylsilanol has been estimated[14,15] to have a pK_a of about 16 which is about 1000 times as great as that of *t*-butyl alcohol. Accordingly, the solvent effect is attributed to the fact that triethylsilanol is a stronger protolytic source[16] than *t*-butyl alcohol and can better terminate polymer chain formation by promoting the proton transfer steps 5 and 6. In the absence of a protolytic source the propagation of the polymer chain (steps 9 and 10) would continue at a much faster rate. However, it is important that the solvent not be too protolytic since the basic catalyst can complex with the solvent and be rendered inactive. Thus, the rate of dimerization is reduced tenfold by the presence of 2,6-di-*t*-butylphenol (p$K_a \cong 10$) in the reaction mixture. It is apparent that a proper balance between nucleophilicity of the phosphine catalyst and protolytic strength of the solvent is quite critical for high yields of II at good conversions of acrylonitrile. The combination of tritolylphosphine catalyst and triethylsilanol solvent is especially propitious.

The isolation of a single cross-condensate, IV, from the tributylphosphine-catalyzed reaction of acrylonitrile with ethyl acrylate is of special interest since it might be expected that two products, IV and V, would be formed. The former (IV) would arise from the reaction of the phosphonium zwitterion, IX, with acrylonitrile (step 11) while the latter (V) would arise from the reaction of X with ethyl acrylate (step 12). Since both I and III are isolated as by-products in approximately equal amounts, intermediates IX and X must be formed in the reaction. The failure to observe V as a product may then be rationalized by assuming that step 12 is much less favorable than step 11. Step 14 which involves proton transfer may also be less favorable than step 13. The results thus indicate that the relative ease of formation of X *vs.* IX is much less important than the succeeding steps in the ultimate determination of the nature of the products formed (Scheme II).

In contrast to acrylonitrile, methyl vinyl ketone reacts with a tributylphosphine catalyst to give exclusively polymer. The 3-methylene-2,6-heptanedione (VI) which may be initially formed in this system reacts too readily with the tributylphosphine for a selective dimerization to occur. However, if the tributylphosphine is replaced with the much less nucleophilic triphenylphosphine, then a discriminating catalyst is present which reacts primarily with the methyl vinyl ketone and not with VI. Nevertheless, the reaction of the initially formed phosphonium zwitterion, $(C_6H_5)_3P^+CH_2^-CHCOCH_3$ (XI), with another molecule of methyl vinyl ketone is still very rapid in that XI is not significantly transformed to a phosphonium ylide, $(C_6H_5)_3P^{+-}CHCH_2COCH_3$, before reacting as in the case with $(C_6H_5)_3P^+CH_2^-CHCN$. This type of reasoning accounts for the failure to observe any significant

(12) R. Oda, T. Kawabata, and S. Tanimota, *Tetrahedron Lett.*, 1653 (1964).

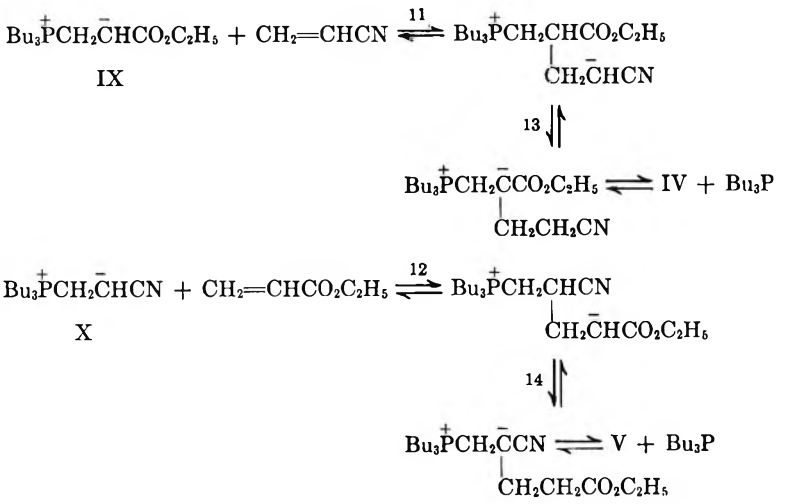
(13) J. D. McClure, *ibid.*, 2401 (1967).

(14) R. West and R. H. Baney, Abstracts, 133rd National Meeting of American Chemical Society, San Francisco, Calif., April 1958.

(15) C. Eaborn, "Organosilicon Compounds," Academic Press, New York, N. Y., 1960, p 244.

(16) Water or alcohols such as methanol which are stronger protolytic sources than *t*-butyl alcohol cannot be used as solvents because Michael addition of the alcohol to acrylonitrile occurs. The sterically hindered triethylsilanol does not react with acrylonitrile to give a Michael adduct at temperatures up to 175°.

Scheme II



amount of 3-octene-2,7-dione in the product mixture.

Experimental Section

Tri(*p*-tolyl)phosphine-Catalyzed Dimerization of Acrylonitrile.—A solution of 40 g (755 mmol) of acrylonitrile, 1.0 g (3.3mmol) of tri(*p*-tolyl)phosphine, and 0.1 g of hydroquinone in 80 g of triethylsilanol[7] in a 350 ml glass-lined reactor sealed under nitrogen was stirred at 160° for 11 hr. The mixture was diluted with 100 ml of benzene and filtered to remove 0.45 g of crude hexamer (3% yield). Benzene and unreacted acrylonitrile were removed by distillation through a Vigreux column at reduced pressure. Analysis of the distillate by gas-liquid chromatography at 80° on a 20-ft column packed with 15%DC-710 on Fluoropak showed the presence of 25.6 g (36% conversion) of acrylonitrile.

The residual liquid separated into two phases on cooling to 0°. Analysis of the lower phase (17.6 g) by gas-liquid chromatography at 150–200° on a 10-ft column packed with 15% Carbowax 20M on Fluoropak showed the presence of 8.3 g of 2-methyleneglutaronitrile[1] (58% yield), 2.1 g of *trans*- and 1.9 g of *cis*-1,4-dicyano-1-butene[1] (27% yield) as well as some triethylsilanol. The upper phase was almost pure triethylsilanol. Distillation of the lower phase through a small Vigreux column separated the dimer, 11.8 g, bp 80–100° (0.5 mm), from triethylsilanol, bp 42–45° (5 mm), and 3.0 g of nonvolatile residue. Separation of the *cis*- and *trans*-1,4-dicyano-1-butene, bp 122–132° (3 mm), from the 2-methyleneglutaronitrile, bp 109–110° (3 mm), was effected by fractional distillation through a 2-ft spinning-band column. Recrystallization of the residue from ethanol recovered 0.7 g (70%) of the tritolylphosphine.

Tributylphosphine-Catalyzed Reaction of Acrylonitrile with Ethyl Acrylate.—A solution of 20 g (378 mmol) of acrylonitrile, 38 g (380 mmol) of ethyl acrylate, 0.9 g (5 mmol) of tributylphosphine, and 0.05 g of hydroquinone in 100 g of *t*-butyl alcohol in a 350 ml glass-lined reactor sealed under nitrogen was maintained at 102 ± 2° for 7 hr. The product mixture was neutralized with 0.35 g of acetic acid. Removal of solvent and unreacted acrylonitrile and ethyl acrylate was effected by distillation under reduced pressure. Analysis of the distillate by gas-liquid chromatography at 70° on the DC-710 column showed the presence of 16 g of acrylonitrile (20%) conversion) and 30 g of ethyl acrylate (21% conversion).

Distillation of the residual liquid through a small Vigreux column afforded 9.0 g, bp 70–85° (0.5 mm). Analysis of the distillate by gas-liquid chromatography at 180–200° on a 10 ft by $^3/_8$ in. column packed with 15% neopentyl glycol sebacate on Chromosorb W showed that the product contained 5.9 g of 2-carbethoxy-4-cyano-1-butane (48% yield), 1.8 g of diethyl 2-methyleneglutarate[8] (22% yield), 1.0 g of 2-methyleneglutaronitrile (25% yield), and 0.3 g of an unknown compound. Separation of IV from the other components was effected by glc trapping on the above described column. Analysis of IV on a 250 ft capillary column packed with Carbowax 20M on Fluoropak showed that it was 97% pure: nmr ($CDCl_3$) δ 1.30 (t, 3, CH_3-CH_2), 4.17 (q, 2, CH_3CH_2), 2.55 (s, 4, CH_2CH_2CN), 5.70 (s, 1, C=CH_2), and 6.23 (s, 1, C=CH_2).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.20; N, 9.14. Found: C, 62.2; H, 7.45; N, 8.95.

Triphenylphosphine-Catalyzed Dimerization of Methyl Vinyl Ketone.—A solution of 20 g (285 mmol) of methyl vinyl ketone, 0.2 g of hydroquinone, and 1.85 g (7.1 mmol) of triphenylphosphine in 100 g of *t*-butyl alcohol in a 350 ml glass-lined reactor sealed under nitrogen was maintained at 118° for 8 hr. Solvent and unreacted methyl vinyl ketone were removed by distillation under reduced pressure. Analysis of the distillate by gas-liquid chromatography at 80° on a 10-ft column packed with 15% DC-170 on Fluoropak showed the presence of 8.0 g (60% conversion) of methyl vinyl ketone.

Distillation of the residual liquid through a small Vigreux column afforded 8.6 g, bp 55–75° (1–2 mm), along with 4.5 g of residue. Analysis of the distillate by gas-liquid chromatography on the DC-710 column at 180–200° showed the presence of 7.2 g of 3-methylene-2,6-heptanedione (60% yield), 0.8 g of 9-acetyl-5,6-dihydro-2-methylpyran (7% yield), and 0.4 g of an unknown compound. The 3-methylene-2,6-heptanedione, bp 91–92° (5 mm), was isolated in pure form by fractional distillation through a 2-ft spinning-band column, mp 5–7°.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.5; H, 8.60; mol wt, 140. Found: C, 68.7; H, 8.70; mol wt, 140 (mass spectroscopy).

Recrystallization of the distillation residue from ethanol recovered 1.4 g (75%) of the triphenylphosphine.

Hydrogenation of 3-Methylene-2,6-heptanedione (VI).—A mixture of 1.4 g of VI, 0.5 g of 10% palladium on barium sulfate and 20 ml of tetrahydrofuran shaken at 25° under 100 psi hydrogen pressure absorbed 0.95 mol equiv of hydrogen in 2 hr. After filtration, distillation afforded 1.2 g (85% yield) of VII:[17] bp 56–58° (1 mm); nmr δ 1.10 (d, 3, CH_3CH), 1.70 (m, 2, $CHCH_2$-CH_2), 2.14 (s, 6, two CH_3CO), 2.4 (m, 3, CH_2CO and $CHCO$).

Registry No.—Acrylonitrile, 107-13-1; tri(*p*-tolyl)-phosphine, 1486-14-2; tributylphosphine, 998-40-3; triphenylphosphine, 603-35-0; IV, 7176-67-2; VI, 22289-05-0.

(17) K. Alder and R. Muders, *Chem. Ber.* **91**, 1083 (1958).

Photochemistry of Some Carbonyl-Conjugated 1,5-Hexadienes[1a]

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Contribution No. 1846 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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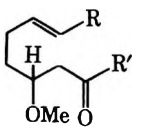
The photochemical reactions of methyl *trans*-hepta-2,6-dienoate (**1a**), methyl *trans,trans*-octa-2,6-dienoate (**1b**), and *trans*-octa-3,7-dien-2-one (**1c**) have been examined. Each of these compounds undergoes geometrical isomerism and deconjugation to their β,γ-unsaturated isomers upon direct irradiation. Sensitization and quenching experiments implicate a singlet excited state for the latter reaction in the case of **1c**. Attempts to sensitize the deconjugation reaction of **1a,b** were unsuccessful, but prolonged irradiation of **1a** in acetone as solvent and sensitizer gave cyclization to the epimeric 5-carbomethoxybicyclo[2.1.1]hexanes. The details of these reactions are discussed in the context of related photochemical processes.

The photochemical reactions of a series of three compounds, methyl *trans*-hepta-2,6-dienoate (**1a**), methyl *trans,trans*-octa-2,6-dienoate (**1b**), and *trans*-octa-3,7-dien-2-one (**1c**), have been examined. Each of these compounds contains a 1,5-hexadiene unit in which one of the double bonds is conjugated with a pendant carbonyl function. At the outset of this work, the photochemical equivalent of the Cope rearrangement was sought. The conjugating carbonyl function of the present series brings the ultraviolet absorption of the diene into a more easily accessible part of the spectrum for excitation. Since the products (**2a–c**) would be nonconjugated systems, this functionalization might also allow photochemical "pumping" to the thermodynamically less stable 1,5-diene, a process of obvious synthetic interest.

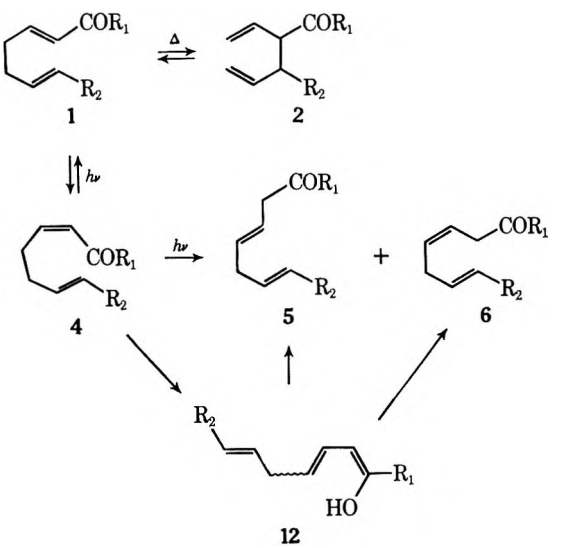
Results

Dienones **1a–c** were prepared by the Emmons–Wadsworth modification[2] of the Wittig reaction using methoxide in methanol as the base. Thus, **1a** was obtained from 4-pentenal and carbomethoxymethyl diethyl phosphonate, **1b** from this phosphonate and *trans*-4-hexenal, and **1c** from 4-pentenal and acetonyl diethyl phosphonate. 4-Pentenal and *trans*-4-hexenal were obtained by thermolysis of allyl vinyl ether and 3-but-1-enyl vinyl ether, respectively, which were obtained by transetherification[3] of 1,4-bis(vinyloxy)butane with allyl alcohol and 3-buten-2-ol. The only significant products of the condensation reactions were the desired compounds **1a–c** and the β-methoxy derivatives (**3a–c**) resulting from nucleophilic addition of methanol. Addition product **3c** was the predominant product in the preparation of **1c**. However, the crude mixture of **1c** and **3c** could be transformed to **1c** by acid treatment. Detailed analysis of the spectral properties described in the Experimental Section demonstrates the assigned structures.



3

Irradiation of a dilute, degassed solution of **1a** in either methanol or hexane in a Rayonet reactor with 2537-Å lamps gave methyl *cis*-hepta-2,6-dienoate (**4a**) and methyl *cis*- and *trans*-hepta-3,6-dienoate (**5a** and **6a**). Formation of **4a** was rapid at first, reaching about 40% of the total sample after 60% transformation of **1a**. Thereafter, the amounts of both **1a** and **4a** diminished until only **5a** and **6a** remained. Although **5a** and **6a** were not separated, analytical glpc on a capillary column indicated that the glpc-collected sample was a 7:3 mixture of two components and the spectral data were consonant with a mixture of **5a** and **6a**. The intensity of the *trans* olefin peak at 10.3 μ in the ir suggests that the *trans* isomer predominates in this mixture. Under these conditions, photolysis of **1a** is exceptionally clean, giving only traces of other materials. An authentic sample of 2-vinylpent-4-enoate (**2a**) was prepared by pyrolysis of **1a** and shown not to be present in the photolysis mixture.



a, $R_1 = OCH_3$; $R_2 = H$
b, $R_1 = OCH_3$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = H$

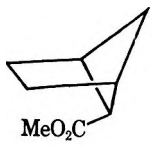
Photolysis of **1a** with 3500-Å lamps in benzene with added benzophenone produced a photostationary mixture of **1a** and **4a** in a 3:1 ratio with less than 1% of any other materials present. Irradiation of a 1% solution of **1a** in acetone at 2537 Å rapidly produced a photostationary mixture of **1a** and *cis* isomer **4a** in a 3:2 ratio. Extended photolysis under these conditions, however, led to formation of additional products. Preparative irradiation of a 1% solution of **1a** in acetone using a 450-W Hanovia source with a Vycor filter gave similar results at a more convenient rate. After 4 hr, a mixture was obtained which glpc indicated to be about

(1) (a) Supported by a research grant from the Public Health Service; (b) Alfred P. Sloan Research Fellow, 1968–1970.

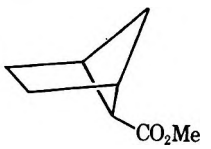
(2) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(3) W. H. Watanabe and L. E. Conlon, *ibid.*, **79**, 2828 (1957).

25% **1a** plus **4a** and 75% of a 4:6:2:1 ratio of four new products. The nmr of this product shows that **1a** and **4a** are the only olefinic components according to the integral of the olefinic region relative to that of the methyl ester region. Glpc provided samples of the two major products which were identified as *endo*- and *exo*-5-carbomethoxybicyclo[2.1.1]hexane (**7** and **8**, respectively). The low return from the glpc collection indicates that substantial transformation to higher molecular weight products also occurred during the photolysis. Unfortunately, this prevented isolation of the two lesser products.

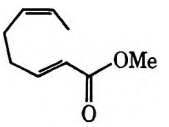


7



8

The results for photolysis of **1b** are fragmentary owing to the complexity of the product mixtures which prevent glpc separation and complete characterization. The starting samples of **1b** were contaminated with about 5% of a component with a slightly longer glpc elution time. An nmr of a sample consisting largely of this impurity did not differ significantly from that of **1b**, suggesting that the impurity is the *cis* isomer of the isolated double bond, methyl *trans,cis*-octa-2,6-dienoate (**9**). Minor amounts of this isomer are to be expected from the synthetic sequence utilized. Irradiation of **1b** in methanol or hydrocarbon solvents again showed rapid isomerization to a material identified as the *cis* isomer **4b**, followed by decline of both **1b** and **4b** leading primarily to **5b** and **6b**. However, about 10% of the glpc-detectable product was composed of unidentified materials. The major side-product is tentatively assigned as methyl *cis,cis*-octa-2,6-dienoate. The remaining unidentified components are also thought to be *cis* isomers at the isolated double bond.



9

Irradiation of **1b** at 3500 Å in benzene with added benzophenone gave a photostationary mixture of **1b** and **4b** in a 3:1 ratio. Small amounts of other products were also formed. Photolysis in acetone at 2537 Å led to a 3:2 mixture of **1b** and **4b** followed by the formation of other products. Prolonged irradiation led to substantial conversion to two new products in a 2:1 ratio. The nmr of this product showed doublets at δ 0.68 and 1.14 which are suggestive of *endo* and *exo* methyls in bicyclo[2.1.1]hexanes.[4]

Photolysis of **1c** in methanol and hydrocarbon solvents at 3500 Å followed the same pattern described for **1a** and **1b** at 2537 Å, but proceeded more slowly. In cyclohexane, a 3:2 ratio of **1c** and **4c** was reached before 5% deconjugation had occurred. No additional products were observed. Neither naphthalene nor piperylene affected the course of the reaction. However, in the presence of large amounts of benzophenone or acetophenone so that these aromatic ketones absorbed most of the incident light, there was essentially no deconjugation observed. Direct irradiation of **4c** gave **1c** and deconjugated ketone; the deconjugated ketone was inert to the photolysis conditions. Glpc comparison of photoproducts with a sample of 3-vinyl-5-hexen-2-one (**2c**), the thermal Cope rearrangement product, demonstrated that this material was not present.

Reaction of **1c** in methanol-O-*d* as solvent gave deconjugated ketone which was a minimum of 88% monodeuterated at C_3 by nmr analysis.

In contrast to the irradiations at 3500 Å, the use of 2537-Å lamps in the photolysis of a cyclohexane solution of **1a** led only to **4c** and did not result in deconjugation even after prolonged reaction times.

Although the spectral data do not specifically demonstrate the *cis* nature of the conjugated double bond of **4c**, analogy with the photolyses of **1a,b** coupled with the spectral data leaves little doubt of the structural assignment. Even capillary glpc would not separate the *cis* and *trans* isomers of deconjugated ketone product (**5c** and **6c**), if indeed both were present. The glpc-collected material gave ir and nmr data comparable to that reported by Conia.[5] A broad band at 14.2 μ in the ir may indicate the presence of some *cis* isomer **5c**, while the *trans* isomer **6c** is readily apparent at 10.3 μ.

Discussion

The results of the present study are in good agreement with developing trends in the literature for related systems. Photo-Cope rearrangements are still not documented, probably because of the unfavorable geometry required for a concerted reaction to follow the orbital symmetry-permitted pathway.[6] Nor does this study provide evidence for 1,3-sigmatropic migration of one of the allyl moieties relative to the second, although such isomerizations are known for other 1,5-diene systems.[7] There are two possible ways by which such a transformation can take place depending upon which allyl fragment is the migrating group. In the case of **1a** and **1c**, one of the possible modes is not an observable process because of the absence of an appropriate label in the unconjugated allyl moiety. However, the alternate possibility would lead to **2a** or **2c**, in contrast to experimental fact. (Either mode of 1,3-sigmatropic rearrangement is potentially observable for **1b** but analytical problems prevented exploration of this point.)

A nonconcerted cyclization mechanism involving the formation of biradical **10** and subsequent cleavage of the 1,4-biradical system in the opposite manner could also lead to formal Cope rearrangement. However, isomerization of triplet **1** to **10** is probably not competitive with the formation of five-ring biradical **11**.[8] This latter species is most likely the precursor of the bicyclo-

(4) J. Meinwald and R. A. Schneider, *J. Amer. Chem. Soc.*, **87**, 5218 (1965); R. S. H. Liu and G. S. Hammond, *ibid.*, **89**, 4936 (1967).

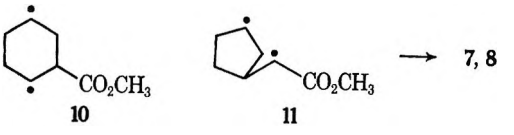
(5) J.-M. Conia and P. le Perchec, *Bull. Soc. Chim. Fr.*, 287 (1966).

(6) The photochemically allowed process would be a rearrangement of order [3a, 3s]: R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(7) R. F. C. Brown, R. C. Cookson, and J. Hudec, *Tetrahedron*, **24**, 3955 (1968); R. C. Cookson, V. N. Gogte, J. Hudec, and N. A. Mirza, *Tetrahedron Lett.*, 3955 (1965); R. C. Cookson, *Quart. Rev.* (London), **22**, 423 (1968).

(8) R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, **89**, 4932 (1967).

[2.1.1]hexanes produced in the acetone photosensitized reactions of **1a**. This type of reaction finds ample precedent.[7,9]



10 **11**

The most significant reactions of system **1** are geometrical isomerism and deconjugation to the β,γ-unsaturated derivatives. Sensitization experiments demonstrated that the first process can occur through the triplet state, but the excited singlet probably also undergoes a similar equilibration. Deconjugation appears to be an excited singlet reaction as judged by its insensitivity to triplet quenchers and the inability of triplet sensitizers to promote this transformation. These conclusions are also consistent with recent literature developments.[10] The reactive isomer (necessarily the *cis* compound for geometrical reasons) transfers a hydrogen atom from the γ position to the carbonyl oxygen through a favorable six-center transition state. This process leads to dienol **12** which subsequently tautomerizes to the ultimate product in a normal ground-state process. This mechanistic description is supported by the uptake of one deuterium atom in the deconjugated product when **1c** is irradiated in methanol-O-*d* as solvent.

Finally, the interesting behavior of **1c** with respect to its photochemical reactivity as a function of excitation energy should be noted. Selective irradiation into the n–π^* absorption band leads to deconjugation in accordance with generally accepted views about the characteristic reactivity of n–π^* excited carbonyl species. However, irradiation into the higher energy π–π^* band does not yield deconjugation; only *cis–trans* isomerization is observed. This is not necessarily unexpected for a π–π^* excited state, but it does indicate that internal conversion to the lowest excited singlet (the n–π^* state) is apparently not competitive with other processes which consume the π–π^* singlet. If this explanation is correct, it violates the usual *assumption* that internal conversion of higher excited states to the lowest energy excited state is fast relative to other modes of energy degradation. The efficient competitive process for depletion of the π–π^* excited singlet may be intersystem crossing which for some reason has a large rate constant in this particular instance. A slightly different interpretation would be that internal conversion to the lowest singlet occurs, but that the highly vibrationally excited species initially formed decompose by other modes than the very rapid vibrational relaxation expected in solution. In any event this unusual phenomenon requires exploration by physical methods for a satisfactory explanation.

Experimental Section

General.—Infrared spectra were obtained with Perkin-Elmer Infracord Model 137 and 137-G spectrophotometers as neat films unless otherwise noted. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard unless otherwise noted. Mass spectra were determined using an AEI MS-9 mass spectrometer at 70 eV. Gas–liquid partition chromatography (glpc) was carried out on a Varian-Aerograph Series 1200 chromatograph (analytical, flame ionization detector) using an 8 ft × $^1/_8$ in. 15% Carbowax 20 M on 60–80 Chromosorb W column and on an Aerograph A-700 chromatograph (preparative) using a 10 ft × $^3/_8$ in. column containing a 30% concentration of either Carbowax 20 M, FFAP, LAC-2R-446, or XF-1150 on 60–80 Chromosorb W. Difficult separations were managed analytically by use of a 250-ft Ucon Polar 2000 capillary column. Percentage composition data were estimated by integrated peak areas (Disc Model 224 integrator) and are uncorrected for compound response. Analyses were performed by Midwest Microlab, Inc.

Fisher reagent grade solvents were used for all experiments without further purification.

4-Pentenal.—Allyl vinyl ether was prepared by the method of Watanabe and Conlon.[3] Thus, a mixture of 298 g of allyl alcohol and 366 g of 1,4-bis(vinyloxy)butane was heated with 5 g of mercuric acetate in a flask set up for distillation through a 22-in. glass-helices packed, vacuum-jacketed column until 315 g of crude allyl vinyl ether had distilled at 66–68° and no further distillation would occur in this range. The crude material was redistilled to give 244 g (57%) of allyl vinyl ether: bp 66–68°; ir 6.10, 6.20, 10.1, and 10.8 μ; nmr (neat) δ 6.4 (m, 1, OCH=C), 5.9 (m, 1, CH=C), 5.2 (m, 2, CH=CH_2), and 4.1 (m, 4, OCH=CH_2 and OCH_2C=C).

Pyrolysis of allyl vinyl ether was performed by the method of Hurd and Pollack[11] using a 300° Pyrex-helices packed Pyrex tube with a nitrogen flow. In this manner, 68 g of ether gave 51 g (75%) of distilled 4-pentenal: bp 103–104°; ir 3.6, 3.7, 5.80, 6.10, 10.0, and 10.9 μ; nmr (neat) δ 9.50 (t, 1, J = 1 Hz, CHO), 5.8 (m, 1, CH=CH_2), 5.0 (m, 2, CH=CH_2), and 2.4 (m, 4).

Carbomethoxymethyl Diethyl Phosphonate.—This ester was prepared by the Michaelis–Arbuzov reaction.[12] The temperature of a mixture of 31 g of triethyl phosphite and 20 g of methyl chloroacetate in a flask equipped with a reflux condenser was slowly raised to 225°. At 130° the mixture began to reflux, and by 200° reflux had almost completely subsided indicating that reaction had ceased. The yield of crude product was 40 g. A portion of this was distilled to obtain a pure sample: bp 153–155° (20 mm); ir 5.75, 7.9, and 9.8 μ; nmr (neat) δ 4.09 (octet, 4, J_{HCCH} = 7 Hz, J_{POCH} = 8 Hz, CH_3CH_2O), 3.67 (s, 3, OCH_3), 3.00 (d, 2, J_{PCH} = 22 Hz, PCH_2), and 1.27 (t, 6, J = 7 Hz, CH_3CH_2O).

Methyl *trans*-Hepta-2,6-dienoate (1a).—This compound was prepared using the Emmons–Wadsworth modification[2] of the Wittig reaction with sodium methoxide as the base. Sodium metal (3.55 g) was dissolved in 125 ml of dry methanol, and 33 g of crude phosphonate was added. The mixture was stirred for 15 min before 12.0 g of 4-pentenal was added with cooling at a rate to keep the temperature below 50°. After an additional 90 min the solution was diluted with water and extracted with ether. The ether solution was dried ($MgSO_4$), the ether was removed at reduced pressure, and the residue was distilled to give 15 ml of colorless liquid, bp 82–90° (20 mm), of which 76% was **1a** by glpc. Glpc collection gave pure **1a**: ir 5.80, 6.03, 6.09, 10.1, and 10.9 μ; nmr (neat) δ 6.91 (d of t, 1, J = 16, 7 Hz, CH=CCO), 5.80 (d of t, 1, J = 16, 1 Hz, C=CHCO), 5.8 (m, 1, CH=CH_2), 5.0 (m, 2, CH=CH_2), 3.64 (s, 3, OCH_3), and 2.2 (m, 4).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.80; H, 8.68.

From the same collection was obtained a sample of the major by-product (15–20%), methyl 3-methoxy-6-heptenoate (**3a**): ir 5.74, 6.10, 10.0, and 10.9 μ; nmr (neat) δ 5.8 (m, 1, CH=C), 5.0 (m, 2, CH_2=C), 3.60 (s, 3, CO_2CH_3), 3.25 (s, 3, OCH_3), 2.38 and 2.40 (2d, 2, J = 6 Hz, CH_2CO_2), 2.1 (m, 2), and 1.6 (m, 2).

Methyl *trans,trans*-Octa-2,6-dienoate (1b).—*trans*-4-Hexenal was prepared by the method of Watanabe and Conlon.[3] A stirred mixture of 25 g of 3-buten-2-ol, 52 g of 1,4-bis(vinyloxy)-butane, and 2.0 g of mercuric acetate was heated to 101° for 24 hr. The solution was cooled, diluted with saturated salt solu-

(9) R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, **19**, 1995 (1963).

(10) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968); M. J. Jorgenson and L. Gundel, *ibid.*, 4991 (1968).

(11) C. D. Hurd and M. A. Pollack, *J. Amer. Chem. Soc.*, **60**, 1905 (1938).

(12) G. M. Kosolapoff, "Organophosphorus Compounds," 1st ed, Wiley, New York, N. Y., 1950, Chapter 7.

tion, and extracted with 50 ml of ether. The extract was washed with saturated salt solution and dried ($MgSO_4$). The ether was removed to give 78 g of crude product estimated by glpc to be half *trans*-4-hexenal. Glpc separation gave *trans*-4-hexenal: ir 3.53, 3.66, 5.79, and 10.3 μ; nmr δ 9.55 (t, 1, J = 1 Hz, CHO), 5.4 (m, 2, CH=CH), 2.3 (m, 4), and 1.6 (m, 3).

Sodium metal (6.03 g-atoms) was added to 200 ml of methanol, and 62 g of crude phosphonate was added. The crude *trans*-4-hexenal (78 g) was added dropwise with cooling. After an additional 15 min the solution was diluted with water and extracted with ether. The solution was dried ($MgSO_4$), and the ether was removed. The residue was distilled to give 24.6 g of colorless liquid (bp 100–110°, 15 mm), which glpc indicated as 67% **1b**. Glpc separation gave pure **1b**: glpc assay, 95%; ir 5.78, 6.02, and 10.3 μ; nmr δ 6.89 (d of t, 1, J = 16, 7 Hz, CH=CCO), 5.77 (d of t, 1, J = 16, 1 Hz, C=CHCO), 5.4 (m, 2, CH=CH), 3.64 (s, 3, OCH_3), 2.2 (m, 4), and 1.6 (m, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.18.

***trans*-Octa-3,7-dien-2-one (1c).**—Iodoacetone was prepared by treatment of chloroacetone (46 g) with sodium iodide (100 g) in 500 ml of acetone at reflux for 8 hr.[13] The solid sodium chloride was removed by suction filtration. The solvent was removed at reduced pressure. The residue was distilled to give 56 g of brown liquid (bp 70–73°, 21 mm) whose nmr showed singlets at δ 3.90 and 2.39 for iodoacetone and at 4.20 and 2.11 for chloroacetone, indicating a 4:1 ratio of these compounds.

Acetonyl diethyl phosphonate was obtained by slow addition of 56 g of crude iodoacetone to 50 g of ice-cold triethyl phosphite with stirring.[14] (Caution is necessary in this addition to prevent a vigorous exothermic reaction.) The solution was heated to 35–40° for 2 hr. Distillation gave 21.7 g of product: bp 76–78° (0.3 mm); nmr (neat) δ 4.10 (octet, 4, J_{HCCH} = 7 Hz, J_{POCH} = 8 Hz, OCH_2), 3.20 (d, 2, J_{PCH} = 23 Hz, PCH_2), 2.26 (s, 3, CH_3CO), and 1.29 (t, 6, J = 7 Hz, CH_3CH_2O).

Sodium metal (2.0 g-atoms) was dissolved in 50 ml of methanol; 16.5 g of acetonyl diethyl phosphonate was added to the solution. Rapid dropwise addition of 6.50 g of 4-pentenal was begun immediately with ice-bath cooling, and 5 min after the addition was completed, the solution was diluted with water. The resulting mixture was extracted with pentane; the extract was washed with saturated salt solution and dried ($MgSO_4$). The pentane was removed, and the residue was distilled to give 7.5 g (bp 88–101°, 22 mm) of colorless liquid indicated by glpc analysis to be an *ca.* 2:1 mixture of 4-methoxyoct-7-en-2-one (**3c**) and **1c**. This mixture was added to a stirred mixture of 150 ml of tetrahydrofuran, 30 ml of 6 *N* sulfuric acid, and 25 ml of concentrated sulfuric acid to give a homogeneous solution. After 1.5 hr the solution was diluted with water and extracted with pentane. The extract was washed with sodium bicarbonate and saturated salt solution. The solvent was removed, pentane was added, and the resulting solution was dried ($MgSO_4$). Removal of the solvent and distillation of the residue through a 12-in. Nester–Faust stainless steel spinning-band column gave 3.85 g of **1c**: bp 88–90° (22 mm); glpc assay, 90%; uv max (hexane) 326 nm (ϵ 32) [lit.[5] uv max (isooctane) 324 mμ (ϵ 34)]; ir 5.96, 6.09, 6.14, 10.1, and 11.0 μ; nmr δ 6.76 (d of t, 1, J = 16, 7 Hz, CH=CCO) 5.97 (d of t, 1, J = 16, 1 Hz, C=CHCO), 5.7 (m, 1, $CH=CH_2$), 5.0 (m, 2, $CH=CH_2$), 2.3 (m, 4), and 2.13 (s, 3, CH_3CO).

Pyrolysis of Methyl *trans*-Hepta-2,6-dienoate (1a).—The apparatus consisted of a horizontal 10-mm i.d. Pyrex tube packed with 0.25-in. o.d. Pyrex helices and inserted through a 170-mm long E. H. Sargent and Co. tube furnace. Samples were placed in a flask at one end of the tube, and the vapors were condensed in a Dry Ice trap at the other end. A pressure of 1 mm was maintained by a vacuum pump attached at the trap.

Pyrolysis at 470° of about 1 g of a sample estimated by glpc analysis to be 75% **1a** gave a product mixture containing about 10% of methyl 2-vinylpent-4-enoate (**2a**). Preparative glpc provided pure **2a**: ir 5.74, 6.08, 10.1, and 10.9 μ; nmr δ 5.7 (m, 2, CH=C), 5.0 (m, 4, $CH_2=C$), 3.62 (s, 3, OCH_3), 3.04 (m, 1, CHCO), and 2.4 (m, 2).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.72.

(13) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4077 (1950); F. Sondheimer, G. Rosenkranz, O. Mancera, and C. Djerassi, *ibid.*, **75**, 2601 (1953).

(14) H. I. Jacobson, M. J. Griffin, S. Preis, and E. V. Jensen, *ibid.*, **79**, 2608 (1957).

Pyrolysis of *trans*-Octa-3,7-dien-2-one (1c).—Pyrolysis of 2.5 g of 83% pure **1c** at 500° using the apparatus described above gave a product mixture containing 8% 3-vinyl-5-hexen-2-one (**2c**). Preparative glpc provided pure **2c**: ir 5.83, 6.10, 10.1, and 10.9 μ; nmr δ 5.6 (m, 2, CH=C), 5.1 (m, 4, $CH_2=C$), 3.15 (q, 1, J = 7 Hz, CHCO), 2.3 (m, 2), and 2.06 (s, 3, CH_3CO).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.22; H, 9.94.

Photolysis of Methyl *trans*-Hepta-2,6-dienoate (1a).—Qualitative photolyses were carried out using a Rayonet photochemical reactor with a bank of sixteen 2537-, 3100-, or 3500-Å bulbs as noted below. Samples were contained in quartz test tubes for work at 2537 Å and in Pyrex test tubes at other wavelengths. Each solution was degassed before irradiation by bubbling prepurified nitrogen through it for 1 min. The tubes were then sealed with rubber serum caps through which glpc samples were removed by syringe.

Solutions were prepared containing 55 ± 5 mg of **1a** in 5.0 ml of hexane, methanol, and acetone. Irradiation at 2537 Å gave methyl *cis*-hepta-2,6-dienoate (**4a**) and methyl *cis*- and *trans*-hepta-3,6-dienoate (**5a** and **6a**) as illustrated in Table I which presents the ratio of **1a**:**4a**:(**5a** + **6a**).

TABLE I

Time, hr	Hexane	Methanol	Acetone[a]
1	40:36:24	29:30:41	60:37:0:3
2.5	24:29:47	14:18:68	54:40:0:6
4	7:11:82	4:0:96	49:40:0:11

[a] The fourth figure represents **7** plus **8**.

Irradiation of a solution of ~50 mg of **1a** and 13 mg of benzophenone in 5 ml of benzene at 3500 Å for 2 hr gave a 3:1 mixture of **1a** and **4a** with no **5a** and **6a** apparent. Further irradiation did not affect the product ratio. Similar irradiation of a sample without benzophenone gave no reaction.

Preparative photolyses were performed using either the Rayonet system or a Hanovia system in which the sample solution was placed in a tubular cell surrounding a water-cooled, quartz immersion well. The source for the latter case was a 450-W Hanovia Type L mercury lamp. Solutions were degassed by bubbling prepurified nitrogen through them vigorously for 1 min, closed by inserting the immersion well, and maintained under a slight nitrogen pressure throughout the photolysis. Aliquots were removed by syringe through a serum cap for glpc examination.

A stirred solution of 1.00 g of methyl *trans*-hepta-2,6-dienoate (**1a**) in 105 ml of methanol was irradiated using the Hanovia source with a Vycor filter. After 115 min glpc analysis revealed that deconjugated esters **5a** and **6a** comprised 93% of the product mixture. The methanol was removed at reduced pressure. Preparative glpc provided a mixture of **5a** and **6a**: ir 5.73, 6.10, 10.0, 10.3, and 10.9 μ; nmr δ 5.6 (m, 3, CH=C), 5.0 (m, 2, $CH_2=C$), 3.59 (s, 3, OCH_3), 3.0 (m, 2), and 2.7 (m, 2). Glpc analysis by capillary column revealed a 3:7 ratio of two components.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.50; H, 8.48.

Irradiation of a solution of 0.50 g of **1a** in 50 ml of acetone in the Rayonet reactor at 3100 Å gave in 4.5 hr a 3:2 mixture of **1a** and **4a**. The acetone was removed at reduced pressure. The residue was glpc separated to obtain **4a**: ir (CCl_4) 5.78, 6.07, 10.1, 10.9, and 14.5 μ; nmr δ 6.13 (d of t, 1, J = 11, 7 Hz, CH=CCO), 5.8 (m, 2, $CH=CH_2$ and C=CHCO), 5.0 (m, 2, $CH_2=C$), 3.64 (m, 3, OCH_3), 2.7 (m, 2), and 2.1 (m, 2).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.44; H, 8.69.

Irradiation of a solution of 1.00 g of **1a** in 110 ml of acetone with the Hanovia source using a Vycor filter led to rapid *cis–trans* equilibration followed by relatively slow conversion to a number of products. Glpc examination after 4 hr indicated a mixture of 14% starting material, 9% **4a**, and four new products in about a 4:6:2:1 ratio. The nmr of this mixture denotes that **1a** and **4a** are the only olefinic components (assuming that all the components are methyl esters). The two major new products were isolated by glpc. The first, *endo*-5-carbomethoxybicyclo[2.1.1]-hexane (**7**), was obtained in 86% purity: ir (CCl_4) 5.74 μ; nmr δ 3.53 (s, 3, OCH_3), 2.7 (m, 2), 2.4 (m, 1, CHCO), 1.6 (m, 4),

1.4 (m, 1, *exo* CH), and 0.79 (d, 1, J = 7 Hz, *endo* CH),[15] in addition to impurity absorptions. The second, *exo*-5-carbomethoxybicyclo[2.1.1]hexane (**8**), was obtained in 97% purity: ir (CCl_4) 5.74 μ; nmr (100 MHz) δ 3.62 (s, 3, OCH_3), 2.7 (m, 2), 2.3 (m, 1, *exo* CH), 2.07 (d, 1, J = 7.5 Hz, CHCO), 1.60 (broad s, 4), and 0.95 (t, 1, J = 7.5 Hz, *endo* CH).[16] The relatively small return obtained upon glpc collection suggests that polymerization consumed much of the monomeric ma erials.

Photolysis of Methyl *trans,trans*-Octa-2,6-dienoate (1b).—Accurately measured solutions of 11.5 mg of 96% pure **1b** in 1.5 ml of cyclohexane, methanol, and acetone were prepared and degassed. Irradiation at 2537 Å produced methyl *cis,trans*-octa-2,6-dienoate (**4b**) and methyl *cis,trans*- and *trans,trans*-octa-3,6-dienoate (**5b** and **6b**). The data are presented in Table II as the ratio of **1b**:**4b**:(**5b** + **6b**), ignoring a number of minor

TABLE II

Time, hr	Cyclohexane	Methanol	Acetone
1	43:38:19	38:38:24	68:31:1
2	24:33:43	23:26:51	60:38:2
3	12:20:68	7:16:77	55:41:4
4	4:8:88	2:7:91	53:43:4

components (maximum ~15% of the mixture) believed to be *cis* isomers at the isolated double bond. Irradiation of a solution of 18 mg of **1b** and 9 mg of benzophenone in 1.8 ml of benzene at 3500 Å for 2.5 hr gave an *ca.* 3:1 mixture of **1b** and **4b** with less than 5% of **5b** and **6b** present. Further irradiation did not affect the ratio of the first two components.

A solution of 0.15 g of **1b** in 10 ml of methanol was irradiated in the Rayonet reactor at 2537 Å for 11 hr. Glpc indicated that 80% of the product mixture was **5b** and **6b** in about a 1:7 ratio. The methanol was removed at reduced pressure. Glpc gave **6b**: glpc assay, 90% (+10% **5b**); ir (CCl_4) 5.73 and 10.3 μ; nmr δ 5.4 (m, 4, CH=C), 3.59 (s, 3, OCH_3), 2.9 (m, 2), 2.6 (m, 2), and 1.6 (m, 3). Compound **5b** was obtained in a 1:1 mixture with **6b**: ir (CCl_4) 5.73 (C=O), 10.3, and 14.5 μ; nmr δ 5.4 (m, 4, CH=C), 3.59 (s, 3, OCH_3), 3.0 (m, 2), 2.7 (m, 2), and 1.6 (m, 3).

A solution of 0.34 g of **1b** in 34 ml of acetone was irradiated at 2537 Å in the Rayonet reactor for 7 hr. Glpc examination disclosed that 78% of the product was a 3:2 mixture of **1b** and *cis* isomer **4b**. The solvent was removed at reduced pressure. Preparative glpc provided **4b**: ir (CCl_4) 5.79 (C=O), 6.06, and 10.4 μ; nmr δ 6.18 (d of t, 1, J = 12, 7 Hz, CH=CCO), 5.70 (d of t, 1, J = 12, 1 Hz, C=CHCO), 5.4 (m, 2, CH=C), 3.61 (s, 3, OCH_3), 2.71 (m, 2), 2.1 (m, 2), and 1.6 (m, 3).

Irradiation of a solution of 1.02 g of **1b** in 110 ml of acetone with the Hanovia source through a Vycor filter initially led to *cis–trans* isomerization. Upon further irradiation several unidentified products were formed, some of which later declined. The nmr of the crude product after 105 min (glpc analysis shows two important new products in a 2:1 ratio forming 65% of the mixture) revealed that the majority of the product was not unsaturated. A doublet (J = 7 Hz) at the unusually high-field positions of δ 0.68 most likely represents an *endo* methyl group in a bicyclo[2.1.1]hexane system, and another doublet at 1.14 (J = 5 Hz) is appropriately positioned for an *exo* methyl group in the same type of system.[4]

Photolysis of *trans*-Octa-3,7-dien-2-one (1c).—Samples were prepared containing 10 mg of **1c** in the following: 1.0 ml of methanol, cyclohexane, and benzene; 0.9 ml of benzene with 0.1 g of added benzophenone, acetophenone, or naphthalene; and 0.8 ml of benzene with 0.2 ml of added piperylene. These samples were simultaneously irradiated at 3500 Å in the Rayonet reactor using a merry-go-round. The solutions in cyclohexane, methanol, and benzene yielded *cis*-octa-3,7-dien-2-one (**4c**) and *cis*- and *trans*-octa-4,7-dien-2-one (**5c** and **6c**). Table III pre-

TABLE III

Time, hr	Cyclohexane	Methanol	Benzene
1	59:39:2	70:24:6	60:38:2
2	52:42:6	56:30:14	51:40:9
4	44:28:28	26:25:49	36:39:25
8	11:9:80	2:8:88	7:8:84

sents these data in terms of the ratio **1c**:**4c**:(**5c** + **6c**). The data for the samples containing naphthalene and piperylene were essentially identical with those for benzene alone. The samples containing benzophenone and acetophenone reached a 3:1 ratio of **1c** and **4c** after 1 hr and did not change upon further irradiation.

Another series of solutions was prepared consisting of 10 mg of **1c** in 1.0 ml of cyclohexane or benzene and 10 mg of **1c** in 0.9 ml of cyclohexane with 0.1 g of added benzophenone or naphthalene. These were simultaneously irradiated at 2537 Å. After 8 hr no more than 10% of any components other than **1c** and **4c** were present. The ratio of these was 2.5:1 in cyclohexane and in the sample with added benzophenone, and about 1:1 in the other samples.

Simultaneous irradiation at 3100 Å of solutions containing 10 mg of **1c**, **4c** (83%, +**5c** and **6c**), and **5c** + **6c** in 1.0 ml of pentane demonstrated that *cis* isomer **4c** yields **1c** and **5c** + **6c**, and that **5c** and **6c** are essentially inert to these conditions.

A solution of 2.51 g of 87% pure *trans*-octa-3,7-dien-2-one (**1c**) in 410 ml of redistilled 30–60° petroleum ether was irradiated with the Hanovia source through a Pyrex filter for 30 min. Glpc examination indicated that a 46:31:16 mixture of **1c**:**4c**:(**5c** + **6c**) comprised 93% of the sample. The solvent was emoved at reduced pressure, and the residue was distilled to give 2.11 g of colorless liquid (bp 66–89°, 10 mm) of the same composition as above. Glpc separation gave a 91% pure sample of **4c** containing **5c** and **6c** as the only impurities: ir 5.90, 6.09, 6.17, 10.1, and 11.0 μ; nmr (neat) δ 6.1 (m, 2, CH=CHCO), 5.8 (m, 1, CH=C), 5.0 (m, 2, CH_2=C), 2.7 (m, 2), 2.12 (s, 3, CH_3CO), and 2.1 (m, 2); mass spectrum *m/e* (rel intensity) 124 (2), 109 (4), 81 (21), 55 (15), 43 (100).

From the same collection was obtained a sample of **5c** and **6c**: capillary glpc assay, 96% (one peak); ir 5.83, 6.09, 10.1, 10.3, 11.0, and 14.2 μ; nmr δ 5.6 (m, 3, CH=C), 5.0 (m, 2, CH_2=C), 3.1 (m, 2), 2.7 (m, 2), and 2.05 (s, 3, CH_3CO).

A solution of 0.10 g of **1c** in 10 ml of deuteriomethanol (82%) was irradiated at 3500 Å in the Rayonet reactor for 22 hr. Glpc examination indicated that the product was about a 1:3 ratio of *cis*-enone **4c** to deconjugated isomers **5c** and **6c**. The solvent and most of the *cis* enone were removed at reduced pressure to give 97% pure **5c** and **6c**: nmr (neat) δ 5.6 (m, 3), 5.0 (m, 2), 3.1 (m, 1.12 ± 0.16, CHD), 2.7 (m, 2.00), and 2.05 (m, 3). Complete monodeuteration of C_3 would be represented by an integrated value of 1.18 for the 3.1 absorption since the methanol was only 82% deuterated. The observed value represents a minimum of 88% of the possible amount of monodeuteration at C_3, not taking into account an isotope effect.

Registry No.—Allyl vinyl ether, 3917-15-5; 4-pentenal, 2100-17-6; carbomethoxymethyl diethyl phosphonate, 1067-74-9; acetonyl diethyl phosphonate, 1067-71-6; **1a**, 25172-04-7; **1b**, 25172-05-8; **1c**, 25172-06-9; **2a**, 922-00-9; **2c**, 25183-60-2; **3a**, 25183-61-3; **4a**, 25172-07-0; **4b**, 25184-12-7; **4c**, 25172-08-1; **5a**, 25172-09-2; **5c**, 25172-10-5; **6a**, 25172-11-6; **6b**, 25184-13-8; **6c**, 25172-12-7; **7**, 20441-29-6; **8**, 824-41-9; *trans*-4-hexenal, 25166-87-4.

(15) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(16) J. Meinwald, C. B. Jensen, A. Lewis, and C. Swithenbank, *J. Org. Chem.*, **29**, 3469 (1964).

Alkylation of Enamines with t-Propargylic Chlorides[1]

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The alkylation of the pyrrolidine enamines derived from cyclohexanone and cyclopentanone with *t*-propargylic chlorides produced, after hydrolysis, the corresponding 2-*t*-alkylated cycloalkanones. The alkylation was catalyzed by cuprous chloride and the yields depended not only on the substrates used but also on the reaction temperature, solvent polarity, and the presence or absence of a basic nonalkylatable amine. 2-(1,1-Dimethylpropargyl)cyclopentanone (1) formed the expected products following hydrogenation, hydration, oxidative coupling, and sodium borohydride reduction. The hydration product formed novel heterocyclic compounds by reactions with ammonia and hydrazine.

It is now well known that *t*-propargylic chlorides, $R^1R^2C(Cl)—C{\equiv}CH$, react in basic media to produce zwitterion carbene intermediates which behave either as ambident electrophiles or as carbenes.[1b] Tertiary amines have been found to produce *t*-propargylic and/or allenic quaternary ammonium chlorides depending on both the *t*-chloride and the amine used.[3] Enamines,[4] which are known to react both as ambident nucleophiles and as carbene acceptors,[5] constitute a special class of tertiary amines whose reactions with *t*-propargylic chlorides have not been studied previously.

The pyrrolidine enamines derived from cyclohexanone and cyclopentanone were successfully alkylated with a variety of *t*-propargylic chlorides to produce, following hydrolysis, the corresponding 2-*t*-alkynylcyclohexanones and -cyclopentanones. The optimum reaction conditions, determined for the alkylation of 1-pyrrolidino-1-cyclopentene with 3-chloro-3-methyl-1-butyne, consisted of dropwise addition of a slight excess of *t*-chloride to a cold (−10 to −15°) solution of enamine, triethylamine, and a trace of cuprous chloride in dimethylformamide (DMF) solvent maintained under a nitrogen atmosphere. Hydrolysis concomitant with steam distillation gave 2-(1,1-dimethylpropargyl)-cyclopentanone in 50–60% yields. The low reaction temperature was essential to minimize HCl elimination from the *t*-chloride. Alkylation was favored by use of polar solvents (*e.g.*, DMF) and small amounts of copper powder or cuprous chloride proved effective as a catalyst.[6] Triethylamine was used to neutralize the hydrogen chloride liberated in the reaction, thus preventing the consumption of a second mole of the parent enamine.

The reactions of a variety of enamines and *t*-propargylic chlorides were studied to determine the scope and limitations of the alkylation. The reactions employing enamines derived from pyrrolidine gave yields higher than those employing enamines derived from piperidine. This observation, previously seen by Stork,[7] has been rationalized on the basis of Brown's observation[8] that the formation of a trigonal carbon is more facile in five-membered than in six-membered rings. Since the transition state for C-alkylation involves the formation of a trigonal nitrogen, enamines in which the nitrogen is contained in a five-membered ring should be more reactive than enamines in which the nitrogen is in a six-membered ring. It was also found that enamines formed from cyclopentanone gave consistently higher yields than those from enamines formed from cyclohexanone. This result can also be explained on the basis of Brown's observation. The alkylation of enamines derived from mono- and disubstituted acetaldehydes was unsatisfactory since these reactions always gave complex mixtures of products in poor yields.

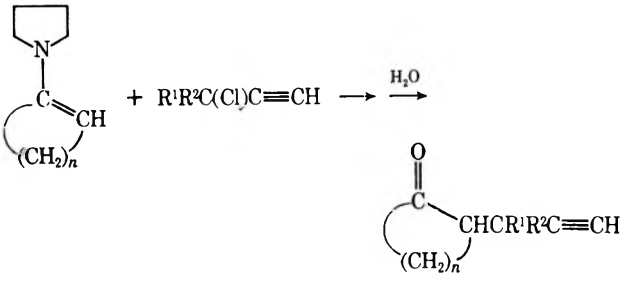
TABLE I

2-(1,1-DIALKYLPROPARGYL)CYCLOALKANONES

$(CH_2)_n—CO—CH—CR^1R^2—C{\equiv}CH$

Compd	n	R^1	R^2	Yield, %	Bp, °C (mm)	$n^{25}D$
1	3	CH_3	CH_3	53	64 (2.2)	1.4642
2	4	CH_3	CH_3	17	77–79 (3)	1.4742
3	3	$-(CH_2)_5-$		33	93–97 (0.5)	1.4986
4	4	$-(CH_2)_5-$		9	85–86 (0.1)	1.5050
5	3	CH_3	C_2H_5	23	63–64 (0.3)	1.4698
6	4	CH_3	C_2H_5	8	47–48 (0.1)	1.4800
7	3	C_2H_5	C_2H_5	12	55–56 (0.2)	1.4745
8	3	H	H	36	58 (2.2)	1.4700

The yield data obtained by variation of the *t*-propargylic chloride paralleled earlier amine alkylation results.[3,6] As the steric bulk of the groups attached to the tertiary carbon was increased, the yields of the alkylated products were sharply reduced. Table I lists the yields and the physical properties of the 2-*t*-alkylated ketones prepared in this work.



(1) (a) Paper No. 88 on substituted acetylenes; (b) previous paper: G. F. Hennion and J. F. Motier, *J. Org. Chem.*, **34**, 1319 (1969).

(2) Eli Lilly Company Fellow, 1967–1969; Lubrizol Corp. Fellow, 1967–1968; Du Pont Teaching Fellow, 1968–1969. Abstracted from a portion of the Ph.D. Dissertation of F. X. Q.

(3) (a) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 3696 (1965); (b) *ibid.*, **31**, 1977 (1966).

(4) For reviews of the preparations and reactions of enamines, see (a) J. A. West, *J. Chem. Educ.*, **40**, 194 (1963); (b) J. Szmuszkovicz in "Advances in Organic Chemistry," Vol. 4, E. C. Taylor, Ed., Interscience, New York, N. Y., 1963, Chapter 1; (c) K. H. Blaha and O. Cervinka in "Advances in Heterocyclic Chemistry," Vol. 6, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1966, p 147.

(5) (a) M. Ohno, *Tetrahedron Lett.*, 1753 (1963); (b) J. Wolinsky, D. Chan, and R. Novak, *Chem. Ind. (London)*, 720 (1965).

(6) Previous studies have shown that other amine alkylations with *t*-propargylic chlorides are similarly catalyzed by copper and/or cuprous chloride. See, G. F. Hennion and R. S. Hanzel, *J. Amer. Chem. Soc.*, **82**, 4908 (1960).

(7) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(8) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

TABLE II

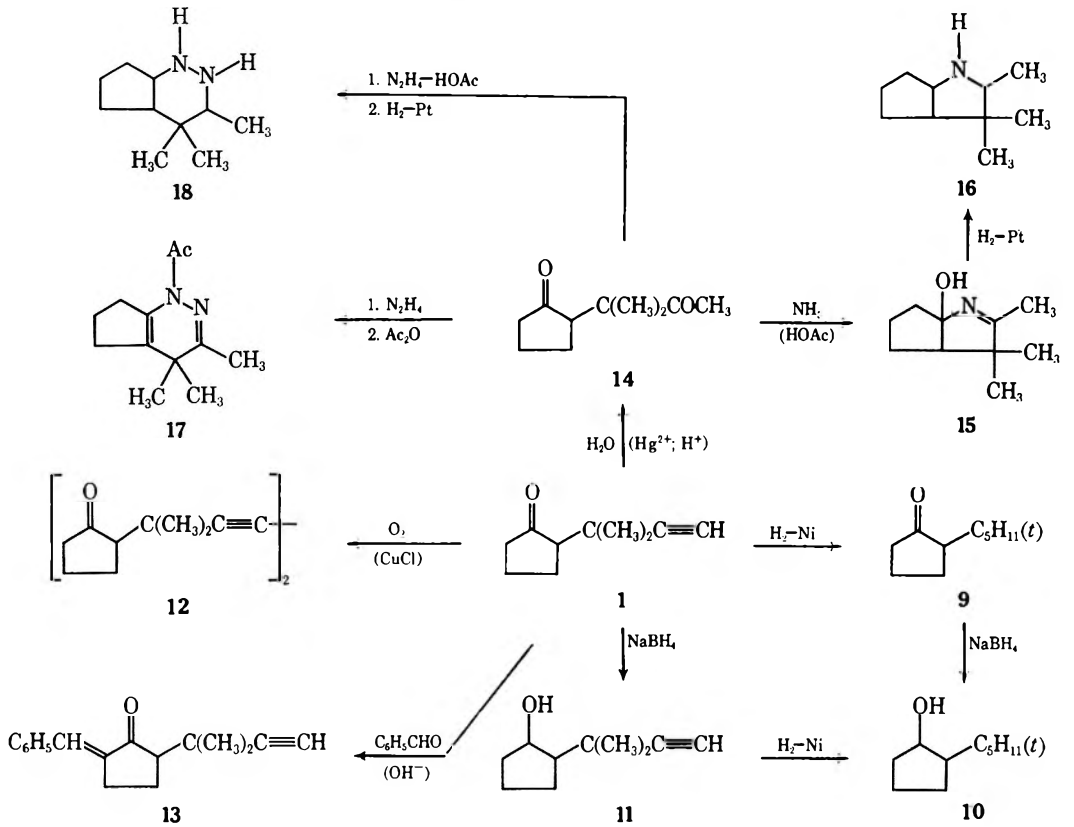
DERIVATIVES OF 2-(1,1-DIALKYLPROPARGYL)CYCLOALKANONES

Deriv[a]	Mp, °C	Formula	% C		% H		% N	
			Calcd	Found	Calcd	Found	Calcd	Found
1 Sc	189–190	$C_{11}H_{17}N_3O$	63.74	63.95	8 27	8.53	20.27	20.49
1 Ph	174–176	$C_{16}H_{18}N_4O_4$	58.17	58.25	5 49	5.71	16.96	17.21
1 Ox	85–86	$C_{10}H_{15}NO$	72.69	72.45	9 15	8.94	8.48	8.28
2 Ph	140–142	$C_{17}H_{20}N_4O_4$	59.29	59.15	5.85	6.05	16.27	16.32
3 Sc	196–197	$C_{14}H_{21}N_3O$	67.99	68.05	8.56	8.38	16.99	16.86
3 Ph	162–164	$C_{19}H_{22}N_4O_4$	61.61	61.73	5.99	5.95	15.13	15.14
4 Sc	194–196	$C_{15}H_{23}N_3O$	68.93	68.97	8.87	9.02	16.08	16.24
5 Sc	176–177	$C_{12}H_{19}N_3O$	65.13	65.39	8.65	8.56	18.99	19.23
5 Ph	169–170	$C_{17}H_{20}N_4O_4$	59.29	59.27	5.85	5.77	16.27	16.37
6 Sc	146–148	$C_{13}H_{21}N_3O$	66.35	66.12	8.99	8.76	17.86	17.80
6 Ph	150–151	$C_{18}H_{22}N_4O_4$	60.32	60.59	6.19	6.26	15.63	15.83
7 Sc	156–157	$C_{13}H_{21}N_3O$	66.35	66.09	8.99	9.01	17.86	18.03
7 Ph	159–160	$C_{18}H_{22}N_4O_4$	60.32	60.34	6.19	6.28	15.63	15.85
8 Ph	131–132	$C_{14}H_{14}N_4O_4$	55.63	55.77	4.67	4.56	18.53	18.61

[a] Sc = semicarbazone; Ph = 2,4-dinitrophenylhydrazone; Ox = oxime.

SCHEME I

REACTIONS OF 2-(1,1-DIMETHYLPROPARGYL)CYCLOPENTANONE



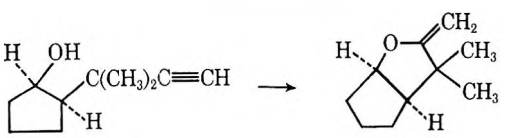
The structures of the alkylated products were established by ir and nmr spectroscopy (see Experimental Section), by the analysis of crystalline carbonyl derivatives (see Table II), and by a variety of chemical reactions characteristic of ketones and terminal ethynyl groups. Furthermore, the dialkylpropargyl moiety was firmly established to be in the position α to the carbonyl by several ring closure reactions (see below).

The reactions of the 2-*t*-alkylated cycloalkanones were then studied using 2-(1,1-dimethylpropargyl)-cyclopentanone (**1**) as a model. A summary of its reactions is presented in Scheme I. The propargylic ketone **1** displayed reactivity typical of acetylenic compounds. Hydration, hydrogenation, and oxidative coupling produced the normal 1,4 diketone **14**, saturated ketone **9**, and conjugated diyne **12** (as a mixture of diastereoisomers), respectively.

All the ketones reacted with 2,4-dinitrophenylhydrazine and semicarbazide in the typical manner. There was no evidence of any subsequent cyclization of the derivatives into the triple bond. Furthermore, ketone **1** formed the normal oxime derivative which could not be thermally cyclized by prolonged heating above its melting point. The reaction of **1** with benzaldehyde produced the normal benzal derivative **13**. There was no evidence of any product formed by reaction through the acetylide anion.

Ketone **1** was reduced by sodium borohydride to a mixture of *cis*- and *trans*-2-(1,1-dimethylpropargyl)-cyclopentanols (**11**). The *cis*/*trans* ratio could not be

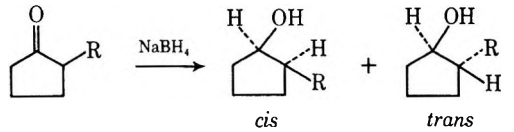
obtained directly by glpc of the reaction mixture owing to the facile cyclization of the *cis* alcohol to form a vinyl ether. However, hydrogenation to the saturated alcohols prior to glpc analysis allowed the *cis/trans* ratio to be obtained. The reaction product (**11**) on glpc analysis produced three fractions identified as vinyl ether (**19**), a mixture of **19** and *cis* alcohol, and *trans* alcohol, re-



cis **19**

spectively. The ir of **19** exhibited bands at 3120 cm^{-1} and 1665 and 1595 cm^{-1} typical of the >C=CH_2 and -O—C=CH_2 groups, respectively. The nmr displayed twin singlets at 1.1 and 1.2 ppm (anisochronous $(CH_3)_2C$ group), an AX pattern at 3.6 and 4.0 ppm (J = 1.5 Hz, -O—C=CH_2), and a broad multiplet centered at 4.75 ppm (-CH—O-). The vinyl ether should have only *cis*-ring fusion and was, therefore, assigned structure **19**. The isolation and the identification of **19**, coupled with the observations that the second fraction contained **19** in a mixture with its alcohol precursor and that the third fraction contained the noncyclizing alcohol, firmly established that the *cis* alcohol had the shorter retention time. This assignment of the structures was further substantiated by the nmr of the respective isomers. Though the *cis* isomer could not be obtained pure, a comparison of the nmr of the pure *trans* isomer with that of the original reduction product allowed an assignment of the *cis* peaks. The important feature of the spectra was the relative positions of the hydroxyl proton resonances. Since hydrogen bonding is known to cause a downfield shift of the proton resonance,[9] the *trans* hydroxyl proton, as expected, appeared at a significantly lower field than the *cis* proton [*e.g.*, 3.9 ppm (*trans*) *vs.* 2.8 ppm (*cis*)]. The saturated alcohols exhibited the same trends in both retention times and nmr. Thus, *cis*-2-*t*-amylcyclopentanol had the shorter retention time and its hydroxyl proton resonance appeared at a considerably higher field than that of its *trans* isomer [*e.g.*, 2.77 ppm (*cis*) *vs. ca.* 3.5 ppm (*trans*)].

2-Propargylcyclopentanone (**8**) was likewise reduced. However, no attempts were made to isolate and separate the *cis*- and *trans*-2-propargylcyclopentanols. Instead, the reduction product was hydrogenated and the 2-propylcyclopentanols were separated and identified. In addition, the saturated ketones were reduced and the *cis/trans* ratios were determined by



cis *trans*

glpc. Table III lists the product ratios for the reductions studied. It is worth noting that the ketones bearing the bulkiest groups (*e.g.*, dimethylpropargyl and *t*-amyl) produce the *cis* isomer preferentially, whereas those ketones bearing relatively small groups

(9) I. V. Aleksandrov, "The Theory of Nuclear Magnetic Resonance," Academic Press, New York, N. Y., 1966, p 149.

TABLE III

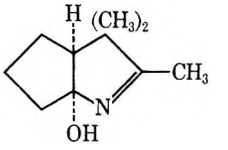
PRODUCT RATIOS FOR THE SODIUM BOROHYDRIDE REDUCTIONS OF SELECTED 2-SUBSTITUTED CYCLOPENTANONES

	Cyclopentanol	
R	% *cis*	% *trans*
$-C(CH_3)_2C{\equiv}CH$	69	31
$-C(CH_3)_2CH_2-CH_3$	61	39
$-CH_2C{\equiv}CH$	34	66
$-CH_2CH_2-CH_3$	28	72
$-CH_3$[a]	26	74

[a] J. B. Umland and B. W. Williams, *J. Org. Chem.*, **21**, 1302 (1956).

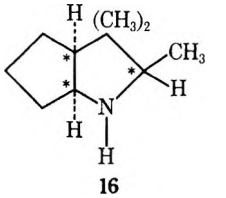
produce the *trans* isomer preferentially. This result appears to be another example of steric approach control (with bulky groups) *vs.* product development control (with the small groups).[10]

The cyclization reactions of diketone **14** with ammonia and hydrazine were also studied. The reaction of **14** with ammonium acetate in glacial acetic acid produced a stable solid identified as 1-hydroxy-3,4-4-trimethyl-2-azabicyclo[3.3.0]-2-octene (**15**). Hydrolysis of **15** regenerated the starting diketone **14**. The ir and nmr spectra of **15** were consistent with the assigned structure (see Experimental Section). The hydroxyl group was assigned to the bridgehead carbon (carbon 1) from the mass spectrum which displayed a strong peak (50%) at m/e 126 (P − 41) corresponding to the loss of CH_3CN. Since the nmr spectrum and the sharp melting point of the solid indicated that the product was not a diastereomeric pair and since the steric features favor *cis*-ring fusion, the product was assigned the structure shown below.



15

Heterocycle **15** was hydrogenated over platinum producing the amine **16** formed by the saturation of the -C=N- group and hydrogenolysis of the hydroxyl group. Though the product could have been a mixture of four diastereomeric pairs, the nmr spectrum indicated that the product consisted of only two diastereomeric pairs. This conclusion was made on the basis of the appearance of only eight peaks due to the methyl groups. Since each pair of diastereomers would be expected to give rise to four peaks, a doublet for >$CHCH_3$ and twin singlets for $(CH_3)_2C$, had the product been a mixture of the four possible *d,l* pairs, a total of 16 peaks would have been predicted.

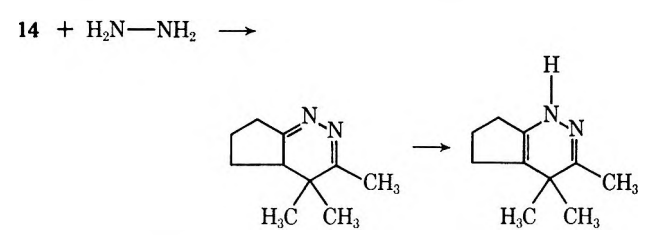


16

The reaction of **14** with hydrazine in glacial acetic acid produced an unstable oil which on distillation suffered extensive decomposition and tar formation. The

(10) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

ir and nmr spectra of the crude distillate (bp 60–90°, 1 mm) indicated that the initial reaction product tautomerized, as shown below. The ir spectrum displayed



a strong band at 1695 cm^{-1} (-C=N-) and a band of medium intensity at 1618 cm^{-1} (C=C). The nmr spectrum exhibited a broad peak (*ca.* 1, N—H) centered at 7.1 ppm, a singlet (3, CH_3C=N-) at 1.87 ppm, and a singlet [6, $(CH_3)_2C$] at 1.13 ppm. The crude product formed a stable acetyl derivative identified as 2-acetyl-4,5,5-trimethyl-2,3-diazabicyclo[4.3.0]-1(6),3-nonadiene (**17**). Hydrolysis of **17** regenerated the starting diketone **14**. The ir and nmr spectra of **17** were consistent with the assigned structure (see Experimental Section). The original reaction mixture (*i.e.*, the solution of the dihydropyridazine in acetic acid) was hydrogenated over platinum to form the hexahydropyridazine **18**.

Experimental Section

The *t*-propargylic chlorides were prepared as previously reported.[11] 1-Pyrrolidino-1-cyclopentene[7] and 1-pyrrolidino-1-cyclohexene[7] were prepared according to the procedure of Herr and Heyl.[12]

The 2-(1,1-dialkylpropargyl)cycloalkanones listed in Table I were prepared according to the procedure described below.

2-(1,1-Dimethylpropargyl)cyclopentanone (1).—A solution of 68.5 g (0.5 mol) of 1-pyrrolidino-1-cyclopentene, 76.5 g (0.75 mol) of triethylamine, and 0.5 g of cuprous chloride in 200 ml of DMF was cooled to −10° under nitrogen and 76.5 g (0.75 mol) of 3-chloro-3-methyl-1-butyne was added dropwise with stirring over 4 hr. The mixture was stirred at near −10° for an additional 5 hr and allowed to warm to room temperature overnight. Then 125 ml of 4 *N* hydrochloric acid was added dropwise and the mixture was steam distilled. The distillate was extracted with ten 50-ml portions of ether. The combined ethereal solution was washed with 50 ml of 10% hydrochloric acid, twice with 50-ml portions of water, with 50 ml of dilute sodium bicarbonate, and finally three times with 50-ml portions of water, and then dried over anhydrous potassium carbonate. Distillation gave 40 g (53%) of 1: bp 64° (2.2 mm); $n^{25}D$ 1.4642; ir (neat) 3310 and 2118 (C≡C—H) and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.1 and 2.5–1.5 (singlet superimposed on a multiplet, 8, ≡C—**H** and $C_4\mathbf{H}_7$ ring protons), and 1.3 and 1.4 (s, 3 each, anisochronous $(CH_3)_2C$).

2-*t*-Amylcyclopentanone (9) was prepared from 15.0 g (0.1 mol) of 1 dissolved in 50 ml of absolute ethanol containing 2 g of Raney nickel. The hydrogenation was carried out at room temperature for 1 hr at an initial pressure of 36 psig. Distillation afforded 13.4 g (87%) of 9: bp 72° (2.2 mm); $n^{25}D$ 1.4523; ir (neat) 1730 cm^{-1} (strong, >C=O), but no absorption at 3330 and 2115 (C≡C—H), 3080 and 900 (=CH_2), nor 1655 cm^{-1} (C=C).

The semicarbazone had mp 177–178°.

Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.86. Found: C, 62.80; H, 9.87; N, 20.12.

The 2,4-dinitrophenylhydrazone had mp 127–129°.

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.63; H, 6.92; N, 17.02.

2-Propylcyclopentanone (9a) was prepared according to the procedure described above. Hydrogenation of a 12.2-g (0.1 mol) sample of 2-propargylcyclopentanone (8) yielded 9.56 g (76%) of 9a: bp 60–61° (5.5 mm); $n^{25}D$ 1.4393 (lit.[13] bp 175–177°; $n^{30}D$ 1.4382).

2-*t*-Amylcyclopentanol (10).—A solution of 10.0 g (0.065 mol) of 2-*t*-amylcyclopentanone (9) in 20 ml of absolute ethanol was added to a solution of 2.0 g (0.05 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 75 ml of absolute ethanol. The reaction mixture was refluxed for 4 hr, cooled to room temperature, and then concentrated on a rotary evaporator. The residue was hydrolyzed with 70 ml of 4 *N* hydrochloric acid and extracted with ether. The extracts were washed with water, dilute sodium bicarbonate, again with water, and dried over anhydrous calcium sulfate. Distillation gave 7.8 g (78%) of 10: bp 70–72° (0.8 mm); $n^{25}D$ 1.4654; ir (neat) 3580–3330 cm^{-1} (-OH) but no absorption at 1730 cm^{-1} (C=O).

The product was shown by glpc to consist of 67% *cis* and 33% *trans* isomer. The isomers were separated by preparative gas chromatography (15% Hyprose on Chromosorb W at 140°; 15 ft × 0.25 in. (OD); helium flow rate, 60 ml/min; retention times *cis* 33 min, *trans* 44 min). The isolated isomers exhibited the following properties: *cis* $n^{25}D$ 1.4651; ir (neat) 3610 (w, nonbonded -OH) and 3580–3100 cm^{-1} (bonded -OH); nmr (neat) δ 4.17 (broad m, 1, CHOH), 2.77 (broad m, 1, -OH), and 2.0–0.5 (overlapping m, 18); *trans* $n^{25}D$ 1.4639; ir (neat) 3600 (w, nonbonded -OH) and 3580–3060 cm^{-1} (bonded -OH); nmr (neat) δ 4.4–3.3 (broad overlapping m, 2, CHOH) and 2.0–0.4 (overlapping m, 18).

The original mixture gave a 3,5-dinitrobenzoate, mp 109.5–111°, and the alcohol recovered by saponification was found by glpc to consist of 94% *cis* and 6% *trans* isomer. Crystallization of the 3,5-dinitrobenzoate from 95% ethanol gave an analytical sample, mp 112.5–114.5°.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.27; H, 6.35; N, 7.87.

2-Propylcyclopentanol (10a).—A 4.2-g (0.03 mol) sample of 2-propylcyclopentanone (9a) was reduced according to the procedure described above using 1.0 g (0.03 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 75 ml of absolute ethanol. Distillation gave 3.0 g (70%) of 10a: bp 69–72° (4 mm); $n^{25}D$ 1.4519.

The product was shown by glpc to be a mixture of the *cis* and *trans* alcohols. These were separated by preparative gas chromatography and exhibited the following properties: *cis* $n^{25}D$ 1.4533 [lit.[14] $n^{9}D$ 1.4600, bp 79–80° (12 mm), lit.[15] $n^{22}D$ 1.4540]; ir (neat) 3610 (w, nonbonded -OH) and 3580–3060 cm^{-1} (bonded -OH); nmr (neat) δ 4.4–3.4 (broad overlapping m, 2, CHOH) and 2.2–0.4 (broad overlapping m, 14); *trans* $n^{25}D$ 1.4509 [lit.[14] $n^{9}D$ 1.4565; bp 78–79° (10 mm)]; ir (neat) 3600 (shoulder, nonbonded -OH) and 3580–3040 cm^{-1} (bonded -OH); nmr (neat) δ 4.7 (m, 1, -OH), 3.6 (broad m, 1, CHOH), and 2.2–0.5 (broad overlapping m, 14).

2-(1,1-Dimethylpropargyl)cyclopentanol (11).—A solution of 2.0 g (0.05 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 15.0 g (0.1 mol) of acetylenic ketone 1 in 100 ml of absolute ethanol was allowed to stand at room temperature overnight. The reaction mixture was then concentrated on a rotary evaporator. The residue was cooled in an ice bath, diluted with 50 ml of water, and hydrolyzed with 75 ml of 4 *N* hydrochloric acid. The acidic solution was extracted with ether and the extracts were washed with water, dilute sodium bicarbonate, and again with water, and finally dried over anhydrous calcium sulfate. Distillation afforded 11.4 g (75%) of 11: bp 62–67° (2.2 mm). Redistillation gave bp 61–65° (2 mm); $n^{25}D$ 1.4697; ir (neat) 3600–3510 (-OH), 3333 and 2110 cm^{-1} (C≡C—H), but no absorption at 1730 cm^{-1} (C=O).

Hydrogenation of a 3.15-g (0.02 mol) sample of 11 with either Raney nickel (1.5 g) or platinum oxide (0.05 g) in absolute ethanol gave 2.5 g (75%) of 2-*t*-amylcyclopentanol (10): bp 47–48° (0.8 mm); $n^{25}D$ 1.4660; ir (neat) corresponded to a mixture of *cis*- and *trans*-2-*t*-amylcyclopentanol (10), described above; glpc showed the isomer ratio to be 87% *cis* and 13% *trans*.

1,6-Di(2-ketocyclopentyl)-1,1,6,6-tetramethyl-2,4-hexadiyne (12).—A solution of 5 g (0.03 mol) of 1 in 25 ml of absolute ethanol was added to a solution of 8 g (0.08 mol) of cuprous chloride, 13.2 g (0.25 mol) of ammonium chloride, 0.5 ml of concentrated hydrochloric acid, and 40 ml of water. The solution was shaken

(11) (a) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, **72**, 3542 (1950); (b) G. F. Hennion and K. W. Nelson, *ibid.*, **79**, 2142 (1957); (c) G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, **26**, 725 (1961).

(12) M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.*, **74**, 3627 (1952).

(13) D. N. Chatterjee, *ibid.*, **77**, 414 (1955).

(14) G. Vavon and J. Flurer, *Bull. Soc. Chim. Fr.*, **45**, 754 (1929).

(15) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 1755 (1951).

mechanically (5 hr) under a slight positive oxygen pressure, diluted with 50 ml of cold water, and filtered. The solid was washed with 75 ml of 10% hydrochloric acid followed by 75 ml of water to yield 4.5 g (91%), mp 103–110°. Crystallization from 60% aqueous methanol gave 4.2 g (85%): mp 107–117°; ir (KBr) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.5–1.5 (overlapping m, 7) and 1.36 and 1.29 (s, 6, anisochronous $(CH_3)_2C$).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.29; H, 8.60.

2-(1,1-Dimethylpropargyl)-5-benzalacyclopentanone (13) was prepared in the usual manner.[16] To a solution of 2.2 g (0.06 mol) of sodium hydroxide in 40 ml of 50% aqueous ethanol was added 5.0 g (0.03 mol) of **1** and 5.0 g (0.05 mol) of benzaldehyde. The yellow solid was collected and washed with water, yield 7.6 g (96%). The product was crystallized from 95% ethanol: mp 122.5–124.5°; ir (KBr) 3330 (≡C—H), 1700 (C=O), 1620 (C=C), and 764 and 690 cm^{-1} (C_6H_5–); nmr ($CDCl_3$) δ 8.0–7.5 (m, 6, olefinic and aromatic protons), 2.13 and 3.3–1.6 (singlet superimposed on overlapping m, 6, C≡C—**H** and C_4H_5 ring protons), and 1.51 and 1.44 (s, 3 each, anisochronous $(CH_3)_2C$).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.88; H, 7.76.

2-(1,1-Dimethylacetonyl)cyclopentanone (14) was prepared from an 11.25-g (0.075 mol) sample of **1** by treatment with a mixture of 3.5 ml of water, 8 ml of methanol, 0.25 g of red mercuric oxide, and 0.5 ml of concentrated sulfuric acid at 55–60° following the procedure of Hennion and Watson.[17] Distillation gave 10.15 g (81%) of **14**: bp 93–94° (2 mm); $n^{25}D$ 1.4665; ir (neat) 1740 (ring >C=O) and 1710 cm^{-1} (chain >C=O); nmr ($CDCl_3$) δ 2.14 and 2.7–1.4 (singlet superimposed on overlapping m, 10, CH_3CO and C_4H_7 ring protons) and 1.19 and 1.15 (s, 3 each, anisochronous $(CH_3)_2C$).

The bis-semicarbazone had mp 222–223°.

Anal. Calcd for $C_{12}H_{22}N_6O_2$: C, 51.05; H, 7.85; N, 29.76. Found: C, 50.85; H, 7.74; N, 29.67.

The bis-2,4-dinitrophenylhydrazone had mp 233–235° dec.

Anal. Calcd for $C_{22}H_{24}N_8O_8$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.26; H, 4.74; N, 21.30.

2-(1-Acetylcyclohexyl)cyclopentanone (14a) was prepared according to the procedure described above. The hydration of a 14.3-g (0.075 mol) sample of 2-(1-ethynylcyclohexyl)cyclopentanone (**3**) afforded 13.0 g (83%) of **14a**: bp 99–102° (0.05 mm); $n^{25}D$ 1.4982; ir (neat) 1740 (ring >C=O) and 1710 cm^{-1} (chain >C=O).

The bis-2,4-dinitrophenylhydrazone had mp 222–223° dec.

Anal. Calcd for $C_{25}H_{28}N_8O_8$: C, 52.81; H, 4.96; N, 19.71. Found: C, 52.79; H, 5.00; N, 19.80.

1-Hydroxy-3,4,4-trimethyl-2-azabicyclo[3.3.0]-2-octene (15).—To a solution of 5.15 g (0.067 mol) of ammonium acetate and 15 g (0.25 mol) of glacial acetic acid was added 6.7 g (0.04 mol) of diketone **14**. The reaction mixture was stirred at 50° for 6 hr, cooled to room temperature, and added slowly to 25 ml (0.38 mol) of cold concentrated ammonium hydroxide. The solid was collected and air dried to yield 5.2 g (78%), mp 120–134°. Crystallization from cyclohexane gave 4.6 g (69%), mp 134–137°. Sublimation provided an analytical sample: mp 134–136.5°; ir (KBr) 3230–3070 (–OH) and 1645 cm^{-1} (>C=N–); nmr ($CDCl_3$) δ 6.8 (broad s, 1, –**OH**), 1.98 and 2.3–1.2 (singlet superimposed on overlapping m, 10, CH_3—C=N– and C_4H_7 ring protons) and 1.27 and 1.07 (s, 3 each, anisochronous $(CH_3)_2C$). Mass spectrum calcd for $C_{10}H_{17}NO^+$: 167. Found: 167.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.79; H, 10.13; N, 8.17.

3,4,4-Trimethyl-2-azabicyclo[3.3.0]octane (16) was prepared by hydrogenation of an 11.0-g (0.07 mol) sample of **15** dissolved in 65 ml of absolute ethanol containing 0.66 g of platinum oxide. The reaction was carried out at room temperature for 15 hr at an initial pressure of 50 psig. Distillation gave 8.18 g (81%) of **16** (as a mixture of diastereoisomers): bp 65–66° (4 mm); $n^{25}D$ 1.4719; ir (neat) 3306 (m, –NH–) and 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 4.0–3.7 (broad m, 1, bridgehead proton adjacent to nitrogen), 2.7 (overlapping q, J = 6.5 Hz, 1, CH_3CH), 2.5–1.1 (overlapping m, 9, ring protons and –NH–), 1.0–0.7 (complex pattern corresponding to two pairs of doublets and four singlets, 9, CH_3CH and $(CH_3)_2C$).

The hydrochloride salt had mp 187–189°.

Anal. Calcd for $C_{10}H_{20}NCl$: C, 63.01; H, 10.63; N, 7.38. Found: C, 63.49; H, 10.73; N, 7.49.

2-Acetyl-4,5,5-trimethyl-2,3-diazabicyclo[4.3.0]-1(6),3-nonadiene (17).—A 6.7-g (0.04 mol) sample of diketone **14** was added to a solution of 4.12 g (0.07 mol) of 85% hydrazine hydrate in 20 g of glacial acetic acid. The reaction mixture was stirred at 40–50° under nitrogen for 8 hr. Then 30 g (0.29 mol) of acetic anhydride was added slowly. The solution was stirred at 90° for 1 hr and poured over crushed ice. The white solid which precipitated was collected, washed with water, and air dried to yield 6.4 g (78%), mp 66–71°. Sublimation provided an analytical sample: mp 72–73°; ir (KBr) 1690–1660 (strong, broad, CH_3C=O and >C=N–) and 1615 cm^{-1} (>C=C<); nmr ($CDCl_3$) δ 3.3–2.8 (broad m, 2, –CH_2—C(N)=C<), 2.30, 2.00, and 2.6–1.6 (two singlets superimposed on overlapping m, 10, CH_3C=O, CH_3C=N–, and CH_2CH_2), and 1.20 (s, 6, $(CH_3)_2C$).

Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.59; H, 8.85; N, 13.31.

4,5,5-Trimethyl-2,3-diazabicyclo[4.3.0]nonane (18).—A 6.7-g (0.04 mol) sample of diketone **14** was added to a solution of 4.12 g (0.07 mol) of 85% hydrazine hydrate in 20 g of glacial acetic acid. The reaction mixture was stirred at 45–50° for 6 hr under nitrogen, cooled to room temperature, and added to 25 ml of glacial acetic acid containing 0.4 g of platinum oxide. The resulting mixture was hydrogenated at roon temperature under an initial hydrogen pressure of 50 psig for a period of 8 hr. The solution was filtered and added slowly to 150 ml of cold concentrated ammonium hydroxide. The product was extracted into ether and the extract was washed twice with water and dried over anhydrous potassium carbonate. Distillation gave 2.6 g (38%) of **18**: bp 65° (0.2 mm); $n^{25}D$ 1.4970; ir (neat) 3360–3180 cm^{-1} (–NH–NH–), but no absorption between 1700 and 1600 cm^{-1}; nmr ($CDCl_3$) δ 3.2 (broad m, 3, –NH–NH–CH), 2.41 (q, J = 7 Hz, 1, CH–CH_3), 2.0–1.2 (overlapping m, 7, ring protons), 1.11 (d, J = 7 Hz, 3, CH_3–CH), and 1.00 and 0.90 (s, 3 each, anisochronous $(CH_3)_2C$). After treatment with deuterium oxide the multiplet (3, –NH–NH–CH) centered at 3.15 ppm reduced to a multiplet (1, –ND–ND–CH) centered at 3.24 ppm.

Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 72.27; H, 12.14; N, 15.99.

Registry No.—**1**, 25111-16-4; **1** Sc, 25111-17-5; **1** Ph, 25111-18-6; **1** Ox, 25111-19-7; **2**, 25111-20-0; **2** Ph, 25111-21-1; **3**, 25111-22-2; **3** Sc, 25158-31-0; **3** Ph, 25111-23-3; **4**, 25111-24-4; **4** Sc, 25111-25-5; **5**, 25111-26-6; **5** Sc, 25184-15-0; **5** Ph, 25184-16-1; **6**, 25184-17-2; **6** Sc, 25184-18-3; **6** Ph, 25184-19-4; **7**, 25184-20-7; **7** Sc, 25184-21-8; **7** Ph, 25184-22-9; **8**, 19842-40-1; **8** Ph, 25184-24-1; **9**, 25184-25-2; **9** Sc, 25184-26-3; **9** Ph, 25184-27-4; **10** *cis*, 25172-39-8; **10** *cis* (3,5-dinitrobenzoate), 25172-40-1; **10** *trans*, 25172-41-2; **10a** *cis*, 25172-42-3; **10a** *trans*, 25172-43-4; **11**, 25184-28-5; **12**, 25184-29-6; **13**, 25150-10-1; **14**, 25184-30-9; **14** bis-Sc, 25184-31-0; **14** bis-Ph, 25150-11-2; **14a**, 25184-32-1; **14a** bis-Ph, 25184-33-2; **15**, 25184-34-3; **16**, 25184-35-4; **16** HCl, 25184-36-5; **17**, 25184-37-6; **18**, 25183-62-4.

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Macrocyclic Synthesis. II. Cyclohexanone Peroxides

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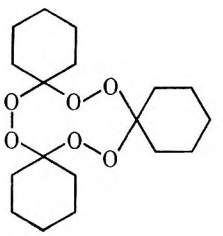
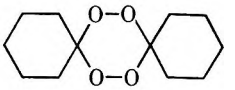
The reaction of cyclohexanone with hydrogen peroxide to yield both the dimeric and trimeric cyclic peroxides has been investigated. It has been found that tricyclohexylidene peroxide is the kinetic product under most conditions and that dicyclohexylidene peroxide is easily formed from it. Improved syntheses of the peroxides, particularly for the trimer, have resulted.

The thermal and photochemical decomposition of peroxides of cyclic ketones has been found to provide a general and facile synthesis of macrocyclic compounds.[1] For this reason a better understanding of the synthesis of the requisite peroxides is required. The most important such peroxides are those of cyclohexanone. The term "cyclohexanone peroxide" has been applied to a number of different compounds, usually in the generic sense to mixtures of peroxides which find application as initiators in polymerization. Frequently, the actual structure of the peroxide in hand is not known. In general, yields are low and there is insufficient information about the intermediates and complex equilibria involved in the synthesis of cyclohexanone peroxides.

This report is concerned primarily with just two of the several cyclohexanone peroxides, dicyclohexylidene peroxide (**2**) and tricyclohexylidene peroxide (**1**). We have correlated much of the available data on the cyclohexanone–(hydrogen peroxide) reaction with our own findings to develop a mechanistic scheme which, in turn, has led to improved synthesis of these peroxides (**1**, **2**).



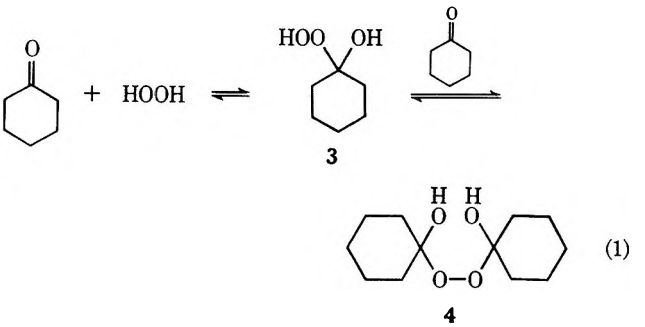
1



2

Probably the focal point of present knowledge is the paper by Antonovskii, Nesterov, and Lyashenko[2] who have made a detailed study of the acid-catalyzed reaction of cyclohexanone and hydrogen peroxide. These investigators have, in part, rewritten the sequence of intermediates proposed by Criegee,[3] by Kharasch and Sosnovsky,[4] and by others.[5]

It was confirmed,[2] as asserted by Kharasch and Sosnovsky,[4] that treatment of cyclohexanone with hydrogen peroxide in neutral solution yields only the 1,1′-dihydroxydieyclohexyl peroxide (**4**), even in the presence of a large excess of hydrogen peroxide (eq 1).



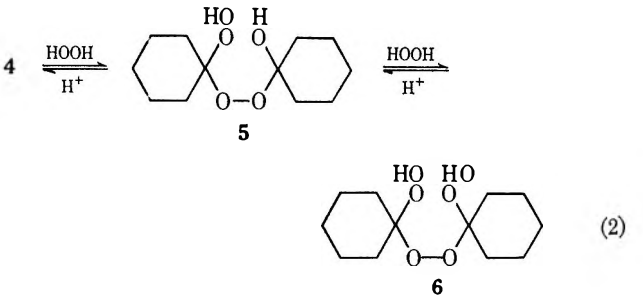
(1)

3

4

The presumed intermediate, **3**, could not be isolated in this case; however, it should be noted that the corresponding derivative of α-halocyclohexanones is known.[4,6]

In acidic solutions, depending on acid concentration, more highly peroxygenated compounds (**5** and **6**) are formed. As pointed out by Antonovskii, *et al.*,[2] earlier investigators had assumed, and quite reasonably, that the more highly peroxygenated derivatives, **5** and **6**, were derived from **4** (eq 2).[3-5,7,8] Antonovskii, *et al.*,[2]

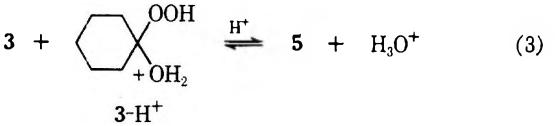


(2)

5

6

report evidence to the contrary. These investigators conclude that 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide (**5**) appears to form directly from **3** in "weakly" acidic solutions, *i.e.*, eq 3. This conclusion is based on



(3)

3-H^+

their observation that conversion of **4** to **5** is appreciably slower than formation of **5** from cyclohexanone and hydrogen peroxide with acid (eq 3). Their argument is difficult to evaluate, however, because of the lack of data reported in the paper.[2]

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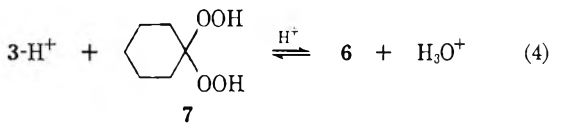
(5) (a) N. Brown, M. J. Hartig, M. J. Roedel, A. W. Anderson, and C. E. Schweitzer, *J. Amer. Chem. Soc.*, **77**, 1756 (1955); (b) W. Cooper and W. H. T. Davison, *J. Chem. Soc.*, 1180 (1952); (c) N. A. Milas, S. A. Harris, and P. S. Panagiotakos, *J. Amer. Chem. Soc.*, **61**, 2430 (1939).

(6) M. Schulz, K. Kirschke, and E. Höhne, *Chem. Ber.*, **100**, 2242 (1967).

(7) A. Rieche, *Angew. Chem.*, **73**, 57 (1961).

(8) M. Schulz and K. Kirschke, *Advan. Heterocycl. Chem.*, **8**, 165 (1967).

In more concentrated acid, **3** is converted to the *gem*-dihydroperoxide (**7**) and the 1,1′-dihydroperoxydicyclohexyl peroxide (**6**) is formed by reaction of **3**-H^+ and **7**, according to Antonovskii, *et al.*[2] (eq 4).



$$\mathbf{3}\text{-}H^+ + \mathbf{7} \rightleftharpoons \mathbf{6} + H_3O^+ \qquad (4)$$

Results and Discussion

Synthesis of dicyclohexylidene peroxide (**2**) has been reported in low yield[4] and it seems to be generally understood that **2** is formed by dehydration of the hydroxyhydroperoxy peroxide (**5**), *i.e.*[8]

$$\mathbf{5} \overset{H^+}{\rightleftharpoons} \mathbf{2} \qquad (5)$$

We have repeated the Kharasch and Sosnovsky preparation of the dimer (**2**), and close examination reveals three distinct stages to the reaction. (1) Initially, on mixing, the cyclohexanone–(hydrogen peroxide) solution becomes warm and homogeneous. (2) On addition of glacial acetic acid and perchloric acid, followed by warming to 40°, a turbid solution develops. (3) Further heating of the solution to about 60° produces a clear solution which on subsequent work-up affords the dimer (**2**) in 14–23% yield.

Our early attempts at the Kharasch–Sosnovsky synthesis yielded the trimeric peroxide **1** instead of the expected dimer **2**. Subsequently, we found that if the reaction is stopped during stage 2 (omitting heating to 40°), only the trimeric peroxide **1** is isolated, 72% yield; dimer **2** is produced by carrying the reaction through stage 3. This suggests that the trimer **1** is the kinetically controlled product and that dimer is the thermodynamically more stable product.

Accordingly, we treated pure trimer **1** under Kharasch–Sosnovsky conditions, *i.e.*, perchloric acid in acetic acid at 60° for 1 hr, and obtained the dimeric peroxide **2** in 53% yield. Repeating the same experiment at room temperature afforded only trimer, which was recovered in 82% yield.

$$\mathbf{1} \overset{H^+}{\rightleftharpoons} \mathbf{2} \qquad (6)$$

We have also investigated the new synthesis of Ledaal[9] and find, there too, that the initial product is trimeric peroxide **1** rather than dimer **2** as reported. The Ledaal procedure involves reacting cyclohexanone, hydrogen peroxide, and perchloric acid in acetonitrile and allowing the solution to evaporate, leaving the solid product. Duplicating the published procedure, we isolate trimer **1** in 82% yield. Further investigation, however, revealed the reaction to be sensitively dependent on temperature. We have not systematically investigated the effect of temperature, but we find that the Ledaal synthesis can yield dimer if the reaction is carried out at higher than average room temperatures, *i.e.*, between 25 and 30°. It is possible that the published Ledaal procedure was carried out at a sufficiently high temperature to yield dimeric peroxide. Alternatively, the trimer may have been converted to the dimer during work-up, possiby during recrystallization.

While it is apparent that trimer **1** is the more easily formed of the two peroxides and that it is a precursor of dimer **2**, it is not certain that the trimer always precedes the dimer. We have prepared pure **5** and subjected it to slightly modified "Kharasch–Sosnovsky" conditions at room temperature and obtain the dimer **2** in 67% yield (eq 5). Rieche and Bischoff[10] have also carried out this transformation. If the reaction is repeated at 5°, however, trimer **1** is isolated in high yield. The Ledaal synthesis can also be modified to yield 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide (**5**) (dilute hydrogen peroxide). We have observed, as also noted by Cooper and Davison,[5b] that this peroxide **5** is partially dissociated in carbon tetrachloride solution as evidenced by the appearance of infrared absorption due to cyclohexanone; in potassium bromide no cyclohexanone absorption appears. We find that solid **5**, prepared by the Ledaal procedure,

$$\mathbf{5} \overset{CCl_4}{\rightleftharpoons} \mathbf{7} + \text{cyclohexanone} \qquad (7)$$

on standing in the open at room temperature is slowly converted to dimer. The conversion can be followed by infrared (KBr). After 4 days a pure (by infrared) sample of **5** was found to contain a detectable amount of dimer **2**. After 1 month the sample had been completely converted to dimer. At no time was

$$\mathbf{5}\ (\text{neat solid}) \xrightarrow[\text{temperature}]{\text{room}} \mathbf{2} + H_2O$$

any detectable concentration of trimer present. We conclude that while it appears that the dimer may be formed directly under some special conditions, it is clear that both the Ledaal and the Kharasch and Sosnovsky syntheses yield the trimer initially.

The acid concentrations used in the synthesis of the peroxides (**1**, **2**) are quite low and fall in the category of "weakly acidic" solutions according to the description of Antonovskii, *et al.*, who carried out their investigations in the absence of added solvent, making a direct comparison of the available data difficult. It was reported[2] that at higher acid concentrations, in the range of 1–3 *N*, even with a deficiency of hydrogen peroxide that a major product of the cyclohexanone–(hydrogen peroxide) reaction is the 1,1′-dihydroperoxydicyclohexyl peroxide (**6**).

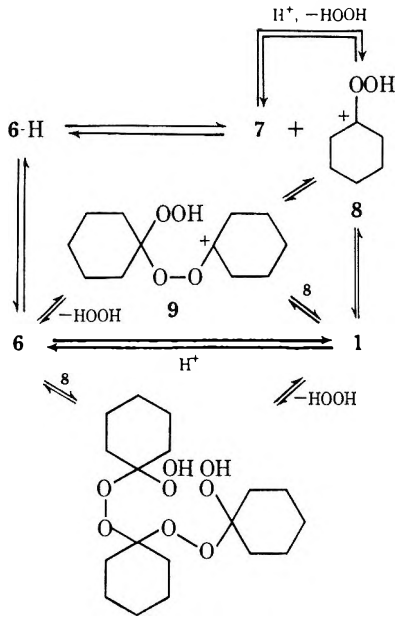
Interestingly, we find that the dihydroperoxy peroxide (**6**) is spontaneously converted to trimer **1** in high yield on its dissolution in methanol. Crude **6** (pure by infrared), prepared by a slight modification of Criegee's method[3] and still containing traces of mineral acid, was dissolved in methanol at room temperature. The solution began to warm immediately, and after a few minutes the methanol began to reflux as the result of a very exothermic reaction. After the reaction subsided, the solution was cooled to give the trimeric peroxide **1** in 81% yield.

Several reasonable pathways seem available for conversion of the dihydroperoxy peroxide (**6**) to trimer. One attractive explanation is that the reversal of the dihydroperoxy peroxide forming reaction occurs, followed either by trimerization of the ion **8** or by con-

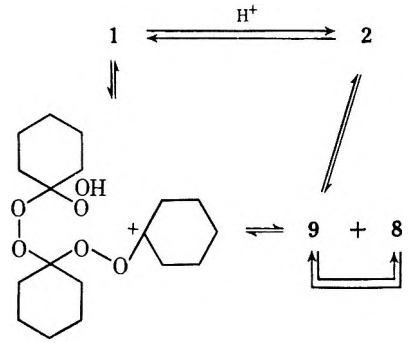
(9) T. Ledaal, *Acta Chem. Scand.*, **21**, 1656 (1967).

(10) A. Rieche and C. Bischoff, *Chem. Ber.*, **95**, 77 (1962).

densation of **8** and **6** and then cyclization. Direct formation of the ion **9** from **6** is equivalent, of course, to the first stage in **8** trimerization.



Although the trimeric peroxide **1** is easily isolated in high yield from the reaction of cyclohexanone and hydrogen peroxide and from the dihydroperoxy peroxide (**6**), its conversion to the dimer **2** is readily accomplished and can be rationalized most economically as follows.



In summary, it is evident that the reaction of cyclohexanone with hydrogen peroxide, under the acidic conditions usually employed, as well as the isolable intermediates along the way, yield tricyclohexylidene peroxide (**1**) as the kinetic product. The apparently thermodynamically more stable dimer **2** may be formed subsequently.

The synthesis of pure cyclohexanone peroxides, particularly the trimer **1**, has been considerably simplified. These findings have also permitted the ready preparation of several substituted cyclohexanone peroxides pursuant to the synthesis of substituted macrocyclic compounds.[1,11]

Experimental Section

Infrared spectra were obtained with Perkin-Elmer spectrophotometers, Models 621 and 257. Nmr spectra were recorded using a Varian HA-100 spectrometer.

Hydrogen peroxide was obtained from the FMC Corp.

(11) P. R. Story, P. Busch, D. D. Denson, B. Lee, K. Paul, and J. A. Alford, unpublished work.

Dicyclohexylidene Peroxide (**2**).—The dimeric peroxide was prepared according to the Kharasch–Sosnovsky procedure[4] and by the Ledaal method.[9] The best yield obtainable by the Kharasch–Sosnovsky method was 23%: mp 128–129°; ir (KBr, cm^{-1}) 3015 (w), 2940 (s), 2845 (m), 1445 (s), 1360 (m), 1340 (m), 1270 (s), 1258 (m), 1160 (s), 1030 (m), 948 (s, doublet), 928 (s), 850 (m), 831 (w), 821 (w).

1-Hydroxy-1′-hydroperoxydicyclohexyl Peroxide (**5**).—(A) The method of Kharasch and Sosnovsky[4] was used: mp 76–77° (65%); ir (KBr, cm^{-1}) 3310 (m), 3210 (m), 2919 (s), 2825 (m), 1496 (m), 1399 (m), 1355 (m), 1278 (m), 1260 (m), 1167 (s), 1069 (s), 1057 (s), 981 (s), 951 (m), 925 (m), 915 (m), 870 (w), 840 (w), 821 (w). (B) Using the general procedure of Ledaal,[9] 981 mg (10 mmol) of cyclohexanone was dissolved in 10 ml of acetonitrile contained in a crystallization dish. To this solution was added 35 mg (10 mmol) of 98% hydrogen peroxide diluted with 2 ml of water and 2 drops of 70% perchloric acid. This mixture was stirred magnetically in an open fume hood until a white solid was obtained. The product amounted to 650 mg (53%) of **5**, pure by infrared analysis. After 1 month in the open at room temperature, this product was completely converted to the dimer **2**.

Preparation of Dicyclohexylidene Peroxide (**2**) **and Tricyclohexylidene Peroxide** (**1**) **from 1-Hydroxy-1′-hydroperoxydicyclohexyl Peroxide** (**5**).—(A) To a solution containing 4 g (16 mmol) of **5** in 100 ml of glacial acetic acid was added 5 ml of 10% perchloric acid in acetic acid. The reaction mixture was stirred at room temperature for 24 hr. After about 1 hr, a white solid began to form in the reaction mixture. On completion, the reaction mixture was filtered and the white solid was washed with water and air-dried. There was obtained 2.5 g (67%) of product, mp 123–126°, identical with the authentic dimer **2** by infrared comparison.

(B) In this general procedure the peroxide **5** was added to an erlenmeyer flask containing acetic acid and 10% perchloric acid in acetic acid. The flask was then shaken until all the solid was dissolved. In experiment C, the mixture of solvent and catalyst was cooled in an ice bath before adding the peroxide.

In some experiments, crystals formed during the noted reaction time and were filtered, washed with water, and dried in air and then in a desiccator. This product was assigned designation "a." The filtrates and those reaction mixtures which yielded no "a" crystals were diluted with water to approximately three times their original volume. All crystals resulting thereform were designated "b" and treated as before. In some experiments a heavy oil resulted from dilution. However, if allowed to stand at room temperature, the oil crystallized within a few hours with no detectable change in composition. Table I summarizes the experiments performed.

Interruption of Kharasch–Sosnovsky Synthesis of 2 prior to Completion.—To 24.5 g (0.25 mol) of cyclohexanone was added 28 ml of 30% hydrogen peroxide (0.25 mol) at room temperature. After 15 min, 50 ml of glacial acetic acid and 3 ml of 10% perchloric acid in acetic acid were added. The reaction mixture was then placed in a boiling water bath whereupon it became cloudy. The cloudy solution slowly became clear, at which point the reaction mixture was removed from the water bath. The hot solution was poured all at once onto 200 g of ice with stirring. After about 10 min, the mixture had deposited a heavy oil at the bottom of the flask. Left suspended in solution was a white precipitate. The precipitate and oil were collected separately, washed with water, dried, and recrystallized from methanol. The heavy oil yielded 2.7 g (9.6%) of cyclohexanone triperoxide (**1**), mp 85–88°, as identified by infrared comparison with authentic material.[3] The white precipitate, after recrystallization yielded 1.1 g (3.9%), mp 128–129°, of dicyclohexylidene peroxide (**2**).

Tricyclohexylidene Peroxide (**1**) **by a Kharasch–Sosnovsky-Type Reaction.**—To an erlenmeyer flask containing 19.6 g (0.20 mol) of cyclohexanone, 22.6 g (0.20 mol) of 30% hydrogen peroxide was slowly added with cooling, if necessary, to maintain room temperature. After stirring for 15 min, 100 ml of glacial acetic acid was added, followed by 2.4 ml of 10% perchloric acid in acetic acid. This mixture was stirred at room temperature for 24 hr. After this time the solution was diluted with 400 ml of water to yield a heavy oil and some solid material. (Note: Best results are obtained if the temperature is held near 20° throughout the reaction period.) The cloudy aqueous solution was decanted and diluted with an equal volume of water. The diluted decantate was cooled at 10° for 24 hr after which time the

TABLE I

REACTIONS OF 1-HYDROXY-1′-HYDROPEROXYDICYCLOHEXYL PEROXIDE (5) IN ACETIC ACID WITH PERCHLORIC ACID AS CATALYST

	Composition of reactants[a]									
Expt	I (g)	II (ml)	III (ml)	Temp	Time, hr	Crystals recovered	Mp, °C	Products[b]	Yield, g	Yield, %
A	2	50	2.5	Room	24	a	128–130	2	0.22	42
						b	126–129	2	0.55	
B	2	50	0.25	Room	24	a	128–129	2	0.45	65
						b	126–129	2	0.76	
C	2	50 (propionic acid)	2.5	6°C	24	b	72–84	1	1.40	76
D	2	50	2.5	Room	1	b	121–129	2	1.26	68
E	2	50	2.5	Room	0.167	b	73–121	2:1 = 4:6	1.27	69
F[c]	2	5	0.25	Room	24	a	71–81	2:1 (90%)	0.80	43
		2.5 ml of water								
G	2	5	0.025	Room	24	a	74–91	1	1.27	68
						b	69–107	2:1 = 1:3	0.10	5
H	2	5	0.25	Room	24	a	73–114	2:1 = 4:6	1.27	68
						b	70–107		0.13	8

[a] Reactants are I = 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide (5), II = acetic acid, III = 10% perchloric acid in acetic acid. [b] The proportions of dimer 2 and trimer 1 in product mixtures were estimated by comparison of infrared spectra with spectra of several known mixtures in the ratios 1:3, 1:1, and 3:1. [c] The water added in this experiment is equivalent to the water content in the Kharasch–Sosnovsky procedure for preparing 2 from cyclohexanone and 30% hydrogen peroxide.

solution had cleared considerably and a white solid was formed. All the resulting oils and solids were combined and recrystallized from methanol to yield 14.8 g (72%) of trimer 1:[3] mp 91–92°; ir (CCl_4, cm^{-1}) 2940 (s), 2860 (m), 1453 (s), 1366 (m), 1279 (m), 1169 (m), 1078 (s), 951 (s), 932 (s), 858 (w).

Tricyclohexylidene Peroxide (1). By Ledaal-Type Reaction.[9]—A mixture of 9.80 g (0.10 mol) of cyclohexanone, 11.3 g (0.10 mol) of 30% hydrogen peroxide, 20 drops of 70% perchloric acid, and 100 ml of acetonitrile was placed in a shallow dish in a fume hood and allowed to stand at room temperature (preferably under 24°) for 5 days. After this time there remained only a white solid, 9.46 g (83%), which was shown to be "pure" trimer 1 by infrared comparison, mp 87–90°.

1,1′-Dihydroperoxydicyclohexyl peroxide (6) was prepared according to the method of Criegee:[3] mp 83.5–84°: ir (CCl_4, cm^{-1}) 3410 (s, singlet), 2940 (s), 2860 (m), 1449 (m), 1382 (m), 1270 (m), 1150 (s, doublet), 1088 (m), 1055 (s), 939 (s), 909 (m).

Conversion of 6 to Triperoxide (1).—To a stirred solution of methanol (10 ml) containing 2–3 drops of hydrochloric acid was added 10.2 g of 6 (44.3 mmol). The solution became warm immediately and a very exothermic reaction ensued causing the methanol to reflux. After 5–10 min the mixture was cooled in an ice bath and then allowed to stand at room temperature for 1 day. A solid sheet of crystals formed and after 4 days in the refrigerator (5°) an oily solid appeared. All the precipitated material was recrystallized from methanol to yield 7.41 g (81%) of cyclohexanone triperoxide (1), mp 91–92°.

Recrystallization of Tricyclohexylidene Peroxide (1).—Recrystallization of trimer 1 can be effected in methanol, 80% acetic acid, or acetone. If the trimer is dissolved in the minimum amount of hot methanol and then cooled, an oil will usually separate. On standing overnight or sometimes longer, the oil will solidify. The oil is pure trimer by infrared. If the trimer is dissolved in a sufficient amount of methanol at room temperature and the solution is allowed to stand open to the air so as to allow evaporation of the methanol, the resulting very large crystals take two forms which can be separated by hand. One crystalline form is clear and melts at 87–87.5°. The other is white and melts at 92–92.5°. The two forms are identical by infrared comparison.

Conversion of Tricyclohexylidene Peroxide (1) **to Dicyclohexylidene Peroxide** (2).—A 50-ml erlenmeyer flask containing 1 g (2.9 mol) of tricyclohexylidene peroxide (1) in 5 ml of acetic acid and two drops of 10% perchloric acid in acetic acid was warmed at 60° for 1 hr. The solution remained clear throughout the warming period. On cooling, a white solid was deposited which on recrystallization from methanol yielded 0.53 g (53%) of dicyclohexylidene peroxide (2), mp 128–129°.

Treatment of Trimer 1 under Kharasch–Sosnovsky Conditions at Room Temperature.—A 50-ml erlenmeyer flask containing 1.0 g of trimer 1 and 5 ml of acetic acid was heated gently, just a sufficient amount to dissolve the solid. The homogeneous solution was cooled to room temperature and 2 drops of 10% perchloric acid in acetic acid was added. The flask was allowed to stand open overnight. The crystalline solid which formed during this time was collected, recrystallized from methanol, and dried to yield 0.82 g of tricyclohexylidene peroxide (1), mp 91–92°.

Registry No.—1, 182-01-4; 2, 183-84-6; 5, 71-18-2; 6, 2699-12-9.

Acknowledgment.—We thank the National Air Pollution Control Administration (AP 00580) for support of this work.

Reactions of Phosphonic Acid Esters with Nucleophiles. I. Hydrolysis

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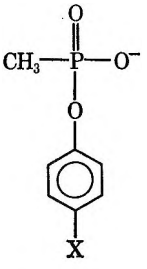
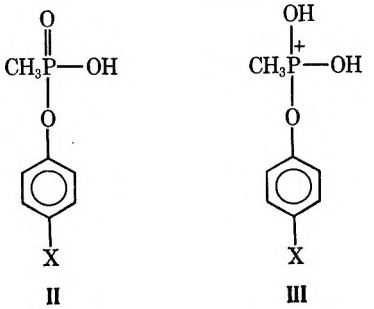
Phenyl methylphosphonic acid (PMP) and *p*-nitrophenyl methylphosphonic acid (*p*-NPMP) have been synthesized. The hydrolysis of PMP and its anion has been studied in acid, neutral, and basic solutions; the hydrolysis of the anion of *p*-NPMP was examined in neutral and basic media. We have observed nucleophilic attack by water on *p*-NPMP in neutral solution. In basic media, both PMP and *p*-NPMP react *via* nucelophilic attack by hydroxide ion at phosphorus. Near pH 9, calcium ions catalyze the hydrolysis of *p*-NPMP. PMP hydrolysis shows a rate maximum in moderately concentrated acid solutions.

In comparison with the large numbers of studies of the reactions between nucleophiles and neutral phosphorus esters, few data have been reported on the reactions of nucleophiles with phosphonic acid ester monoanions.[2-6] The monoanions of the monoesters of phosphoric acid exist over a very small pH range, so that broad surveys of their reactivity with nucleophiles have not been possible. This complication is avoided with the monoanions of phosphonic acid monoesters; virtually the entire pH range is available for study. Nucleophilic displacements on phosphonic acid ester monoanions are also of some practical importance since they may be used as model systems for the study of cholinesterase inhibition by certain organophosphorus compounds.[7,8] For these reasons, the investigation of the reactions of various classes of nucleophiles with phosphonic acid ester anions of the type I was initiated.

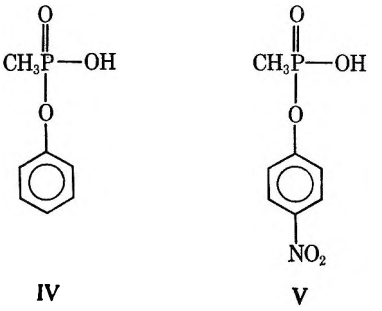


I

The first approach was an examination of the hydrolysis of phosphonic acid esters of type I in acid, neutral, and basic media. In highly acidic solution, I exists as the neutral species II, and possibly also the positively charged species III. Phenyl methylphosphonic acid (PMP), IV, and *p*-nitrophenyl methylphosphonic acid (*p*-NPMP), V, were the substrates studied.



II III



IV V

We have also investigated the reactivity of a variety of other nucleophiles toward *p*-NPMP, the results of which are reported in other papers.[9,10]

Experimental Section

Substrates. 1. Phenyl Methylphosphonic Acid (PMP).—Two previous syntheses have been reported.[11,12] We used a new route based on partial hydrolysis of diphenyl methylphosphonate, which was prepared by condensation of methyl iodide and triphenyl phosphite followed by hydrolysis of the phosphonium iodide according to Berlin and Butler,[13] except that the reflux time was cut to 16 hr.[14] These procedures are based on the syntheses of Michaelis and Käehne.[15] The ether wash of the phosphonium iodide was omitted and the material was decomposed directly with water. The diphenyl methylphosphonate was extracted into ether and this phase was washed with aqueous alkali. Removal of the ether yielded crude diphenyl methylphosphonate. Distillation gave a 68% yield of material, bp 173–180° (3 mm) [literature values: bp 145–148° (0.4 mm),[13] 190–195° (11 mm)[15]]. Diphenyl methylphosphonate (87.6 g, 0.35 mol) was added to a refluxing solution of 40 g (0.70 mol) of NaOH in 750 ml of water. Refluxing was continued for 25 min, at which time the oily layer of diphenyl methylphosphonate was no longer visible. The solution was rapidly cooled, neutralized to pH 7 with HCl, and extracted with ether to remove phenol. The aqueous phase was then strongly acidified and extracted with chloroform. Removal of the chloroform from the nonaqueous extract yielded crude phenyl

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methylphosphonic acid as a viscous oil (47 g, 80%). The material was characterized as the silver salt.[11]

LiOH (140 ml, 2 *M*) was slowly added to 47 g of IV with cooling and stirring. The neutral solution was filtered and 1 l. of boiling acetone was gradually added while stirring. After standing overnight, 37 g of the lithium salt was filtered off. Additional material (9 g) was obtained by further additions of acetone for a final yield of 46 g (95%) of the lithium salt. The material was washed with acetone and ether and air-dried to yield a nonhygroscopic microcrystalline powder. A small portion was recrystallized from 95% ethanol. The uv spectrum of the salt in water gave 261 mμ (ε 483). Ir and nmr spectra were consistent with the assigned structure.

Anal. Calcd for $C_7H_8PO_3Li$: C, 47.2; H, 4.53; P, 17.4. Found: C, 47.6; H, 4.58; P, 17.6.

The pK_a of IV was determined by two techniques.[16] A 10-ml sample of a 0.10 *M* LiPMP solution was titrated with a 1.00 *M* HCl solution. The pH was measured (using a Beckman Model G pH meter) after each addition. A pK_a value of 1.28 was obtained which when corrected for ionic strength effects[17] was 1.39. The pK_a was also determined spectrophotometrically by measuring the fraction of total PMP present in the anionic form as a function of pH. Solutions were 1.00×10^{-3} *M* in phosphonate. pH values were adjusted with 0.10 *M* HCl–KCl solutions. After correction for ionic strength effects, the pK_a was found to be 1.47.

2. ***p*-Nitrophenyl Methylphosphonic Acid (*p*-NPMP).**[18]—The preparation of bis(*p*-nitrophenyl) methylphosphonate was carried out using a procedure analogous to that for diphenyl methylphosphonate.[11] Methylphosphonodichloride[19] (10 g, 0.075 mol) was placed together with *p*-nitrophenol (20 g, 0.145 mol) in a 100-ml flask, fitted with reflux condenser, drying tube, and thermometer. This mixture was heated slowly over a course of 3 hr to a temperature of 160°. Hydrogen chloride evolution began at 70°. The temperature was held at 160° for an additional hour. The black oily mixture was dissolved in toluene, treated with decolorizing charcoal, and then recrystallized twice from a mixture of toluene and ether to give 11.3 g (49%) of bis(*p*-nitrophenyl) methylphosphonate.

The hydrolysis of this phosphonate was carried out as follows: 5 g (0.0147 mol) of phosphonate was placed together with 0.0326 mol of NaOH (10% excess) in 100 ml of water and heated to boiling. After 5 min almost all of the phosphonate had dissolved. The solution was cooled, acidified to pH 3.5, and extracted with three 50-ml portions of ether. The ether layers gave a 110% yield of *p*-nitrophenol based on conversion of phosphonate to *p*-nitrophenyl methylphosphonic acid. The aqueous layer was then strongly acidified with concentrated HCl. (At this point some dark oily precipitate appeared; this was found to have no observable influence on the following steps.) The aqueous phase was continually extracted with ether for 2 hr. The ether solution was dried with anhydrous magnesium sulfate and the product was allowed to crystallize in the refrigerator. If no product appeared in 6–8 hr, *n*-hexane was added to the cloud point and the product then crystallized overnight. Recrystallization from refluxing ether gave 1.6 g of product in the form of white needles, mp 113–114°; this represents a yield of 48% *p*-NPMP based on phosphonate. The uv spectrum of *p*-NPMP in water gave 291 mμ (ε 9360). Ir and nmr spectra were consistent with the assigned structure. Neutralization equivalents of 219 and 220 were obtained; the calculated value is 217. Alkaline hydrolysis gave *p*-nitrophenol in 100.3% of the theoretical quantity.

Anal. Calcd for $C_7H_8NO_5P$: C, 38.72; H, 3.71; N, 6.45; P, 14.27. Found: C, 38.83; H, 3.80; N, 6.42; P, 14.44.

The spectra of the anions of phenol and *p*-nitrophenol yielded extinction coefficients of 2600 and 18,200 at 286 and 400 mμ, respectively; these values were used in the calculation of rate constants where appropriate.

Inorganic materials (reagent grade) were used without further purification. *s*-Collidine (2,4,6-trimethylpyridine) was distilled twice under nitrogen at reduced pressure, bp 35° (5 mm). Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Kinetics.—The rates of hydrolysis of the two aryl methylphosphonates were followed by observing the rate of formation of the phenolate ion at 286 mμ or of the *p*-nitrophenolate ion at 400 mμ. Molar absorptivities were measured on a Beckman Model DU spectrophotometer in 1-cm quartz cuvettes. A water blank was used. Where necessary, aliquots of reaction solutions were made basic before spectral analysis so that all of the phenol or *p*-nitrophenol (pK_a values 10.0 and 7.15, respectively) existed in the anionic forms. Reactions were carried out in volumetric flasks suspended in a constant temperature bath (±0.1°). Aliquots were withdrawn at appropriate time intervals. Some reactions were monitored in thermostated glass-stoppered cuvettes in the spectrophotometer. The pH values of solutions were maintained constant by use of appropriate buffers.

The decrease of PMP and *p*-NPMP concentrations in all hydrolysis experiments followed first-order kinetics at any specified pH. Runs were generally followed for at least one half-life. Several hydrolysis experiments in basic solution were carried out through ten half-lives and the predicted yields of phenolate or *p*-nitrophenolate ions were observed within an experimental error of ±3%. For basic hydrolysis of both substrates and neutral hydrolysis of *p*-NPMP, second-order rate constants were obtained by dividing the pseudo-first-order rate constant by the hydroxide ion or water concentrations as appropriate. Frequently, for slow reactions, the initial concentration of phosphonic acid ester was increased and the reaction carried out under pseudo-zero-order conditions. Division of the pseudo-zero-order rate constant by both initial substrate and hydroxide ion concentrations gave second-order rate constants in good agreement with those obtained by the pseudo-first-order technique.

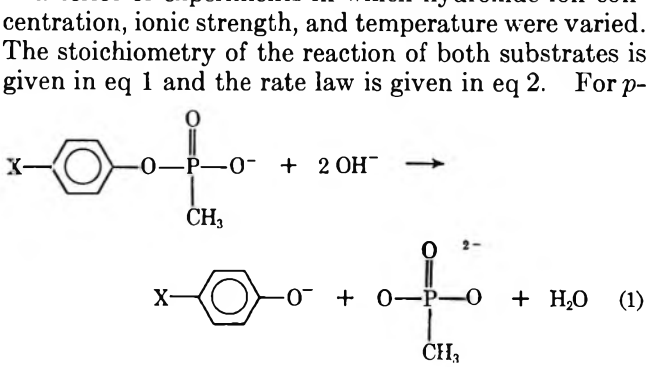
In acid solutions it was necessary to prevent the loss of phenol from the acid solutions. Ground-glass stoppers were greased and the flasks were shaken before aliquots were removed to mix in any phenol that might have condensed on the cooler necks of the flasks.

Experiments in the Presence of Calcium Ion. Attempts to buffer reaction solutions with borate and phosphate in the presence of Ca^{2+} were unsuccessful due to the precipitation of the calcium salts. One series of experiments used 0.2 *M* NaOH to establish a pH of 9.0; however the rate began to drop after ~2% of reaction due to a decrease in pH since the solution was unbuffered. In a second series, *s*-collidine was employed to maintain the pH of reaction solutions. Because of the limited solubility of *s*-collidine in water, kinetic experiments were performed in solutions containing 81% H_2O–19% EtOH by volume in which *s*-collidine is soluble up to at least 1.0 *M*. The pH of solutions of 0.05–0.60 *M* *s*-collidine in this solvent system is between 8.80 and 9.30.

(We assumed that the effect of the 19% ethanol on the accuracy of the pH measurements is negligible and comparative data in water indicate that this assumption is valid—see Table VI. The extinction coefficient of the *p*-nitrophenolate ion in 19% ethanol solution is within 3% of the value in water (1.82×10^4).)

Results

Alkaline Hydrolysis.—Tables I and II give the results of a series of experiments in which hydroxide ion concentration, ionic strength, and temperature were varied. The stoichiometry of the reaction of both substrates is given in eq 1 and the rate law is given in eq 2. For *p*-



$$\text{rate} = k_2[\text{substrate}][OH^-] \quad (2)$$

NPMP at constant ionic strength (I = 3.36) the quantity $k'/[OH^-]$, where k' is the pseudo-first-order rate

(16) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Metheun and Co., London, 1962.

(17) See ref 16, p 59.

(18) In the course of our investigation a synthesis of *p*-NPMP by another method was reported: K. A. Petrov, R. A. Baksova, L. V. Korkhoyanu, L. P. Sinogeikina, and T. V. Skudina, *J. Gen. Chem. USSR*, **35**, 723 (1965).

(19) A sample of methylphosphonodichloride was kindly supplied by the U. S. Army Research Laboratories, Edgewood Arsenal, Md.

TABLE I

ALKALINE HYDROLYSIS OF PHENYL METHYLPHOSPHONIC ACID

[NaOH], M	[Salt], M	I	[PMP] $\times 10^3$, M[a]	Temp, °C	$k' \times 10^3$, min^{-1}	$k'/[OH^-] \times 10^3$, M^{-1} min^{-1}
2.120		2.12	2.00	78	7.97	3.76
1.060	1.060[b]	2.12	2.00	78	3.64	3.43
0.424	1.696[b]	2.12	2.00	78	1.37	3.23
0.212	1.908[b]	2.12	2.00	78	0.668	3.15
0.106	2.014[b]	2.12	2.00	78	0.334	3.15
0.212		0.21	2.12	78	0.288	1.36
0.212	0.85[c]	1.06	2.12	78	0.523	3.44
0.212	1.91[c]	2.12	2.12	78	0.730	3.76
0.212	1.91[b]	2.12	2.12	78	0.668	3.15
2.12		2.12	2.00	78	7.83	3.69
2.12		2.12	2.00	68.5	3.73	1.76
2.12		2.12	2.00	58.8	1.60	0.755
2.12		2.12	2.00	39	0.228	0.108

[a] Initial concentration of lithium phenyl methylphosphonate. [b] $NaClO_4$. [c] NaCl.

TABLE II

ALKALINE HYDROLYSIS OF *p*-NITROPHENYL METHYLPHOSPHONIC ACID[a]

[NaOH], M	[$NaClO_4$], M	I	Temp, °C	$k' \times 10^3$, min^{-1}	$k'/[OH^-] \times 10^3$, M^{-1} min^{-1}
3.38		3.38	30	21.5	6.36
1.69	1.67	3.36	30	7.27	4.30
1.69	1.67	3.36	30	7.39	4.37
0.845	2.50	3.35	30	3.21	3.80
0.339	3.00	3.34	30	1.13	3.33
0.169	3.22	3.39	30	0.572	3.38
0.169	1.69	1.86	30	0.424	2.51
0.169		0.17	30	0.237	1.40
0.169		0.17	39.4	0.630	3.73
0.169		0.17	50	1.44	8.52
0.169		0.17	60	3.24	19.2

[a] The initial concentration of *p*-nitrophenyl methylphosphonic acid was 1.33×10^{-4} M.

constant, increases with increase in base concentration; however a plot of $k'/[OH^-]$ *vs.* $[OH^-]$ gives a line which extrapolates to 3.0×10^{-3} M^{-1} min^{-1} (Figure 1) and this intercept may be taken as the second-order rate constant for the reaction with hydroxide ion at 30°. A similar trend of smaller size can be seen in the data for PMP; the intercept has a value of 3.0×10^{-3} M^{-1} min^{-1} at 78° (Figure 1). The ionic strength effects given in Tables I and II are in the expected direction for the reaction between two particles of like charge sign;[20] their magnitude deserves no special comment. The variation of rate with temperature allowed calculation of activation parameters for both substrates; activation parameters were as follows: for PMP, E_a = 19.8 ± 0.3 kcal/mol and $\Delta S^{\pm}$ = −23.5 ± 0.8 eu (78°); and for *p*-NPMP, E_a = 17.3 ± 0.4 kcal/mol and $\Delta S^{\pm}$ = −25 ± 1 eu (30°).

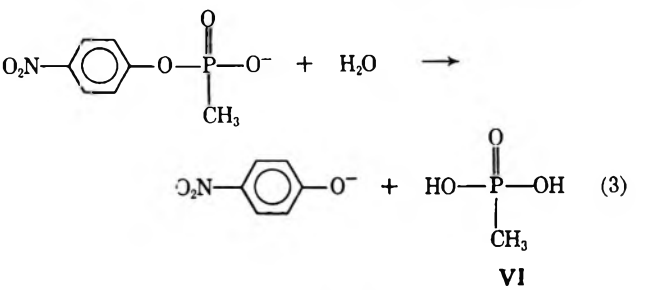
Hydrolysis in Buffered Solutions.—Below approximately pH 12 at 80° the rate of hydrolysis of PMP becomes too slow to follow conveniently. Table III shows data obtained at 60° for buffered solutions of *p*-NPMP from pH 7 to pH 12. The predicted first-order rate constant for hydroxide ion attack at pH 7 from the data of Table II is ~2×10^{-9} min^{-1}. The observed rate constant is about three powers of ten above this value, so another mechanism must be operating in this pH range. Since the rate does not seem to depend on pH (below pH 9) or on buffer concentration, we have attributed the observed rate to nucleophilic attack by water on *p*-NPMP. The stoichiometry for such an attack is given in eq 3 and the rate law in eq 4. (Compound VI will ionize to the methyl-

TABLE III

HYDROLYSIS OF *p*-NITROPHENYL METHYLPHOSPHONATE ION IN BUFFER SOLUTIONS FROM pH 7 TO pH 12[a]

Buffer, M	[*p*-NPMP$^-$] $\times 10^4$, M	pH	k', min^{-1}
Phosphate, 0.04	1.33	11.90	2.60×10^{-4}
Carbonate, 0.08	1.33	10.25	2.05×10^{-5}
Phosphate, 0.08	1.33	7.05	2.80×10^{-6}
Carbonate, 0.08	2.00	10.25	2.1×10^{-5}[b]
Phosphate, 0.08	2.00	6.90	2.9×10^{-6}[b]
Phosphate, 0.02	2.00	6.90	2.5×10^{-6}[b]
Borate, 0.1	4.00	8.55	4.3×10^{-6}
Borate, 0.02[c]	4.00	8.50	3.6×10^{-6}

[a] Temp = 60°. [b] Final ionic strength made up to 0.16 with $NaClO_4$. [c] $NaClO_4$ = 0.08 M.



VI

$$\text{rate} = k_2[p\text{-NPMP}][H_2O] \quad (4)$$

(20) K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1965, pp 220–221.

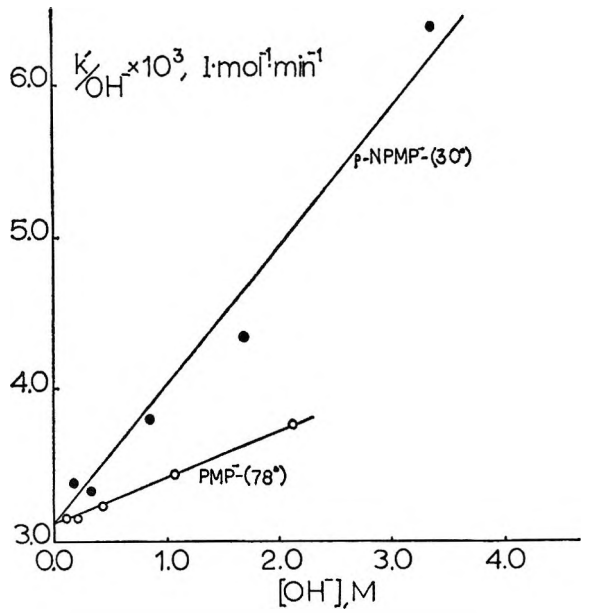


Figure 1.—Plot of pseudo-first-order rate constants divided by hydroxide ion concentration ($\times 10^3\ M^{-1}\ min^{-1}$) *vs.* hydroxide ion concentration [*M*] for the reaction of hydroxide ion with PMP and *p*-NPMP; see Tables I and II.

phosphonate mono- or dianion in a rapid step after the rate-determining attack by water.)

Table IV gives the rate constants and activation parameters for water attack on *p*-NPMP.

TABLE IV

NUCLEOPHILIC ATTACK BY H_2O ON *p*-NITROPHENYL METHYLPHOSPHONATE[a]

pH[b]	Temp, °C	k', min^{-1}	k_2, $M^{-1}\ min^{-1}$[c,d]
7.60	29.7	1.18×10^{-7}	2.13×10^{-9}
7.50	60	4.34×10^{-6}	7.81×10^{-8}

[a] [*p*-NPMP⁻] = 5.90×10^{-4} *M*. [b] Buffer: 0.108 *M* KH_2PO_4–0.092 *M* NaOH. [c] E_a = 23.8 kcal/mol. [d] $\Delta S^{\ddagger}$ (60°) = −29.7 eu.

Acid Hydrolysis.—Data for the variation of the rate of hydrolysis of PMP as a function of acidity are presented in Table V; the activation parameters are also given. Figure 2 is a plot of k_{obs} against the calculated pH. A rate maximum is observed at approximately 3 *M* acid. No rate maximum is observed, however, if k_{obs}/a_{H_2O} (which is shown by the dotted line) is plotted instead of k_{obs} (Figure 2).

Catalysis by Added Calcium Ion.—Addition of $Ca(NO_3)_2$ to an aqueous solution of *p*-NPMP at pH 9.0 increased the rate of hydrolysis by approximately 12-fold (Table VI). The pseudo-first-order constant with 0.05 *M* $Ca(NO_3)_2$ present was 1.2×10^{-4} min^{-1} as compared to 8.0×10^{-6} min^{-1} in the absence of the added salt. In order to be certain that an ionic strength effect was not operating, the reaction was run in the absence of $Ca(NO_3)_2$ but with sufficient NaCl present to equal the ionic strength of the 0.05 *M* $Ca(NO_3)_2$ experiments (*i.e.*, $I = 0.15$); the rate constant $k' = 9.0 \times 10^{-6}$ min^{-1} was found. Nitrate ion was found to be a weak nucleophile toward *p*-NPMP; the rate of hydrolysis of *p*-NPMP in the presence of 0.1 *M* NO_3^- was equal to that of the rate at pH 9.0 without nitrate. We conclude that the rate enhancement when $Ca(NO_3)_2$ is present is due to the presence of Ca^{2+} ions.

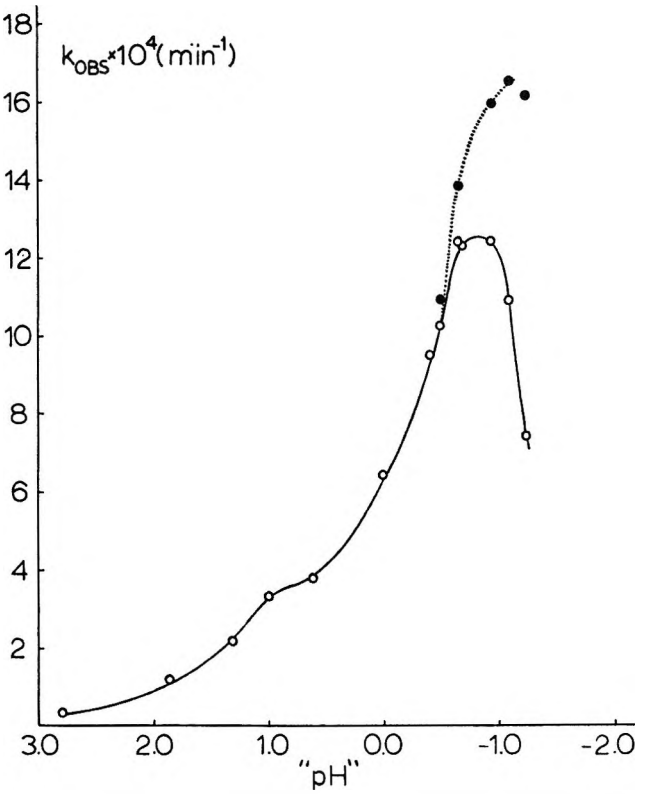


Figure 2.—(-O-) $k_{obs} \times 10^4$ (min^{-1}) *vs.* calculated pH for the hydrolysis of PMP in acid solution; (····●····) k_{obs} has been divided by a_{H_2O}. See Table V.

TABLE V

HYDROLYSIS OF PMP IN ACID SOLUTION

$[PMP]_t \times 10^3$, *M*[a]	$[H_2SO_4]$, *M*	pH[b]	H_0[c]	Temp, °C	a_w[d]	$k_{obs} \times 10^4$, min^{-1}
2.0		2.80		80.5	1	0.33
2.0		1.90		80.5	1	1.22
2.0	0.024	1.32		80.0	1	2.15
2.0	0.050	1.00		80.4	1	3.32
2.0	0.119	0.62	+0.80	80.0	1	3.87
2.0	0.475	0.02	+0.10	80.0	0.98	6.45
3.0	1.189	−0.38	−0.30	80.0	0.95	9.54
2.0	1.610	−0.51	−0.60	80.0	0.94	10.25
2.0	2.375	−0.68	−0.95	80.4	0.90	12.4
5.0	2.500	−0.70	−1.12	80.0	0.89	12.3
9.0	4.325	−0.94	−1.90	80.0	0.78	12.4
10.0	6.125	−1.09	−2.80	80.0	0.66	10.9
10.0	9.300	−1.27	−4.50	80.0	0.46	7.43
2.0	2.375	−0.68		52.6	0.90	0.89[e]
2.0	2.375	−0.68		65.0	0.90	2.76[e]
2.0	0.024	1.32		52.6	1	0.087[e]
2.0	0.024	1.32		65.0	1	0.374[e]

[a] $[PMP]_t$ values are total concentrations of PMP added to the reaction mixtures as lithium phenyl methylphosphonate. [b] Sulfuric acid was used except for the first two entries. The run at pH 2.8 was in 0.05 *M* chloroacetate buffer; the run at pH 1.9 was in 0.06 *M* KCl–HCl. The run at pH 1.32 was unaffected by the addition of sodium perchlorate to a final ionic strength of 2. [c] M. A. Paul and F. A. Long, *Chem. Rev.*, 57, 1 (1957). [d] H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 574; by linear extrapolation of the data at 0, 25, 40, and 60°. [e] Arrhenius plots of the data at pH −0.68 and at 1.32 yield activation energies of 21.8 and 26.8 kcal/mol, respectively; calculated entropies of activation are −20.7 and −9.0 eu.

The rate of hydrolysis of *p*-NPMP in the presence of 0.05 *M* $Ca(NO_3)_2$ with the pH maintained at 9.0 by the addition of *s*-collidine in an 81% H_2O–19% EtOH sol-

TABLE VI

EFFECT OF Ca^{2+} ON THE RATE OF HYDROLYSIS OF *p*-NPMP[a]

[NaCl], *M*	[$Ca(NO_3)_2$], *M*	pH	k', min^{-1}	Buffer	Solvent
	0.05	9.0[b]	1.2×10^{-4}	None	H_2O
		9.0[b]	8.0×10^{-6}	None	H_2O
	0.05	9.0	1.4×10^{-4}	*s*-Collidine	81% H_2O–19% EtOH
		9.0	9.0×10^{-6}	*s*-Collidine	81% H_2O–19% EtOH
0.15		9.0[b]	9.0×10^{-6}	None	H_2O

[a] [*p*-NPMP] = 1.20×10^{-3} *M*. [b] pH established by added NaOH.

vent system was unchanged from the experiments using NaOH to adjust pH in water. We feel therefore that a direct comparison of the data in the mixed solvent and those in pure water is legitimate. A series of kinetic experiments were performed at constant $Ca(NO_3)_2$ concentration (0.05 *M*) and variable *s*-collidine concentration (from 0.0454 *M* to 0.610 *M*, Table VII). The reaction pH varied from 8.80 to 9.30; k' varied from $\sim 7 \times 10^{-5}$ min^{-1} at low *s*-collidine concentration and pH (~8.80) to $\sim 2 \times 10^{-4}$ min^{-1} at high *s*-collidine concentration and pH (~ 9.30).

Discussion

Alkaline Hydrolysis.—Experimental data show that the alkaline[2,4,5,21-24] hydrolysis of most neutral esters of phosphoric acid [$(RO)_3PO$] and phosphonic acids [$(RO)_2(R')PO$] and the neutral halides [$(RO)_2POX$, $(RO)(R')POX$, and $(R)_2POX$] proceed *via* direct nucleophilic substitution by hydroxide ion at the phosphorus atom. Hydroxide ion also reacts with monoanions of the diesters of phosphoric acid and related

TABLE VII

DEPENDENCE OF RATE ON COLLIDINE CONCENTRATION AND pH AT 0.05 *M* $Ca(NO_3)_2$[a]

[Collidine], *M*	pH	$k' \times 10^4$, min^{-1}
0.0454	8.90	0.67
0.0454	8.80	0.78
0.0755	8.82	1.04
0.0755	8.95	0.90
0.151	9.22	1.35
0.227	9.08	1.17
0.305	9.20	1.47
0.305	9.20	1.25
0.454	9.30	1.85
0.454	9.30	1.80
0.610	9.30	2.14
0.610	9.25	2.22

[a] Temp = 60°, [*p*-NPMP] = 1.20×10^{-3} *M*, run in 81% H_2O–19% EtOH.

compounds[2,25,26] in a bimolecular fashion; with these compounds, however, the attack by hydroxide ion is predominately at the ester carbon, unless a good leaving group is bound to phosphorus.[2,4,26-28] The hydrolysis of mono- and dianions of phosphate monoalkyl or aryl esters[2,25,29-39] are thought to proceed *via* a unimolecular elimination of the monomeric metaphosphate species PO_3^- over a wide pH range (*i.e.*, pH 2–12). In most cases the monoanion $ROPO_3H^-$ is most reactive. At high pH, nitro-substituted monoaryl phosphates[35] apparently react with hydroxide ion *via* a bimolecular attack at both phosphorus and aromatic carbon; the unimolecular pathway (*i.e.*, spontaneous dianion heterolysis) may also proceed at high pH.[35]

The reactions of PMP and *p*-NPMP in aqueous alkaline solution can be interpreted as involving a bimolecular attack on the phosphorus atom by the hydroxide ion thereby displacing the phenolate and *p*-nitrophenolate anions (Tables I and II) [PMP, E_a = 19.8 ± 0.3 kcal/mol, $\Delta S^{\pm}$ = −23.5 ±0.8 eu (78°); *p*-NPMP, E_a = 17.3 ± 0.4 kcal/mol, $\Delta S^{\pm}$ = −25 ± 1 eu (30°)]. The activation parameters for these two phosphorus substrates are of the magnitude associated with bimolecular displacements on tetrahedral organophosphorus compounds.[40] Attack by hydroxide ion at aromatic carbon can be excluded on the grounds that the observed rate constants are too large. At 39° the value of k_2 for the hydroxide ion reaction with 1-chloro-4-nitrobenzene in 16.7% dioxane–83.3% H_2O is 1.34×10^{-6} M^{-1} min^{-1};[41] k_2 for hydroxide reaction with the dianion of *p*-nitrophenyl phosphate, *p*-NPP^{2-} at 39°, was found to be 4.9×10^{-7} M^{-1} min^{-1}.[3a] It was concluded that hydroxide ion most probably attacks the aromatic site of the *p*-NPP^{2-}, although the possibility of some hydroxide ion attack at phosphorus cannot be excluded. With *p*-NPMP, k_2 for the hydroxide ion reaction at 30° is 3.0×10^{-3} M^{-1} min^{-1} and for PMP, k_2 at 78° is 3.0×10^{-3} M^{-1} min^{-1}; these values are high compared to the expected displacements at carbon. We believe that the size of the rate constants for hydroxide ion attack on *p*-NPMP and PMP are most consistent with expectations for attack at phosphorus.

For both substrates k_2 increases linearly with in-

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(37) M. C. Bailly, *Bull. Soc. Chim. Fr.*, **9**, 340, 405 (1942).
(38) A. Desjobert, *ibid.*, **14**, 809 (1947).
(39) C. A. Bunton, D. Kellerman, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc. B*, 292 (1966).
(40) Reference 5, p 302.
(41) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3217 (1965).

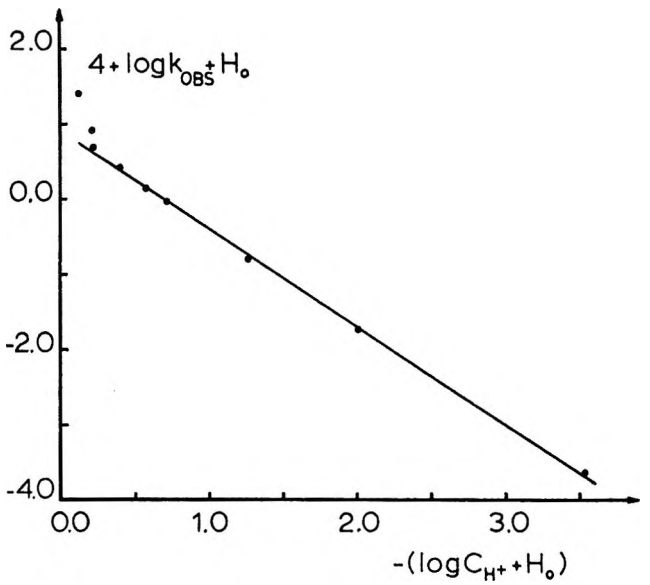

Figure 3.—Plot of 4 + log k_{obs} + H_0 *vs.* −(log C_{H^+} + H_0) for the hydrolysis of PMP in sulfuric acid solutions. See Table V.

creasing hydroxide ion concentration. The probable explanation for this observation is a salt effect, rather than a term which is second-order in base. The rate of hydrolysis of monoaryl phosphate ester dianions[35] is dependent on the size of the cations present, which suggests a close interaction of the cation with the arylphosphate dianion. A similar interaction between methylphosphonate monoaryl ester monoanions is a reasonable assumption.

Neutral Hydrolysis.—Hydrolysis of *p*-NPMP near neutral pH probably proceeds *via* a bimolecular displacement reaction involving water as a nucleophile. For *p*-nitrophenyl phosphate monoanion at pH 3.7 $k_1 = 4.15 \times 10^{-3}$ min^{-1} at 73.0°;[33] for *p*-NPMP, $k_2 = 1.30 \times 10^{-9}$ M^{-1} min^{-1} at 60.0°. It is worthy of note that the methyl group attached to phosphorus prevents a unimolecular breakdown of the monoanion to form the metaphosphate intermediate PO_3^- as suggested in various phosphate hydrolyses. Therefore, a unimolecular mechanism for *p*-NPMP hydrolysis appears to be excluded. The value of $\Delta S^{\pm}$ for *p*-NPMP hydrolysis taken from the first-order rate constant (before correction for water concentration) is −21.9 eu; after correction, a value of −29.7 eu is obtained. These values are in the range expected for nucleophilic displacement by solvent water. The hydrolysis of the bis(2,4-dinitrophenyl) phosphate[26] monoanion in the pH region 3.5–7 gives a $\Delta S^{\pm}$ of −26 eu and the reaction is interpreted as a nucleophilic attack of water. Isotope data show that reaction is largely at phosphorus for this compound. With *p*-NPMP, attack at phosphorus is probable, but attack at aromatic carbon is not excluded by our data.

Acid Hydrolysis.—H_2O^{18} tracer studies of the hydrolysis of aryl phosphate and phosphonate esters in strongly acid media have shown that reaction occurs by P–O bond cleavage;[26,33,42,43] for aryl phosphonate esters, cleavage is assumed to occur also by P–O bond rupture. Further examination of the hydrolysis of aryl phosphate[26,33-36,44] and phosphinate esters[42] in strongly acid media have shown the existence of rate maxima, such as that found here, if an electron-withdrawing substituent such as a nitro or acetyl function was present on the leaving group. (Triphenyl phosphate is a mild exception.) Although protonation of the substrate in the transition state is presumed to be important, the data do not indicate that any substantial portion of the substrate is converted to conjugate acid form at the rate maximum. For example, basicity measurements[45] have shown that *p*-nitrophenyl phosphate, triphenyl phosphate, and *p*-nitrophenyl diphenyl phosphate are not substantially protonated at the acid concentrations of maximum rates.

The article by Bunton and Farber[43] provides the most recent insight into the subject of rate maxima in the acid-catalyzed hydrolyses of weakly basic substrates. A possibly oversimplified explanation of these rate maxima is the incursion of an acid-catalyzed path for phosphate hydrolyses (causing a rate increase with acidity) and to a decrease in water activity which more than compensates for the rate increase. Other explanations given[43] are based on the presence of a strongly electron-attracting group on the leaving function (which case does not apply here). Our data for the hydrolysis of PMP is analogous to the phosphate and phosphinate cases. The rate maximum of PMP occurs in the range of acid concentration where similar aryl phosphorus esters have displayed rate maxima. The activation parameters for PMP hydrolysis are roughly the same as for the esters known to display maxima. The linear free energy approach of Bunnett and Olsen[46] has been applied to the hydrolysis of PMP. Figure 3 is a plot of 4 + log k_{obs} + H_0 *vs.* −(log C_{H^+} + H_0) from the data in Table V; the slope $\phi \cong 1.3$. The ϕ values for the hydrolysis of phosphates and PMP are quite similar.[26,34,35,44] The ϕ values are consistent with a strong dependence of the reaction rate on water activity, because of solvation of the transition state in which proton transfers may be important.

In Figure 3, a deviation is observed in low acid concentrations. Bunnett and Olsen[46] point out that nonlinearity in an LFER plot may occur when a substrate that is weakly basic "becomes protonated within the acid range of kinetic study." It is reasonable that the converse is also true and we interpret the deviation from linearity in Figure 3 as due to the partial conversion of phenyl methylphosphonic acid (PMP) to phenyl methylphosphonate and hydrogen ions.

We conclude that the mechanism for PMP hydrolysis in acid solution is probably similar to the hydrolysis of aryl phosphates when the aryl ring contains an electron-withdrawing group. Also it is probable that rate maxima for aryl organophosphorus esters is not confined solely to those cases where an electron-withdrawing substituent is bonded to the aryl ring. In addition to PMP, methyl methylphenylphosphinate and its *p*-methyl derivative show rate maxima at approximately 7 M $HClO_4$.[47]

Hydrolysis with Added Calcium Ion.—Catalysis of the hydrolysis reactions of the neutral and anionic species of organophosphorus esters by metal ions has been reported.[4,5] The enhanced rate of the hydrolysis

(42) P. Haake and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).
(43) C. A. Bunton and S. J. Farber, *J. Org. Chem.*, **34**, 3396 (1969).
(44) C. A. Bunton, S. J. Farber, and E. J. Fendler, *ibid.*, **33**, 29 (1968).
(45) Reference 43 and references therein.
(46) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).
(47) D. V. Wells, J. F. Bunnett, and J. O. Edwards, unpublished results.

of *p*-NPMP in the presence of added calcium ions is another example of such catalysis.

Since rapid attack by *s*-collidine at the phosphorus site is unlikely due to the presence of methyl groups in the 2 and 6 positions,[2-4,10] the larger part of the increase in k' with increasing *s*-collidine concentration (Table VII) is most probably caused by the corresponding increase in pH. The hydrolysis of Sarin[48] has been shown to be catalyzed by the addition of divalent metal ions where the catalyzing species is the hydroxy complex $[M(H_2O)_{x-1}(OH)]^+$ formed by the ionization of the aquated metal ion $[M(H_2O)_x]^{2+}$. A calcium–hydroxo complex of the type VII can be invoked to explain the catalysis of the hydrolysis of *p*-NPMP by added calcium ions. At 60°, the pK_a for the ionization of $[Ca(H_2O)_x]^{2+}$ (eq 5) is 12.3.[49]

$$Ca(H_2O)_x^{+2} \rightleftarrows [Ca(H_2O)_{x-1}(OH)]^+ + H^+ \quad (5)$$
VII

It has been reported[48] that the second-order rate constant $(k_2)_{OH^-}$ for the uncatalyzed attack of hydroxide ion on Sarin and $(k_2)_{Mg}$, the second-order rate constant for attack by $[Mg(H_2O)_{x-1}(OH)]^+$, are roughly equal. With *p*-NPMP, $(k_2)_{OH^-} = 1.9 \times 10^{-2}\ M^{-1}\ min^{-1}$ at 60° and $(k_2)_{Ca} = 4.2\ M^{-1}\ min^{-1}$ at a calcium ion concentration of 0.05 *M*. Thus, with the monoanionic substrate the reactivity of $[Ca(H_2O)_{x-1}(OH)]^+$ is approximately 200 times greater than that of OH^-. According to the data presented[49] the reactivity of the calcium ion should be somewhat lower than that of the magnesium ion (based on pK_a values) so that, in fact, the ratio of $(k_2)_{Mg}/(k_2)_{OH^-}$ could conceivably be greater than 200. The difference in behavior between Sarin and *p*-NPMP is reasonable on the basis of two effects. First, the positively charged metal ion should be more strongly attracted to the anion of *p*-NPMP than to the neutral Sarin. Second, hydroxide ion should have more difficulty attacking the anion of *p*-NPMP than Sarin. Both effects are based on electrostatic factors and both should increase the relative effectiveness of cation catalysis toward *p*-NPMP.

Registry No.—PMP, 13091-13-9; PMP anion, 24903-87-5; *p*-NPMP, 1832-64-0; *p*-NPMP anion, 24886-86-0.

Acknowledgment.—We gratefully acknowledge the support of the Department of the U. S. Army.

(48) J. Epstein and W. A. Mosher, *J. Phys. Chem.*, **72**, 622 (1968), and references therein.

(49) J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, *Chem. Soc., Spec. Publ.* **No. 6** (II), 1 (1957).

Reactions of Phosphonic Acid Esters with Nucleophiles. II. Survey of Nucleophiles Reacting with *p*-Nitrophenyl Methylphosphonate Anion

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Rate constants have been determined for the reactions of a variety of nucleophiles with the anion of *p*-nitrophenyl methylphosphonic acid (*p*-NPMP). The reaction in each case is second order, first order each in nucleophile and in substrate. The orders of reactivity are compared. The bulkiness of the nucleophile near the donor site is important. Certain anionic nucleophiles display a large α effect; peroxide, hydroxamate, and hypochlorite ions are the most reactive of those investigated. Fluoride ion reacts with *p*-NPMP, but chloride and bromide ions do not. Thiophenolate ion is about 50 times as reactive as the phenolate ion. The relative reactivity of hydroperoxide ion as compared with hydroxide ion is similar to that observed for neutral phosphorus substrates. The data are explained by a mechanism in which the nucleophile attacks the substrate at the phosphorus atom.

This paper continues a survey of the reactivities of various nucleophiles with phosphonic acid ester monoanions. The anion of *p*-nitrophenyl methylphosphonic acid (*p*-NPMP) was chosen as the substrate for this study because of its reactivity. As noted in the previous paper in this series,[2] phosphonic acid esters exist as monoanions over a wide pH range so that an investigation of nucleophiles of varying basicity was possible.

Experimental Section

Synthesis of *p*-nitrophenyl methylphosphonic acid and techniques of following the release of the *p*-nitrophenolate anion have been previously described.[2] Either the pseudo-first-order or pseudo-zero-order kinetic method was used. Measurements of pH were made on a Leeds and Northrup Model 7401 or a Beckman Model G meter. The buffers used and their concentrations are described in Tables I–II. When the reaction pH was less than 9, 2 ml of the reaction mixture was diluted with 1 ml of a 1 *M* K_2CO_3 solution (cell capacity 3.3 ml) in order to insure that the phenol was completely in its anionic form (pK_a *p*-nitrophenol = 7.15).[3] The pH of the resulting solution was approximately 11 and the absorbance was corrected for dilution. Alternatively the pH of the solution was measured and the fraction of *p*-nitrophenol present as the anion was calculated. For each nucleophile studied, a blank was run to correct for the hydrolysis of *p*-NPMP due to hydroxide and water attack; this blank consisted of a solution containing exactly the same components as the reaction solution except for the nucleophile.

Nucleophiles. A. Peroxides.—Methyl hydroperoxide was prepared according to the directions of Rieche and Hitz.[4] However, since it was not necessary to use water-free peroxide, the following simplification was used. The ether extraction was omitted. The material obtained from the first distillation was distilled once more and cut into five approximately equal fractions. The fractions were analyzed for hydrogen peroxide and

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(2) E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3063 (1970).

(3) J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, *Chem. Soc., Spec. Publ.*, **No. 6** (I), 1 (1957).

(4) A. Rieche and F. Hitz, *Ber.*, **62**, 2458 (1929).

TABLE I

RATE CONSTANTS FOR THE REACTION OF NUCLEOPHILES WITH *p*-NITROPHENYL METHYLPHOSPHONATE ANION

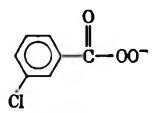
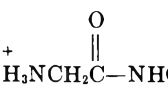
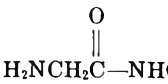
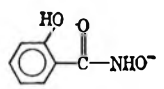
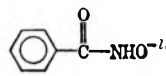
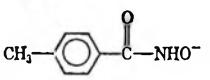
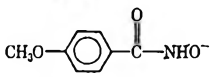
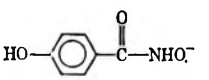
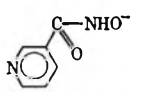
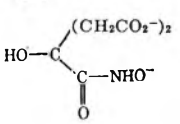
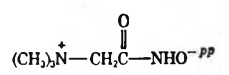
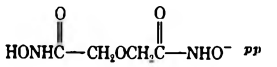
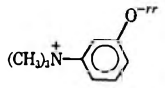
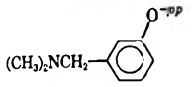
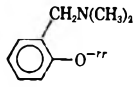
Nucleophile	Registry no.	Temp, °C	pK_a[a,b]	pH	Ionic strength	Nucleophile[c] concn range, *M*	[*p*-NPMP] × 10^4, *M*	k_2, M^{-1} min^{-1}
OH^-		30	15.74[d]	...[e]	3.36	0.169–3.36	1.33	3.00×10^{-3}
		30	15.74	...[f]	0.17	0.169	1.33	1.40×10^{-3}[g]
		60	15.74	...[f]	0.17	0.169	1.33	1.92×10^{-2}[g]
H_2O		30	−1.74[d]	7.55[h]	0.16	55.5	5.90	2.13×10^{-9}[i]
OCl^-	7790-92-3	30	7.7[d]	10.2[j]	0.21	0.0181	12.5	2.74×10^{-3}
F^-	16984-48-8	60	3.45[d]	7.00–7.05[k]	0.15	0.12	2.00	7.20×10^{-4}
HOO^-	7722-84-1	30	11.6[l]	...[m]	0.443–0.553	0.055–0.165	1.33	1.55×10^{-1}
CH_3OO^-	3031-73-0	30	11.5[l]	...[n]	0.447–0.564	0.177–0.234	1.33	3.20×10^{-3}
$(CH_3)_3COO^-$	75-91-2	30	12.8[l]	...[o]	0.474–0.965	0.140–0.290	1.33	1.0×10^{-3}
	937-14-4	30	7.6[p]	10.8[q]	1.42	0.05	2.00	6.6×10^{-3}[r]
H_2NNH_2	302-01-2	60	7.77[e,s]	9.67[u]–10.31	0.05–0.1	0.074–0.185	9.40	1.92×10^{-3}[s]
NH_2OH	7803-49-8	60	6.0[d]	7.1[v]	0.034	0.1	2.00	3.3×10^{-3}
	110-86-1	30	5.23[w]	8.70[x]	0.05–0.1	0.414–0.745	13.5–24.7	6.71×10^{-6}[aaa]
		60	5.23[w]	8.60[x]–8.80	0.05–0.1	0.0495–0.0988	14.1	1.62×10^{-4}
$CH_3CH_2CH_2NH_2$	107-10-8	60	10.60[w]	11.58–11.71[u]	0.05–0.10	0.121–0.726	1.18	3.66×10^{-3}
$H_2NCH_2CO_2H$	56-40-6	30	9.60[d,y]	9.3[z]	0.22	0.22	1.30	4.0×10^{-5}
	5349-80-4	30	7.4[aa]	8.50[bb]	0.10	0.1	2.7	2.0×10^{-4}
				9.28[cc]	0.21	0.124	3.5	1.7×10^{-3}
				9.35[dd]	0.11	0.1	2.7	1.0×10^{-3}
		30	9.4[aa]	10.00[ee]	0.3	0.1	1.3	2.5×10^{-3}
				10.60[ff]	0.4	0.1	1.3	2.3×10^{-3}
				10.60[gg]	0.12	0.1	2.7	2.2×10^{-3}
	89-73-6	30	7.4[hh]	8.5[ii]	0.3	0.05	2.7	2.3×10^{-3}
			7.4	9.3[jj]	0.3	0.05	2.7	3.3×10^{-3}
			7.4	9.8[kk]	0.3	0.05	2.7	3.3×10^{-3}
	495-18-1	30	8.75[mm]	9.85[j]	0.34	0.093	1.33–5.32	2.0×10^{-3}
	2318-82-3	30	8.93[cc]	9.62[cc]	0.25	0.061	3.50	2.01×10^{-3}
	10507-69-4	30	9.03[mm]	9.70[cc]	0.27	0.067	3.50	1.84×10^{-3}
	24886-97-3	30	9.03[mm]	9.40–9.68[cc]	0.27	0.064–0.068	3.50	1.19×10^{-3}
	5657-61-4	30	8.30[mm]	9.88[nn]	0.25	0.045	3.50	3.07×10^{-4}
	24886-99-5	30	8.94[p,oo]	9.86[cc]	0.25	0.041	3.50	5.70×10^{-4}
	24887-00-1	30	7.14[qq]	7.56[cc]	0.25	0.0945	3.50	1.50×10^{-4}

TABLE I (*Continued*)

Nucleophile	Registry no.	Temp, °C	pK_a[a,b]	pH	Ionic strength	Nucleophile[c] concn range, *M*	[*p*-NPMP] × 10⁴, *M*	k_2, M^{-1} min^{-1}
 [pp]	24887-01-2	30	9.24[qq]	9.45[cc]	0.22	0.0693	3.50	1.12×10^{-3}
 [rr]	2498-27-3	30	8.12[ss]	9.30[tt]	0.096	0.035	16.7	1.03×10^{-4}
 [pp]	24887-03-4	30	8.88[ss]	8.93[tt]	~0.1	0.072	17.5	$\leq 4.4 \times 10^{-5}$
 [rr]	24887-04-5	30	8.62[ss]	9.15[tt]	~0.1	0.128	17.5	$\leq 2.5 \times 10^{-5}$
	3229-70-7	30	9.98[d]	10.0[j]	0.3	0.0366–0.183	13.3	1.2×10^{-5}
		60	9.98[d]	11.6[vv]	0.08	0.075		6.6×10^{-4}
		30	11.02[ww]	10.91[zz]	~0.35[vv]	0.362–0.413	13.3	1.3×10^{-5} [zz]
	13133-62-5	30	8.02[ww]	11.42–12.17[zz]	~0.35[vv]	0.0259–0.0323	13.3	7.0×10^{-4} [zz]

[a] For conjugate acid of nucleophile. [b] Values are at 20–30°. [c] Total nucleophile added; uncorrected for fraction existing in acid form; correction was applied for rate constant calculation. [d] "Handbook of Chemistry and Physics," R. C. Weast and S. M. Selby, Ed., 47th ed, The Chemical Rubber Company, 1966. [e] Hydroxide ion concentration varied. [f] 0.169 *M* NaOH. [g] E_a = 17.3 kcal/mol; $\Delta S^{\ddagger}$ = −25 eu. [h] 0.108 *M* KH_2PO_4–0.092 *M* NaOH buffer. [i] See ref 2. [j] 0.2 *M* carbonate buffer. [k] 0.2 *M* phosphate buffer. [l] A. J. Everett and G. J. Minkoff, *Trans. Faraday Soc.*, **49**, 410 (1953). [m] 0.388 *M* NaOH. [n] 0.330 *M* NaOH. [o] 0.330–0.675 *M* NaOH. [p] Measured potentiometrically by us. [q] 0.50 *M* carbonate buffer. [r] Corrected for peracid decomposition—see Experimental Section. [s] From R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958). [t] Statistically corrected. [u] 0.16 *M* boric acid–NaOH buffer. [v] 0.02 *M* phosphate buffer. [w] Data in ref 3. [z] 0.16 *M* boric acid–sodium borate buffer. [y] For equilibrium $H_2NCH_2CO_2H \rightleftharpoons H_2NCH_2CO_2^- + H^+$. [z] pH established using mixtures of 10 ml of 1.0 *M* glyine and 5 ml of 1.0 *M* NaOH solutions. [aa] Measured by us potentiometrically:

$$^{+}NH_3CH_2C(=O)NHOH \underset{}{\overset{K_1}{\rightleftharpoons}} NH_3CH_2C(=O)NHO^- + {}^{+}H \quad (K_1 = 7.4)$$

$$^{+}NH_3CH_2C(=O)NHO \underset{}{\overset{K_2}{\rightleftharpoons}} NH_2CH_2C(=O)NHO^- + H^+ \quad (K_2 = 9.4)$$

[bb] In water. [cc] 0.134 *M* carbonate. [dd] 0.0048 *M* NaOH. [ee] 0.013 *M* NaOH–0.174 *M* Na_2CO_3. [ff] 0.13 *M* Na_2CO_3. [gg] 0.012 *M* NaOH. [hh] Data in ref 21. [ii] 0.185 *M* pH 10 carbonate buffer–0.069 *M* NaOH. [jj] 0.185 *M* pH 9 carbonate buffer–0.069 *M* NaOH. [kk] 0.191 *M* pH 9 carbonate buffer–0.035 *M* NaOH. [ll] See Table II. [mm] R. Swidler, R. F. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959). [nn] Added as sodium salt. [oo] A. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959). [pp] Added as hydrochloride salt. [qq] Determined by us spectrophotometrically. [rr] Added as the hydriodide salt. [ss] J. Epstein, *et al.*, *J. Amer. Chem. Soc.*, **86**, 3075 (1964). [tt] 0.13 *M* borate buffer. [uu] Data in ref 10. [vv] 0.005 *M* phosphate buffer. [ww] In 50:50 MeOH:H_2O volume. [zz] Apparent pH; 0.33 *M* K_2CO_3 was used as base. [vv]Ionic strength approximate since pK_a values of carbonic acid in 50:50 MeOH:H_2O are not known. [zz] Run in 50:50 MeOH:H_2O by volume. [aaa] E_a = 21.3 kcal/mol, $\Delta S^{\ddagger}$ = −22 eu.

for methyl hydroperoxide. Hydrogen peroxide was determined specifically by reaction with titanium sulfate.[5] Total peroxide was measured by the standard iodometric procedure using a reaction time for iodide oxidation of about 90 min. The first fraction proved to be 3.85 *M* in MeOOH and 0.001 *M* in H_2O_2 and was used without further purification.

Measurement of the rate of reaction of the anion of *m*-chloroperoxybenzoic acid is complicated by the occurrence of the following side reactions.[6]

$$RCO_3^- + OH^- \longrightarrow RCO_2^- + HOO^- \quad (a)$$

$$RCO_3^- + RCO_3H \longrightarrow 2RCO_2^- + O_2 + H^+ \quad (b)$$

$$RCO_3^- + RCO_3H \longrightarrow RCO\text{-}OO\text{-}COR + HOO^- \quad (c)$$

$$RCO_3^- + HOOH \longrightarrow RCO_2^- + O_2 + H_2O \quad (d)$$

The reaction was run in carbonate buffer at pH 10.8 at which the half-time for the disappearance of *m*-chloroperoxybenzoic acid alone is 457 min. The rate of appearance of *p*-nitrophenol under these conditions measured using the pseudo-zero-order technique for the first 60 min was 7×10^{-8} mol/l.-min. The maximum concentration of H_2O_2 measured simultaneously by ceric ion titrimetry was 7.2×10^{-4} *M*. At various time intervals aliquots were withdrawn from the reaction and titrated according to the method of Greenspan and MacKellar[7] for both hydrogen peroxide and peracid. Corrections were made for HOO^- attack on *p*-NPMP and the corrected value is reported in Table I.

B. Hydroxamic acids. Unsubstituted, *p*-methyl-, *p*-methoxy-, and *p*-hydroxybenzhydroxamic acids were prepared according to the method of Hauser and Renfrow.[8] Glycinehydroxamic acid was synthesized by the procedure of Safir and Williams.[9] The betaine, 3-pyridyl, citric, and glycinehydroxamic acids were kindly supplied by the Department of the Army, Edgewood Arsenal, Md. Determination of the pK_a values[10] of betaine, citric, and glycinehydroxamic acids were made by titrating approximately 0.01 *M* solutions of the acid (exact concentrations were determined by weight of acid used) with a 0.1246 *M* NaOH solution. Each acid sample was dissolved in 50 ml of deionized

(5) G. M. Eisenberg, *Ind. Eng. Chem., Anal. Ed.*, **15**, 327 (1943).

(6) (a) J. D'Ans and J. Mattner, *Angew. Chem.*, **63**, 368 (1951); (b) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **58**, 1846 (1962); (c) J. F. Goodman and P. Robson, *J. Chem. Soc.*, 2871 (1963); (d) E. Koubek, G. Levey, and J. O. Edwards, *Inorg. Chem.*, **3**, 1331 (1964), plus other references therein.

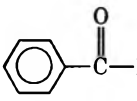
(7) E. P. Greenspan and D. G. MacKellar, *Anal. Chem.*, **20**, 1061 (1948).

(8) C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 67.

(9) S. R. Safir and J. H. Williams, *J. Org. Chem.*, **17**, 1298 (1952).

(10) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., London, 1962.

TABLE II

STUDY OF  REACTION WITH *p*-NPMP[a-c]

[N],[d] *M*	[*p*-NPMP] × 10⁴, *M*	pH	Buffer	Buffer concn, *M*	*I*	$k_2 \times 10^3$, M^{-1} min^{-1}
0.0324	10.6	8.43	Phosphate	0.1	0.25	1.71
0.0933	5.32	9.89	Carbonate	0.2	0.34	1.95, 1.77
0.0924	1.33	9.83	Carbonate	0.2	0.34	2.21, 2.32
0.100	5.32	12.23	Phosphate	0.164	0.44	1.99
0.019	5.32	8.12	Citrate	0.018	0.23	1.51
0.090	5.32	9.70	Carbonate	0.2	0.33	1.84
0.0816	5.32	9.40	Carbonate	0.2	1.81[e]	2.46
0.050	5.32	10.40	Carbonate	0.2	0.35	1.80

[a] Temp = 30°. [b] $pK_a(C_6H_5CONHOH) = 8.75$. [c] Corrected where appropriate for benzhydroxamic acid (acid form) in solution [d] N = anionic form of benzhydroxamic acid. [e] Added $NaClO_4$.

water containing ~0.1 *N* KCl. pK_a values were determined from the half-neutralization point.

C. Phenols.—*m*-Hydroxyphenyltrimethylammonium iodide, *m*-hydroxybenzyldimethylamine hydrochloride, and *o*-hydroxy benzyldimethylamine hydriodide were supplied by the Department of the Army, Edgewood Arsenal. At 60° the reaction of phenoxide ions with undissociated phenols to form colored materials interferes with the assay of the *p*-nitrophenolate anion. Interference was minimized by a run at pH 11.6 in 0.005 *M* phosphate buffer in which two flasks were used, one containing 0.125 *M* and the other 0.05 *M* phenoxide ion. The change in molar absorptivity with time in these flasks was corrected for the relatively small change observed at this pH in the absence of *p*-NPMP. The difference in the corrected molar absorptivity changes between the two was then taken as the rate due to 0.075 *M* phenoxide ion.

D.—All other reagents were commercial products of the highest purity obtainable and further purified by conventional methods where necessary.

Hypochlorite solutions were standardized by reaction with a known excess of hydrogen peroxide[11] followed by acidification and back-titration with a standard ceric solution.

50:50 MeOH:Water (by Volume).—Apparent pK_a values of phenol and thiophenol were determined by titrating 0.1 *M* solutions of the acid form of these compounds with a standardized 0.1 *M* KOH solution. Aliquots of base were added to each acid solution and the "pH" measured. Based upon the concentrations of ions present after each addition of base, a pK_a value was calculated. The average of the pK_a values determined within a titration was taken as the value for the particular titration.

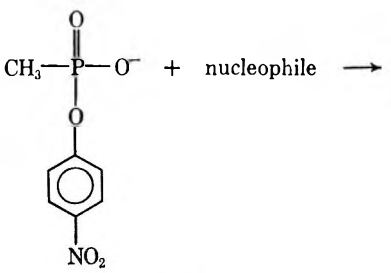
Kinetic experiments were carried out in this solvent system in the same manner as in the aqueous medium. Care was taken to avoid evaporation of methanol. The pK_a of *p*-nitrophenol was not determined since the pH values of reaction solutions in 50:50 MeOH:water were always high enough to preclude the possibility of any *p*-nitrophenol existing in the undissociated form.

Results

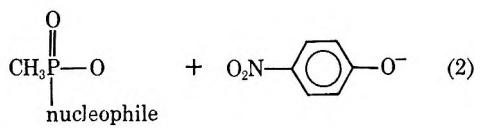
The second-order rate constants for the reaction of a series of nucleophiles with the *p*-NPMP monoanion in aqueous solution are given in Table I. The rate is first-order each in both substrate and nucleophile (eq 1)

$$\text{rate} = k_2[p\text{-NPMP}][\text{nucleophile}] \quad (1)$$

suggesting a SN2(P) bimolecular mechanism.[12,13] The stoichiometry of the probable rate-determining step is the reaction of 1 mol of nucleophile with 1 mol of *p*-NPMP (eq 2); an anionic nucleophile is used for



I



II

illustrative purposes. Subsequent to the rate-determining step, compounds of type II may be hydrolyzed by the solvent; a study of this latter reaction was not made. There was no evidence for specific or general acid and base catalysis other than in the hydrolysis case discussed in the previous paper.[2] Since both hydroxide ion and water have been found to react as nucleophiles with *p*-NPMP, the rate constants in Table I have been corrected for attack by these species.

The activation parameters (Table I) for both negatively charged and neutral nucleophiles are consistent with a bimolecular mechanism. Several reagents examined showed no detectable reactivity toward the phosphorus site of *p*-NPMP. The rate of release of *p*-nitrophenolate ion is identical with that of the combined hydroxide–water rate. These reagents were Cl^-, Br^-, CN^-, NCO^-, NCS^-, $HONHCO\text{-}OC\text{-}NHO^-$, $B(OH)_4^-$, HPO_4^{2-}, PO_4^{3-}, HCO_3^-, and CO_3^{2-}. The latter five were used as constituents in the buffers for the study of reactive nucleophiles. Table II gives data for the reaction of the benzhydroxamate anion with *p*-NPMP under conditions of varying nucleophile and substrate concentrations, buffer nature, buffer concentration, and ionic strength. The second-order rate constant k_2 is independent of benzhydroxamate and *p*-NPMP concentrations as well as buffer. At the ionic strength used ($I \geq 0.25$), k_2 was found to increase only slightly with increasing ionic strength. Thus, although the kinetic experiments whose data are given in Table I were not performed at constant ionic strength, we think that the values of the rate constants are not substantially altered by this variation. Table II shows

(11) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed, Macmillan, New York, N. Y., 1952, p 560.

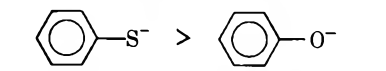
(12) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

(13) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, Chapter 10.

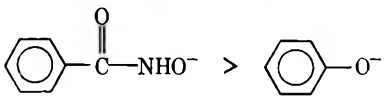
that k_2 is independent of pH above the pK_a of benzhydroxamic acid. At reaction pH values below the pK_a of benzyhydroxamic acid (8.75 at 25°), k_2 is somewhat lower than at higher pH values after correction for benzhydroxamate existing as the conjugate acid, but this may result from use of a slightly incorrect value of the pK_a which is itself reasonably sensitive to ionic strength.[14]

The basic forms of the nucleophiles presented in Table I were the reactive species detected under the experimental conditions. A Brönsted plot[15] is given in Figure 1 for nucleophiles reacting with *p*-NPMP at 30°. The scatter is obvious. However, four series of interesting comparisons of orders of reactivity may be made.

$$OOH^- > CH_3OO^- > (CH_3)_3COO^-$$



$$OOH^- >> OCl^- \cong OH^-$$



Nucleophiles containing an unshared pair of electrons on an atom adjacent to the attacking atom (α nucleophiles) appear to be most reactive.[16] For example, although hydroxide ion is $\sim 10^8$ more basic than the hypochlorite ion, they are approximately equally reactive. The hydroperoxide ion is $\sim 10^4$ less basic than hydroxide, yet it is $\sim 10^2$ more reactive. Second-order rate constants for attack by hydroperoxide and hydroxide anions on neutral tetrahedral phosphorus esters have been reported.[17-21] A log–log plot (Figure 2) for the reactions of HO_2^- with these esters *vs.* the reactions of OH^- with these esters is linear with a slope of unity. When plotted on this graph the point for *p*-NPMP falls on the correlation line; this indicates a similar mechanism for our anionic substrate and the many neutral phosphorus substrates.

The fluoride ion is reactive toward the anion of *p*-NPMP, whereas chloride and bromide are not. At pH 7.00–7.05, fluoride reactivity is not complicated by the presence of HF and HF_2^-.[22]

Zwitterionic nucleophiles, containing a positively charged site as well as a negatively charged site, do not seem to be unusually reactive toward *p*-NPMP (Table I, Figure 1). In fact, the monoanionic glycinehydroxamate (H_2NCH_2CO–NHO^-) is is more reactive than the zwitterionic species (H_3N^+–CH_2–CO–NHO^-) (as shown in Table I), and the favorable electrostatic situation in forming a transition state is presumably compensated for by a reduction of electron density at the reaction site. Quaternary ammonium substituents

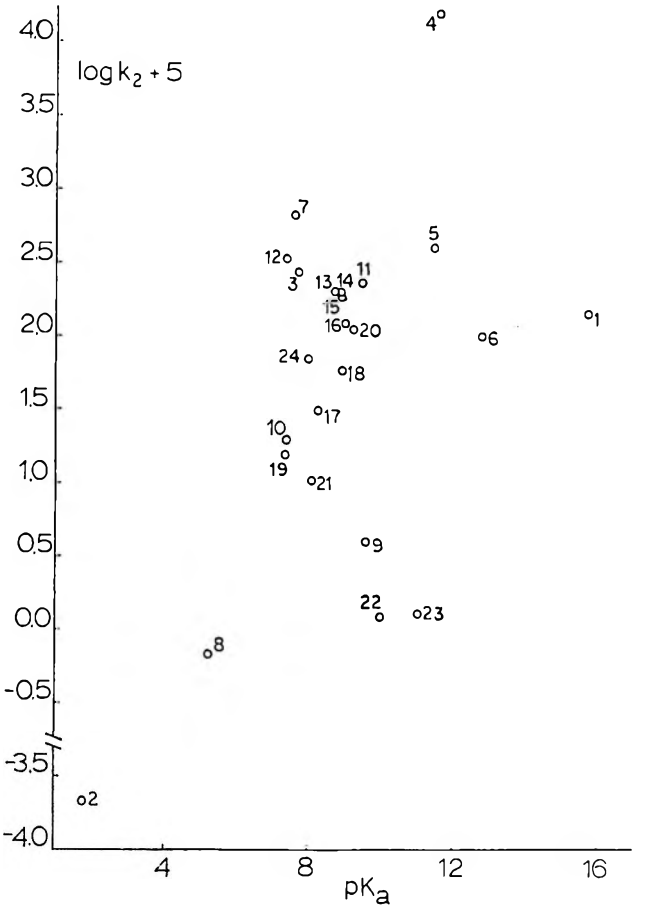


Figure 1.—A plot of log k_2 + 5 *vs.* pK_a of the conjugate acid of nucleophiles reacting with *p*-NPMP: (1) hydroxide, (2) water, (3) hypochlorite ion, (4) hydroperoxide ion, (5) methyl hydroperoxide ion, (6) *t*-butyl hydroperoxide ion, (7) *m*-chloroperoxybenzoate ion, (8) pyridine, (9) glycine, (10) glycinehydroxamic acid, (11) glycinehydroxamate ion, (12) *o*-hydroxybenzhydroxamate ion, (13) benzhydroxamine ion, (14) *p*-methylbenzhydroxamate ion, (15) *p*-methoxybenzhydroxamate ion, (16) *p*-hydroxybenzhydroxamate ion, (17) nicotinhydroxamate ion, (18) citric monohydroxamate trianion, (19) trimethylammonium glycinehydroxamate zwitterion, (20) $HONHCO$-CH_2OCH_2CO–NHO^-, (21) *m*-trimethylammonium phenolate zwitterion, (22) phenolate ion, (23) phenolate ion (50:50 MeOH:H_2O), (24) thiophenolate ion (50:50 MeOH:H_2O).

on aromatic nucleophiles, however, tend to increase the nucleophilicity of phenolates. Thus, *m*-trimethylammonium phenolate anion displays a low but detectable reactivity toward *p*-NPMP while *o*- and *m*-benzyldimethylamine phenolate anions do not (Table I).

Considerable difficulty was experienced in the investigation of thioanion nucleophiles. The mercaptide ions were slowly oxidized to the corresponding disulfides. It is not known whether this oxidation was by the nitro group on the aromatic ring of the substrate or by trace amounts of oxidizing impurities such as oxygen. In any event, the disulfide, being insoluble, produced a cloudy solution; from such a solution with thiophenolate ion, diphenyl disulfide was isolated and identified. In general, the resulting cloudy aqueous solutions made spectrophotometric determinations of the *p*-nitrophenolate ion impossible. A 50:50 MeOH–H_2O solvent system was used in which many disulfides are soluble. However in this system the calculated second-order rate constants, k_2, were not constant but increased with decreasing initial concentration of the anionic

(14) R. Swidler and G. M. Steinberg, *J. Amer. Chem. Soc.*, **78**, 3594 (1956).
(15) J. N. Brönsted and K. J. Pedersen, *Z. Physik. Chem.*, **108**, 185 (1924).
(16) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).
(17) L. Ginjaar, Ph.D. Thesis, Leiden University, 1960.
(18) L. Larsson, *Acta Chem. Scand.*, **12**, 723 (1958).
(19) B. Gehauf, J. Epstein, G. B. Wilson, B. Witten, S. Sass, V. F. Bauer, and W. H. C. Rueggeberg, *Anal. Chem.*, **29**, 278 (1957).
(20) J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).
(21) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).
(22) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Wiley-Interscience, New York, N. Y., 1962, p 291.

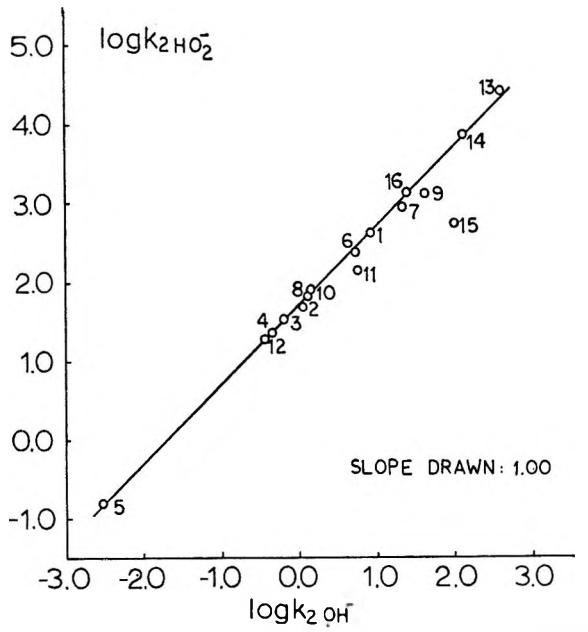


Figure 2.—Log–log plot of the second-order rate constants for the reactions of HO_2^- and OH^- with organophosphorus esters.

R_1	R_2	No.
	$R_1R_2POC_6H_4(p\text{-}NO_2)$ — 25°	
$-OC_2H_5$	$-C_2H_5$	1
-O-*i*-Pr	-*i*-Bu	2
$-OC_2H_5$	$-OC_2H_5$	3
-O-*n*-Pr	-*n*-Pr	4
$-O^-$	$-CH_3$	5 (30°)
	$R_1R_2POC_6H_4(o\text{-}NO_2)$ — 25°	
$-OCH_3$	$-OCH_3$	6
$-OC_2H_5$	$-C_2H_5$	7
$-OC_2H_5$	$-OC_2H_5$	8
	$R_1R_2POC_6H_4(m\text{-}NO_2)$ — 25°	
$-OCH_3$	$-CH_3$	9
$-OCH_3$	$-OCH_3$	10
$-OC_2H_5$	$-C_2H_5$	11
$-OC_2H_5$	$-OC_2H_5$	12
	$R_1R_2P(O)F$ — 25°	
$-OCH_3$	$-OCH_3$	13
$-OC_2H_5$	$-OC_2H_5$	14
-O-*n*-Pr	-O-*n*-Pr	15
-O-*i*-Pr	$-CH_3$	16

form of the sulfur nucleophile.[23a] The pK_a values for phenol and thiophenol in H_2O are 9.98[3,10] and 6.52,[23b] respectively. In 50:50 MeOH–H_2O solutions, they are 11.02 and 8.02 as measured here. The rate constant for the thiophenoxide ion, which showed only a slight increase in k_2 upon decrease in initial thiophenoxide concentration, is the only sulfur nucleophile reported in Table I. Rate constants for phenoxide ion in both H_2O and 50:50 MeOH–H_2O were determined for comparative purposes. Thiophenoxide ion reactivity is seen to be ~50 times as great as phenoxide ion reactivity even though the former is $\sim 10^3$ less basic than the latter.

(23)(a) This is explicable on the basis of reduction of the nitro group by mercaptide ion (RS^-) producing the corresponding disulfide. RS^- was always present in excess of *p*-NPMP; thus at higher RS^- concentrations, more of the $-NO_2$ group was reduced than at lower RS^- concentrations leading to a lower calculated rate constant. The rate of release of *p*-nitrophenolate anion is the method used to monitor the reaction, so the apparent variation in k_2 with RS^- is believed to be an artifact of the system. (b) B. Miller, *J. Amer. Chem. Soc.*, **84**, 403 (1962).

Discussion

Prior to this investigation reactions of neutral nucleophiles with tetrahedral organophosphorus ester anions have been demonstrated;[24-30] however, little data on the reactivity of anionic nucleophiles toward anionic substrates are available. This study reveals that both neutral and anionic compounds react as nucleophiles in a bimolecular fashion with monoaryl ester monoanions, in this case *p*-NPMP. Analogies can be drawn to the reactivities of other organophosphorus esters. The reactions of amines are discussed separately, although several amines are listed in Table I for comparative purposes.

Generally the reactivities of various classes of nucleophiles in tetrahedral organophosphorus substitution reactions cannot be correlated with basicity;[12,17,26,31] this has been shown for neutral phosphorus esters on which most kinetic studies have been performed. However, reactivity can be correlated with nucleophile basicity where nucleophiles containing a common reacting group are examined.[17,24,25,27,31] For example, the rate of reaction of isopropyl methylphosphorofluoridate[17,32] (Sarin) with representative nucleophiles of various classes does not correlate simply with nucleophile basicity; however linear Brönsted relationships are found with specific classes such as hydroxamates,[21] catechols,[33] and amines.[34] A similar result is obtained with *p*-NPMP. Figure 1 shows that reactivity is poorly correlated with nucleophile basicity. However the rates for reaction of pyridines[35] yield a linear Brönsted relation. A correlation of hydroxamate ion reactivity with basicity cannot be made since the pK_a values of the hydroxamic acids studied (Table I) are not sufficiently different for comparative purposes.

The orders of reactivity obtained with *p*-NPMP are similar to those obtained with other organophosphorus esters. The α effect has been shown to be operative in tetrahedral organophosphorus displacements;[17,18,21,32-34,36,37] this is also observed with *p*-NPMP. Peroxides, hypochlorite, and hydroxamates are the most reactive nucleophiles studied. It appears that anionic nucleophiles exhibit a definite α effect while neutral nucleophiles display at best a small one; hydrazine and hydroxylamine are not extremely reactive with *p*-NPMP.

(24) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).
(25) W. P. Jencks and M. Gilchrist, *ibid.*, **87**, 3199 (1965).
(26) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 6, and references therein.
(27) G. Di Sabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4393 (1961).
(28) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. B*, 135 (1968).
(29) G. O. Dudek and F. H. Westheimer, *J. Amer. Chem. Soc.*, **81**, 2641 (1959).
(30) R. Blakely, Thesis, Harvard University, 1963.
(31) Reference 13, Chapter 6, and references therein.
(32) L. Larsson, *Svensk Kem. Tidskr.*, **70**, 405 (1958).
(33) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 341 (1956).
(34) P. Cannon, private communication.
(35) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, **92**, 4675 (1970).
(36) J. Epstein, V. E. Bauer, M. Saxe, and M. M. Demek, *ibid.*, **78**, 4068 (1956).
(37) N. G. Lordi and J. Epstein, *ibid.*, **80**, 509 (1958).

The relative reactivities of hydroperoxide and hydroxide anions are of special interest. The second-order rate constant, $(k_2)_{HO_2^-}$, for the attack of HO_2^- on *p*-NPMP is approximately 50 times as great as $(k_2)_{OH^-}$, the second-order rate constant for attack by hydroxide ion. Previous studies[17-21,32] show that the ratio $(k_2)_{HO_2^-}/(k_2)_{OH^-}$ is near 50 for attack by these two nucleophiles on various neutral organophosphorus esters of the type

$$R_1R_2\overset{\overset{O}{\|}}{P}—OC_6H_4NO_2(o,m,p) \text{ and } R_1R_2\overset{\overset{O}{\|}}{P}—X$$

where R_1 is an alkoxy group, R_2 is an alkyl or alkoxy group, and X is a halogen; this is reflected in the linear free energy relation in Figure 2. Bimolecular displacements at tetrahedral phosphorus appear to be partially governed by the stereochemistry of the attacking reagent.[13,31,38] The constant ratio for attack by HO_2^- and HO^- at tetrahedral phosphorus indicates that the manner in which these anions react must be independent of variation in R_1 and R_2, as well as charge on the substrate.

The reactivities of HOO^-, CH_3OO^-, and $(CH_3)_3COO^-$ toward *p*-NPMP are in the ratios 155:3:1; toward *p*-nitrophenylacetate this ratio has been found to be 18:5:1.[39,40] These ratios are suggestive of an increased dependence of reactivity on bulkiness of the nucleophile in displacements at tetrahedral phosphorus relative to carbonyl carbon. Dependence of reactivity on amine steric effects has been shown to be greater for tetrahedral phosphorus than carbonyl carbon.[35]

Fluoride ion has the reputation of being an effective nucleophile toward tetrahedral phosphorus. This has been shown with diisopropyl phosphorochloridate[41] (DClP) and acetylphosphate monoanion.[27] The nature of the nucleophilic species with these two substrates is in doubt, however. The reactions of DClP were carried out in absolute ethanol where the extent of ion pairing of the nucleophiles is not known. The reaction of fluoride and acetylphosphate was run in acidic solution where HF and HF_2^- are present.[22] Fluoride ion does not react with phosphate dianions, but does react with phosphoramidate monoanion.[25] Fluoride ion reactivity toward the monoanions of mono- and bis(2,4-dinitrophenyl) phosphates has been reported.[28] Table I shows that the reactivity of fluoride ion toward *p*-NPMP is roughly equal to that of phenolate ion. Chloride and bromide ion reactivity was not detected.

Mercaptide ions have been reported to be equally effective[23b] or less effective nucleophiles[41] toward tetrahedral phosphorus than are similar oxygen nucleophiles. This is in contrast to the reactivity at aliphatic carbon where the more polarizable mercaptide ions are more reactive.[42] The reactivities of thiophenoxide and phenoxide ions are approximately equal toward O,O-diphenyl phosphorochlorothioate[23b] in "90%" *t*-butyl alcohol–dioxane; however the necessary correction for ion pairing was not made. In ethanol, PhS^- is less reactive than PhO^- with diisopropyl phosphorochloridate.[41] With *p*-NPMP in 50:50 $MeOH:H_2O$, PhS^- is about 50 times as reactive as PhO^-, reversing the previously reported order of reactivity. Clearly, a further study to clarify the relative reactivities of sulfur and oxygen nucleophiles toward tetrahedral phosphorus is warranted.

Registry No.—*p*-NPMP anion, 24886-86-0.

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(40) (a) M. C. Sauer, unpublished results; (b) J. E. McIsaac, Jr., H. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Organic Section, paper 70.
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Arylsulfonoxylation of Aromatic Compounds. II. Partial Rate Factors for the Nitrophenylsulfonoxylation of Alkylbenzenes[1a-c]

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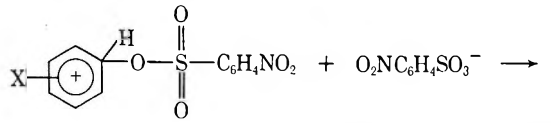
Ethyl acetate is resistant to attack by nitrobenzenesulfonyl peroxides and is a suitable solvent for sulfonoxylations. In the thermal decomposition of *o*- and *m*-nitrobenzenesulfonyl peroxides in alkylbenzenes there are no products resulting from a side-chain hydrogen abstraction characteristic of a homolytic reaction. Competitive *o*- and *m*-nitrophenylsulfonoxylations gave, respectively, for k_{Ar}/k_B: benzene, 1.0; toluene, 13.3, 19.0; ethylbenzene, 11.5, 17.6; cumene, 9.0, 13.5; *t*-butylbenzene, 6.0, 11.9. The *ortho*, *meta*, and *para* orientations (partial rate factors) for *o*-nitrophenylsulfonoxylations follow: toluene, 35.3, 2.7, 62.0% (14.1, 1.1, 49.5); ethylbenzene, 30.6, 4.4, 65.0% (10.5, 1.5, 44.8); cumene, 22.3, 8.9, 68.0% (6.0, 2.4, 36.8); *t*-butylbenzene, 9.0, 19.8, 71.2% (1.6, 3.4, 25.6). The corresponding figures for *m*-nitrophenylsulfonoxylations are: toluene, 31.8, 3.5, 64.7% (18.1, 2.0, 73.8); ethylbenzene, 29.9, 4.3, 65.8% (15.8, 2.3, 69.4); cumene, 23.5, 6.5, 70.0% (9.5, 2.6, 56.7); *t*-butylbenzene, 7.4, 18.1, 74.5% (2.6, 6.5, 53.3). These data are all consistent with an electrophilic classification of the substitution reaction. *m*-Nitrophenylsulfonoxylation is somewhat more selective than *o*-nitrosulfonoxylation.

In the first paper of this series, the partial rate factors obtained for the substitution of toluene and chlorobenzene by *m*-nitrobenzenesulfonyl peroxide led tentatively to an electrophilic ionic classification of the

$$(O_2NC_6H_4SO_3)_2 + C_6H_5X \longrightarrow$$



$$XC_6H_4OSO_2C_6H_4NO_2 + O_2NC_6H_4SO_3H$$

mechanism of the reaction. Confirmation of this ionic classification is needed, however, for heterolytic dissociations of symmetrical peroxides are not common in the absence of strong Lewis acids. In the present work, the decompositions of *o*- and *m*-nitrobenzenesulfonyl peroxides in toluene, ethylbenzene, cumene, and *t*-butylbenzene were studied to determine first, whether higher order side-chain hydrogens would undergo abstraction such as is common in the presence of free radicals; second, the degree of steric hindrance encountered toward *ortho* substitution with increasing bulk of the alkyl group; third, the relation of the *meta* and *para* partial rate factors to the Baker–Nathan order; and fourth, whether the position of the nitro group in the peroxide affects the course of the reactions.

Results and Discussion

In previous work[1b,2] and the first efforts of the present investigations, the sulfonoxylations of benzene derivatives were performed using the aromatic compound as both substrate and solvent. In a general study of the substitution reaction this dual use of the aromatic component is sometimes impossible and always undesirable. It is impossible if the substrate is a crystalline solid. It is undesirable even with liquid aromatics because a change in substrate may also produce major changes (for example, a variation in the dielectric constant) in the reaction mixture. Therefore, in the present work, some of the first efforts were devoted to the selection of an appropriate inert solvent. Ethyl acetate and acetonitrile were found to be more resistant to attack by the nitrobenzenesulfonyl peroxides than other common organic liquids. Ethyl acetate is particularly useful in the nitrophenylsulfonoxylations because it not only ensures reasonable similarity of the reaction mixtures while using different aromatic substrates, but in addition provides homogeneous solutions, for the nitrobenzenesulfonic acids which form are soluble in ethyl acetate, although they are quite insoluble in aromatic hydrocarbons. Essentially identical orientations and relative reactivities were obtained for the nitrophenylsulfonoxylation of several alkylbenzenes in both the absence and presence of ethyl acetate. Therefore, some substitution experiments which already had been completed using an arene as both substrate and solvent were not repeated using ethyl acetate as a solvent.

The ionic classification of the peroxide decomposition is now supported by the absence of any side-chain-attack products in the reactions of both *o*- and *m*-nitrobenzenesulfonyl peroxides with toluene, ethylbenzene, and cumene, although concentrations as low as 1% of such products could be detected. Cumene is normally particularly susceptible to side-chain hydrogen abstraction by free radicals and yields bicumyl when treated with many typical free-radical reagents such as benzoyl peroxide,[3] Fenton's reagent,[4] or diisopropyl peroxydicarbonate.[5] The complete absence of bicumyl in the present work therefore provides strong evidence that the nitrobenzenesulfonyl peroxides are not undergoing any homolytic scission.

Competitive reactions in which *m*-nitrobenzenesulfonyl peroxide decomposed in a mixture of benzene and an arene gave k_{Ar}/k_B as follows: toluene, 19.0; ethylbenzene, 17.6; cumene, 13.5; and *t*-butylbenzene, 11.9. For *o*-nitrophenylsulfonoxylation the figures obtained were: toluene, 13.3; ethylbenzene, 11.5; cumene,

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S078. Taken in part from the Ph.D. Thesis of J. E. Gagen, Case Western Reserve University, 1967. (b) For the previous paper in this series, see R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966). (c) Supported in part by the U. S. Army Research Office (Durham) through Grant No. DA-ARO(D)-31-124-G42. (d) NASA Trainee, 1965–1967.

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9.0; *t*-butylbenzene, 6.0. Therefore with both the peroxides the sequence of the reactivities of the hydrocarbons parallels the Baker–Nathan order. The magnitudes of the relative reactivities are similar to those for nitration of the arenes with acetyl nitrate in acetic anhydride.[6] The yields of esters (65–93%, Table VI) compare favorably with those for other electrophilic substitutions.

A comparison of the isomer distributions, Table I, shows a regular decrease in *ortho* substitution with increasing bulk of the alkyl group. However, the *meta*/*para* ratio also increases markedly, which is characteristic of electronic and not steric influences. The arylsulfonoxy entering group cannot have a much larger steric requirement than a nitronium ion, for the *ortho* substitution of *t*-butylbenzene is fairly similar for introduction of these two substituents.

TABLE I
ISOMER DISTRIBUTIONS FOR THE NITROPHENYLSULFONOXYLATIONS OF ALKYLBENZENES

	o-Nitrophenylsulfonoxylation			*m*-Nitrophenylsulfonoxylation		
Substrate	% *o*	% *m*	% *p*	% *o*	% *m*	% *p*
Toluene	35.3	2.7	62.0	31.8	3.5	64.7
Ethylbenzene	30.6	4.4	65.0	29.9	4.3	65.8
Cumene	22.3	8.9	68.0	23.5	6.5	70.0
t-Butylbenzene	9.0	19.8	71.2	7.4	18.1	74.5

The partial rate factors calculated from these data (Table II) strongly support the heterolytic classification of the substitution. They are numerically in the same general range as those for nitration, bromination, etc.[7] The magnitude of all of the partial rate factors, but particularly the *para* values (25.6–73.8), are much greater than the comparable figures (*para*, 1.4[3]) for the phenylation of alkyl benzenes, a well-established free radical process. Again support for an electrophilic mechanism is obtained.

TABLE II
PARTIAL RATE FACTORS FOR THE NITROPHENYLSULFONOXYLATION OF ALKYLBENZENES

	o-Nitrophenylsulfonoxylation			*m*-Nitrophenylsulfonoxylation		
Substrate	*o*	*m*	*p*	*o*	*m*	*p*
Toluene	14.1	1.1	49.5	18.1	2.0	73.8
Ethylbenzene	10.5	1.5	44.8	15.8	2.3	69.4
Cumene	6.0	2.4	36.8	9.5	2.6	56.7
t-Butylbenzene	1.6	3.4	25.6	2.6	6.5	53.3

There is a regular decrease in the *para* partial rate factors using both peroxides when the branching of the alkyl group increases. This parallels the Baker–Nathan order and, in agreement with the series of relative reactivities, substantiates a σ complex formation as the rate-determining step. The *meta* partial rate factors, in contrast, increase in the progression from toluene to *t*-butylbenzene for both *o*- and *m*-nitrophenylsulfonoxylation. This is expected from the inductive effect of the alkyl substituents, for resonance influences are not predominant for the *meta* substitutions.

The orientations and partial rate factors demonstrate qualitatively a slightly greater selectivity for *m*-nitrophenylsulfonoxylation than for *o*-nitrophenylsulfonoxylation. This selectivity difference perhaps might have been anticipated because the *ortho* peroxide is less stable (more reactive) than its *para* isomer. The selectivity factors, S_f, are about 1.6 for both reactions but are of limited accuracy because they are dependent on the precision of measurement of very small quantities of the *meta* isomers.

In summary, all of these data are consistent with an electrophilic substitution reaction with no evidence of any free-radical characteristics.

The potential use of this substitution as a synthesis of phenols leads to a comparison with the similar substitution using a peroxydicarbonate and aluminum chloride.[8] The nitrophenylsulfonoxylation is preferred in that it is successful with both activated and deactivated nuclei,[9] while peroxydicarbonate substitution essentially has the Friedel–Crafts limitations. The nitrobenzenesulfonyl peroxides are also safer to work with than the unstable peroxydicarbonate esters. The nitrophenylsulfonoxylation is the less attractive synthesis, however, in that the nitrobenzenesulfonate esters produced are much more difficult to hydrolyze than carbonate esters. The reactions are therefore probably best described as competitive in value.

Experimental Section

Materials.—Spectroquality reagent grade benzene and reagent grade toluene, ethylbenzene, cumene, and *t*-butylbenzene were all redistilled before use. Ethyl acetate was purified by the method of Hurd and Strong.[10] Bicymyl- and *meso*- and DL-2,3-diphenylbutanes[11] were prepared by treatment of the proper alkylbenzene with *t*-butyl peroxide. In the experiments determining the half-lives of the *m*-nitrobenzenesulfonyl peroxide in various solvents, the highest grade commercially available solvents were used as received.

***m*-Nitrobenzenesulfonyl peroxide** was obtained in improved yield using minor modifications of the literature[1b] synthesis. *m*-Nitrobenzenesulfonyl chloride (11.1 g, 0.05 mol) in chloroform (15 ml) was added to a cold (−20°) solution of potassium carbonate (8.5 g) in water (140 ml), ethanol (70 ml), and hydrogen peroxide (20 g, 30%) in a Waring blender cup. Agitation was slowly increased to full power and held there for 1 min. Ethanol (100 ml) was then added and the mixture agitated slowly for a few minutes. The resulting precipitate was collected by filtration, washed thoroughly with water, and dried under vacuum. The crude material (96% yield, 95% pure by peroxide titration) decomposed explosively at 105° (lit.[1b] mp 112° dec). The crude peroxide was dissolved in acetone at room temperature, the solution filtered, and the filtrate concentrated under reduced pressure to yield 97% pure peroxide (5 g, 49.5% yield) which decomposed at 107°.

By an identical procedure, *o*-nitrobenzenesulfonyl peroxide (30% yield, 98% pure) is obtained as crystals which sometimes explode on touching and decompose explosively at 94° (lit.[1b] 97°). If this peroxide is stored at room temperature, it loses about 10% of its active oxygen content in 30 days. The same procedure gives *p*-nitrobenzenesulfonyl peroxide (40% yield, 99% pure) as a white powder which is stable to handling but at 127° decomposes explosively (lit.[1b] mp 128° dec).

Nitrobenzenesulfonate esters were prepared from the phenols and the sulfonyl chloride in alcohol–benzene (procedure A)[12]

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(7) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 36 (1963).
(8) P. Kovacic and M. Kurz, *J. Amer. Chem. Soc.*, **87**, 4811 (1965).
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(11) B. Zaremsky, Ph.D. Thesis, Western Reserve University, Cleveland, Ohio, 1954.
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or aqueous alkali (procedure B).[13] The physical parameters and yields of these compounds are listed in Tables III and IV.

TABLE III

MELTING POINTS AND SYNTHESIS METHODS[a] OF ARYL *m*-NITROBENZENESULFONATES (*m*-$O_2NC_6H_4SO_3C_4H_4R$)

R	Registry no.	Mp, °C	Synthesis method
H		92–94[b]	A
o-Methyl		61–62[c]	A
m-Methyl		73[d]	A
p-Methyl		106–108[e]	A
o-Ethyl	25238-10-2	Liq	B
m-Ethyl	25238-11-3	Liq	B
p-Ethyl	25238-12-4	42–44	B
o-Isopropyl	25238-13-5	31–32	B
m-Isopropyl	25238-14-6	Liq	B
p-Isopropyl	25238-15-7	34–36	B
o-*t*-Butyl	25238-16-8	80–82	A
m-*t*-Butyl	25238-17-9	Liq	B
p-*t*-Butyl	25238-18-0	95	A

[a] All C, H, N values within ±0.3% for new compounds. [b] Lit. mp 93–95.[1b] [c] Lit. mp 61–63.[1b] [d] Lit. mp 72–74.[1b] [e] Lit. mp 109–110.[1b]

TABLE IV

MELTING POINTS AND ANALYSES[a] OF ARYL *o*-NITROBENZENESULFONATES (*o*-$O_2NC_6H_4SO_3C_6H_4R$)

R	Registry no.	Mp, °C	Yield, %
H		55–56[b]	18
o-Methyl	25238-19-1	57–58	50
m-Methyl	25238-20-4	64–65	75
p-Methyl		90–91[c]	75
o-Ethyl	25238-21-5	35–36	19
m-Ethyl	25238-22-6	24.5–26	19
p-Ethyl	25238-23-7	62	60
o-Isopropyl	25238-24-8	Liq	15
m-Isopropyl	25238-25-9	36–37	27
p-Isopropyl	25238-26-0	27–28	40
o-*t*-Butyl	25238-27-1	106.5–108	42
m-*t*-Butyl	25237-68-7	54–56	24
p-*t*-Butyl	252382-57-9	44–46	30

[a] All C, H, N values within ±0.3% for new compounds. [b] Lit. mp 57°: R. Vizgert and E. K. Savchuk, *Zh. Obshch. Khim.*, **26**, 2261 (1956). [c] Lit. mp 88–90°: G. Schetty, *Helv. Chim. Acta*, **32**, 24 (1949).

Aryl trimethylsilyl ethers were prepared by refluxing for 6 hr the phenol (0.025 mol) and hexamethyldisilazane (0.25 mol) with a little sand and vacuum distilling the product. The physical parameters and yields of these compounds are listed in Table V.

Selection of a Suitable Solvent.—Aliquots (5 ml) of solutions (0.03–0.04 *M*) of *m*-nitrobenzenesulfonyl peroxide in various solvents at room temperature were removed at intervals and titrated for the peroxide content.[14] The half-lives in hours at room temperature were: chloroform, 1.5; diglyme, 3; acetone, 4.7; nitroethane, 19; ethyl acetate, 20; and acetonitrile, 23. In dimethylformamide the decomposition was immediate. The decomposition in ethyl acetate was first-order with respect to peroxide but in acetonitrile the order was complex. Ethyl acetate was the solvent of choice because of its inertness to the peroxide, its excellent solvent characteristics for the nitrobenzenesulfonic acids, and because in it the kinetic order for disappearance of the peroxide was the same as for the peroxide in pure aromatic substrates.

***m*-Nitrophenylsulfonoxylation of Alkylbenzenes.**—To a mixture of alkylbenzene (0.01 mol) and benzene (0.05 mol), diluted to 50 ml with ethyl acetate, was added *m*-nitrobenzenesulfonyl peroxide (0.0005 mol). After 3 hr at room temperature the peroxide content had disappeared. The toluene, benzene, and ethyl acetate were removed by distillation and ether was used to transfer the residue to an aerosol compatibility tube. The ether was removed by gentle warming of the tube which was purged with nitrogen. A solution (15 ml) of 20% potassium hydroxide in methanol–water (50–50) was added and the closed tube was heated to 145° for 19 hr. The tube was cooled, opened, and the mixture acidified with 50 ml of hydrochloric acid (3 *N*) and extracted with benzene (100 ml). The benzene extract was dried with magnesium sulfate and filtered. The benzene was evaporated from the filtrate, and hexamethyldisilazane (4 ml) and a pinch of sand were added to the residue. After this mixture had been refluxed for 2 hr and an internal standard added (Table VI), the mixture was analyzed by glpc using a 10 ft × 0.25 in. column packed with 5% STAP on 80–100 mesh Chromosorb G. From a rough calculation of the composition of the mixture, assuming areas and concentrations were proportional, a mixture of the pure trimethylsilyl ethers of approximately the same composition was prepared and calibration factors were determined. Using these factors, the true composition of the trimethylsilyl ether mixture was determined and using the hydrolysis yields the composition of the original ester mixture calculated.

In no case was a fraction obtained with a retention time corresponding to that of a side-chain coupling product, although a 1% yield would be detected.

In the *t*-butylbenzene run, the glpc analysis was performed using a 150-ft capillary column coated with SE-30 Silicone "Z." Even using this column the resolution of the *ortho* and *meta* peaks was not complete and the reproducibility was poor.

Calibration Factors for the Conversion of Aryl Nitrobenzenesulfonate Esters to Silyl Ethers.—A mixture of pure isomeric alkylphenyl and phenyl nitrobenzenesulfonate esters in the same ratio of composition, calculated roughly from the chromatogram of a substitution reaction, was subjected to the hydrolysis procedure just described. As yields varied appreciably with minor variations in procedure, calibration runs were always performed along with the substitution determinations. Typical overall yields of silyl ethers are given in Table VII.

Although some of these yields are as low as 40.3%, the isomer percentages are considered generally accurate to about 5% of the significant figures. This is confirmed by a comparison of *o*- and *p*-nitrophenylsulfonoxylation figures which show regular relationships although they are based on different conversion figures obtained by two independent experimentalists using somewhat different times of hydrolysis reactions and techniques.

Validity of the Analytical Procedure.—If hydrolysis of some of the sulfonate esters occurred in the reaction mixture before the alkaline hydrolysis, excessively high yields of phenolic esters would be obtained by using the calibration factors. To determine if this were true, *m*-nitrobenzenesulfonyl peroxide (0.0005 mol) was dissolved in benzene (0.05 mol), *t*-butylbenzene (0.01 mol), and enough ethyl acetate to give a total volume of 50 ml.

TABLE V

PROPERTIES[a] OF ARYL TRIMETHYLSILYL ETHERS ($RC_6H_4OSi(CH_3)_3$)

R	Registry no.	Bp, °C (1 mm)	$n^{25}D$ (temp, °C)
H		51–51.5	1.4761[b]
o-Methyl	10009-02-5	50–50.5	1.4805 (20)[c]
m-Methyl	17902-31-7	53–53.5	1.4790 (20)[c]
p-Methyl	17902-32-8	53.53.5	1.4755[c]
o-Ethyl	17993-88-3	65.5–66	1.4770[d]
m-Ethyl	17993-89-4	64–64.5	1.4784 (20)[d]
p-Ethyl	17993-90-7	66.5–67	1.4760[d]
o-Isopropyl	25237-75-6	64.5–65	1.4768
m-Isopropyl	25237-76-7	71	1.4785 (20)
p-Isopropyl	25237-77-8	74.5	1.4760
o-*t*-Butyl	25282-58-0	85.5	1.4838
m-*t*-Butyl	25237-78-9	78.0	1.4773 (20)
p-*t*-Butyl	25237-79-0	83.0	1.4807 (20)

[a] All C, H values within ±0.3%. [b] Lit. $n^{20}D$ 1.4782: S. H. Langer, I. Connell, and S. Wender, *J. Org. Chem.*, **23**, 50 (1958). [c] Lit. *ortho* $n^{20}D$ 1.4812, *meta* $n^{20}D$ 1.4796, *para* $n^{20}D$ 1.4738: F. A. Henglein and J. Kramer, *Chem. Ber.*, **92**, 2585 (1959). [d] S. H. Langer, P. Pantages, and S. Wender, *Chem. Ind. (London)*, 1664 (1958).

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TABLE VI

REACTION OF *o*- AND *m*-NITROBENZENESULFONYL PEROXIDES WITH ARENES

Compd or quantity	Toluene Run 1	Toluene Run 2	Ethylbenzene Run 1	Ethylbenzene Run 2	Cumene Run 1	Cumene Run 2	*t*-Butylbenzene Run 1	*t*-Butylbenzene Run 2
o-Nitrophenylsufonoxylation								
Peroxide (mmol)	0.0005	0.0005	0.001	0.001	0.0005	0.0005	0.0005	0.0005
RC_6H_5 (mmol)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Benzene (mmol)	0.50	0.50	0.50	0.50	0.50	0.50	0.05	0.5
Ethyl acetate	0	0	0	0	0	0	to 50 ml	0
Sulfonate esters, % yield	86	93	84	75	64.6	65.0	76.6	73.8
k_{Ar}/k_B	13.06	13.52	11.5	11.4	8.8	9.2	6.0	6.0
Isomer distribution								
% *ortho*	35.8	34.8	30.4	30.9	21.0	23.7	10.4	7.6
% *meta*	3.15	2.27	3.57	5.18	9.2	8.6	19.8	19.8
% *para*	61.1	62.9	66.0	63.9	69.8	67.7	69.8	72.6
Partial rate factor								
ortho	14.0	14.1	10.5	10.6	5.53	6.6	1.9	1.4
meta	1.2	0.92	1.2	1.8	2.4	2.4	3.6	3.6
para	48.0	51.0	45.7	43.8	36.8	36.0	25.1	26.2
Internal standard	*p*-Trimethylsilyl-oxyethylbenzene		*o*-Trimethylsilyl-oxytoluene		*p*-Trimethylsilyl-oxytoluene		*p*-Trimethylsilyl-oxytoluene	
m-Nitrophenylsulfonoxylation								
Peroxide (mmol)	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
RC_6H_5 (mmol)	0.01	0.01	0.1	0.01	0.1	0.1	0.01	0.1
Benzene (mmol)	0.05	0.05	0.5	0.05	0.5	0.5	0.5	0.5
Ethyl acetate	To 50 ml	To 50 ml	None	To 50 ml	None	None	To 50 ml	None
Sulfonate esters, % yield	76.1	72.4	89.2	91.6	92.2	77.5	83	53.8
k_{Ar}/k_B	18.8	19.1	18.5	16.7	13.2	13.9	13.2	10.6
Isomer distribution								
% *ortho*	31.7	31.9	30.2	29.6	23.6	23.4	8.4	6.4
% *meta*	3.5	3.5	4.1	4.5	6.3	6.7	18.0	18.2
% *para*	64.8	64.6	65.7	65.9	70.1	69.9	73.6	75.4
Partial rate factors								
ortho	17.9	18.3	16.7	14.8	9.3	9.8	3.3	2.0
meta	2.0	2.0	2.3	2.3	2.5	2.8	7.1	5.8
para	73.0	74.6	72.9	66.0	55.5	58.2	58.2	47.9

TABLE VII

OVERALL YIELDS FOR THE CONVERSION OF NITROPHENYL AND PHENYL SULFONATES TO THE PHENOLIC TRIMETHYLSILYL ETHERS

Ester source: Peroxide	Ester source: Hydrocarbon	% yield of ether: Phenyl	% yield of ether: *ortho* R	% yield of ether: *meta* R	% yield of ether: *para* R
m-Nitro	Toluene	39.4	54.1	83.5	57.8
m-Nitro	Ethylbenzene	45.9	64.5	61.5	67.6
m-Nitro	Cumene	42.8	40.3	87.4	90.7
m-Nitro	*t*-Butylbenzene	46.0	64.8	62.0	67.9
o-Nitro	Toluene	96	100	91	92
o-Nitro	Ethylbenzene	87	90	90	100
o-Nitro	Cumene	91	91	97	97
o-Nitro	*t*-Butylbenzene	50.4	36.7	88.9	80.8

After 24 hr at 25°, the solvents were removed by distillation and the residue was refluxed with hexamethylsilazane (4 ml) for 2 hr. Analysis (glpc) showed that the phenyl and all three isomeric *t*-butylphenyl trimethylsilyl ethers were absent. Therefore no hydrolysis of the sulfonate esters occurs in the reaction mixture.

Registry No.—Table V, R = *m*-Me, 17902-31-7; Table V, R = *p*-Me, 17902-32-8; Table V, R = *o*-Et, 17993-88-3; Table V, R = *m*-Et, 17993-89-4; Table V, R = *p*-Et, 17993-90-7; Table V, R = *o*-*i*-Pr, 25237-75-6; Table V, R = *m*-*i*-Pr, 25237-76-7; Table V, R = *p*-*i*-Pr, 25237-77-8; Table V, R = *o*-*t*-Bu, 25282-58-0; Table V, R = *m*-*t*-Bu, 25237-78-9; Table V, R = *p*-*t*-Bu, 25237-79-0; *o*-nitrobenzenesulfonyl peroxide, 5279-06-1; *m*-nitrobenzenesulfonyl peroxide, 5354-00-7.

Acknowledgments.—The authors wish to thank Paul K. Tornstrom and Franklin N. Keeney for the experiments regarding the choice of solvent.

The Rearrangement of Aliphatic Primary, Secondary, and Tertiary Alkyl Hydroperoxides in Strong Acid

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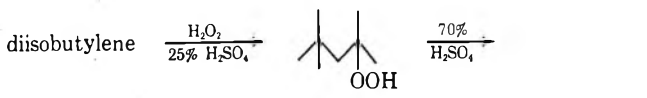
Aliphatic primary, secondary, and tertiary alkyl hydroperoxides rearrange in 60–98% H_2SO_4 at 25°. With tertiary alcohols, the hydroperoxides can be generated *in situ* and the conversion of tertiary cycloalkanols to ω-hydroxy ketones is an excellent synthetic reaction with yields of >90%. A novel degradation of primary alcohols to their next lower homolog is developed. The migratory aptitudes propyl ≈ H > ethyl ≫ methyl were found. Solutions of $K_2S_2O_8$ (effectively H_2SO_5) in 20–60% H_2SO_4 are advantageous for the Baeyer–Villiger oxidation of ketones. Yields are quantitative and differences in migratory aptitudes are as large as or larger than those found with other peracids.

Migrations to electron deficient oxygen have been extensively studied in connection with the Criegee solvolysis of peresters,[1–5] the Baeyer–Villiger oxidation of ketones,[3–9] and the rearrangement of benzylic hydroperoxides.[3–5,8] All three of these reactions can be considered as 1,2 alkyl or aryl shifts in RO^+, though there is ample evidence that the reactions are concerted and that RO^+ is never a true intermediate.

Acid-catalyzed rearrangements of aliphatic alkyl hydroperoxides are less known. The best example is shown in eq 1.[10] The following further rearrangements have been reported. A series of secondary alkyl hydroperoxides were rearranged to ketones in 39-65% yields.[11] 1-Methylcyclopentyl hydroperoxide produced 6-hydroxy-2-hexanone in 15% yield.[12] 1-Methylcyclohexyl hydroperoxide formed 7-hydroxy-2-heptanone in unspecified yield.[11] Finally, *t*-butyl hydroperoxide formed acetone and methanol in low yield.[13]



acetone + $(CH_3)_3CCH_2OH$ (40%) (1)

It has been well documented that aliphatic alkyl hydroperoxides are far more resistant to acid-catalyzed rearrangement than benzylic or allylic hydroperoxides.[1,3–6] They are not only generally stable in 5–50% aqueous sulfuric acids, but are usually prepared under such conditions.[1–6,10,12,14,15] With the exception of the work in ref 10 (eq 1), the rearrangements of aliphatic alkyl hydroperoxides had been conducted at elevated temperatures in media of relatively low acidity. It was suspected that thermal cleavage competed and made the products unduly complex. This suspicion was confirmed when it was found that 1-methylcyclopentyl, 1-methylcyclohexyl, and *t*-butyl hydroperoxides gave quantitative yields of the rearranged products when higher levels of acidity were employed.

With this result, studies were extended to an examination of propyl, H, ethyl, and methyl migratory aptitudes. Prior work had established that *t*-R > *sec*-R > primary R > methyl in both the Criegee rearrangement[2] and the Baeyer–Villiger,[9] but the position of H had not been located and no difference had been noted between propyl and ethyl in the Baeyer–Villiger.[9]

Primary Alkyl Hydroperoxides.—These have become readily available from the treatment of alkyl tosylates with aqueous alkaline hydrogen peroxide.[16,17] Thermal decomposition forms RCOOH plus H_2.[16] Acid-catalyzed rearrangement does not seem to have been investigated despite statements that H migration occurs predominantly.[18,19] It is now found that propyl migrates more than H and ethyl somewhat less.

Addition of propyl hydroperoxide to 98% H_2SO_4 gave 22 ± 8% ethyl hydrogen sulfate from ethyl migration. A more precise analysis was not possible because of the complexity of products. The product of H migration, propionaldehyde, was shown in independent experiments in 98% H_2SO_4 to form protonated 2-methyl-2-pentenal in >90% yield. However, this pentenal was not a dominant product from the propyl hydroperoxide decomposition. It is presumed that formaldehyde, the coproduct of ethyl migration, interacted to give more complex products than would have arisen from propionaldehyde alone.

Addition of butyl hydroperoxide to 80% H_2SO_4 for 5 min at 55° gave 60% of 1-propanol. The same 60% propyl migration was observed in 98% H_2SO_4 at 25° although in this higher acidity, one observes only isopropyl hydrogen sulfate, the known rearrangement

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(17) C. Walling and S. A. Buckler, *ibid.*, **75**, 4372 (1953); **77**, 6032 (1955).

(18) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 824.

(19) P. A. S. Smith, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 575.

product of 1-propanol.[20] These results indicate propyl:H:ethyl migration ratios of 6:2:1 after correcting for the statistical effect of 2 H.

Equation 2 represents a novel method for degrading primary alcohols to their next lower homologs.

$$RCH_2OH \longrightarrow RCH_2OTs \longrightarrow RCH_2OOH \longrightarrow ROH + (CH_2O) \quad (2)$$

It is appropriate to comment on two unsuccessful attempts to produce the BuO^+ moiety from butoxyamine. Addition to 96% H_2SO_4 gave an nmr spectra whose pattern was identical with that of the original butoxyamine but displaced to lower fields. The spectrum was shown to differ from that of $BuOSO_3H$. It is concluded that butoxyamine simply protonated.

It has been reported that nitrous acid deamination of butoxyamine gave only 1-butanol.[21] This has been confirmed by monitoring the reaction by nmr. No trace of any product other than 1-butanol could be detected at pH 5 as long as butoxyamine was in excess. The reaction is probably eq 3 though N_2O formation was not investigated.

$$C_4H_9ONH_2 \xrightarrow{HNO_2} C_4H_9ON{=}NOH \xrightarrow{-N_2O} C_4H_9OH \quad (3)$$

Secondary Alkyl Hydroperoxides.—The acid-catalyzed rearrangement of secondary alkyl hydroperoxides has been reported to produce ketones.[11] It is now found that alkyl migration competes significantly so that the generalization that only H migrates[18] must be modified.

2-Pentyl hydroperoxide gave 37% isopropyl hydrogen sulfate (from *n*-propyl migration) and 63% 2-pentanone (from H migration). 3-Pentyl hydroperoxide gave 39% $C_2H_5OSO_3H$ and 61% 3-pentanone (all percentages are % yields). After the statistical correction for 2 ethyl groups in the 3-pentyl derivative, the migratory ratios of C_3H_7:H:C_2H_5 were 2:3:1. This differs from the 6:2:1 found in the rearrangement of primary alkyl hydroperoxides.

2-Butyl hydroperoxide gave 78% 2-butanone and 22% $C_2H_5OSO_3H$. This is a slightly higher H:C_2H_5 ratio than found with 3-pentyl hydroperoxide. 2-Propyl hydroperoxide gave exclusively acetone (100%). Methyl migration of greater than 1% would have been detected. Since ethyl migrates much better than methyl[2,9] and H better than ethyl, the exclusive formation of acetone was anticipated.

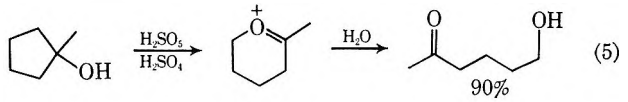
Tertiary Alkyl Hydroperoxides.—The rearrangements of tertiary alkyl hydroperoxides are quantitative. Typical is *t*-butyl hydroperoxide. Addition to 96% H_2SO_4 gave a solution whose nmr showed a 1:1 mixture of protonated acetone and methyl hydrogen sulfate, eq 4. No trace of any other product could be detected.

$$(CH_3)_3COOH \xrightarrow{H_2SO_4} CH_3COCH_3\ (100\%) + CH_3OSO_3H\ (100\%) \quad (4)$$

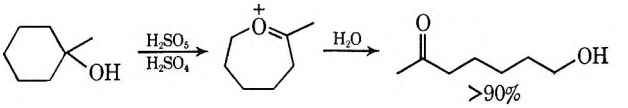
We regard the above result as remarkable since it was feared that ionization of $(CH_3)_3COOH$ to t-$C_4H_9^+$ would at least compete. The t-$C_4H_9^+$ would have yielded the complex mixture of C_4–C_{16} alkanes and C_{10}–C_{16} cyclopentenyl cations with great rapidity.[22] Even more remarkable, it was found that *t*-butyl alcohol or isobutylene could be added to H_2SO_5 in 96% H_2SO_4 with formation of products entirely derived from 1,2 alkyl shift in RO^+. The reaction was not as simple as when t-C_4H_9OOH was used because the acetone produced was necessarily in longer contact time with H_2SO_5 and some Baeyer–Villiger oxidation to acetic acid and CH_3OSO_3H occurred.

The 2-methyl-2-butyl (*t*-amyl) system also gave nearly as good yields by addition of the alcohol to $K_2S_2O_8$ in sulfuric acid as by addition of the hydroperoxide to sulfuric acid. In 80% H_2SO_4, the latter reaction gave 100% $C_2H_5OSO_3H$ and 100% acetone and the former gave 100% $C_2H_5OSO_3H$, 88% acetone, 6% CH_3OSO_3H, and 6% CH_3COOH. Note that ethyl migration occurred exclusively, illustrating the enormous variation in migratory aptitudes which is such a feature of these rearrangements.

The procedure of adding the alcohol directly to solutions of $K_2S_2O_8$ in H_2SO_4 was of particular value with the reactions shown in eq 5 and 6. In both cases, the ketone resisted further attack so that yields were >90%. It has been shown that ω-hydroxy ketones exist as cyclic oxonium ions in sulfuric acid.[23] The nmr of the product from eq 5 and 6 may well be that of the cyclic oxonium ions shown in the equations, and the formation of such species is probably related to their resistance to the Baeyer–Villiger oxidation.



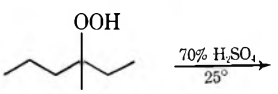
(5)



(6)

Equation 5 had been reported in 15% yield at lower acidities and higher temperatures,[12] and eq 6 had been reported in unspecified yield.[11] Equations 5 and 6 are attractive routes for the preparation of ω-hydroxy ketones.

Treatment of 3-methyl-3-hexyl hydroperoxide for 2 hr at 25° in 70% H_2SO_4 gave the products and yields shown in eq 7. The preference of propyl over ethyl migration was 60:38, comparable to that found in the secondary alkyl hydroperoxides.



1-propanol (60%) + ethanol (38%)
2-butanone (60%) + 2-pentanone (38%) (7)

+ a trace of methanol

Baeyer–Villiger Oxidation of Ketones.—A review of the Baeyer–Villiger reaction[7] pointed out that only one simple aliphatic ketone had been reported and that other peracids were preferable to H_2SO_5. It was thus of some interest to find that solutions of $K_2S_2O_8$ in 50% H_2SO_4 gave quantitative yields of the Baeyer–Villiger

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(23) C. U. Pittman, Jr., and S. P. McManus, *ibid.*, **91**, 5917 (1969).

products for a variety of simple aliphatic ketones. The reactions were complete in minutes at 25°, and we cannot understand why this extremely simple procedure has not been utilized. Although $K_2S_2O_8$ was used to generate H_2SO_5, addition of H_2O_2 would undoubtedly have led to identical results.

The following examples are representative. 2-Butanone gave 100 ± 1% of ethanol (or its hydrogen sulfate above ~ 70% H_2SO_4) and 100 ± 1% acetic acid from 20% aqueous H_2SO_4 to 10% oleum. These two coproducts arise from ethyl migration. No trace of the coproducts of methyl migration (methanol and propionic acid) could be detected by nmr.

2-Pentanone gave 1-propanol and acetic acid in quantitative yield at 50% H_2SO_4. At higher acidities the 1-propanol became increasingly subject to rearrangement and degradation[20,22] so that 40–60% H_2SO_4 would be chosen for production of the alcohol. The carboxylic acid fragment could be isolated from any strength of sulfuric acid.[24]

4-Methyl-2-pentanone gave isobutyl alcohol and acetic acid (isobutyl migration) and 3-methyl-2-butanone gave 2-propanol and acetic acid (isopropyl migration). 3,3-Dimethyl-2-butanone gave acetic acid (100%) and the decomposition products[22] of *t*-butyl alcohol.

In these examples, products arose exclusively from migration of the ethyl, propyl, isobutyl, isopropyl, and tertiary butyl groups rather than methyl. An even more dramatic example was 3-hexanone in which the products of propyl migration, 1-propanol and propionic acid, were formed in 75% yield, whereas the products of ethyl migration, ethanol and butyric acid, formed in 25% yield. This is of interest in view of the report that usual Baeyer–Villiger conditions give comparable propyl and ethyl migration.[9] However, 3-heptanone was reported to give 2:1 butyl to ethyl migration[25] using CF_3CO_3H in $CHCl_3$.

Attempted Alkoxylations with RO^+.—The most favorable situation for alkoxylation would be internal cyclization. Accordingly, 2-phenylethyl hydroperoxide and 1-phenyl-2-methyl-2-propyl hydroperoxide were added to 96% H_2SO_4. Formaldehyde was produced from the former and acetone from the latter. There was no evidence for the products of cyclization.

Experimental Section

Except for the two cases noted below, products were identified by comparison of nmr spectra with those of authentic samples. This was done by adding the authentic sample to the reaction mixture and observing exact superposition. For clean spectra with narrow lines, this method is regarded as being of the greatest reliability. This is particularly true in sulfuric acid solutions where protonation equilibria and hydrogen bonding cause the spectra to vary with sulfuric acid concentration.

Yields were computed from nmr band areas.

The primary and secondary alkyl hydroperoxides were prepared from the alkyl tosylates and alkaline aqueous hydrogen peroxide as described.[16,17] Although the peroxides were not distilled, the nmr spectra of the CH_2Cl_2 solutions were observed and only samples of >90% purity were used. The impurities were the corresponding alcohol and tosylate. Although they give the same nmr pattern, it was sufficiently displaced (different δ values) to allow analysis.

The tertiary alkyl hydroperoxides were prepared in a manner identical with that described for 2,4,4-trimethyl-2-pentyl hydroperoxide.[10]

The hydroperoxide rearrangements were conducted by stirring a CH_2Cl_2 solution of the hydroperoxide with the sulfuric acid at −15 to +5°. The initial mixing was generally made at −15–0° and the exothermicity of mixing and the reaction caused the temperature to rise.

Although eq 5 and 6 had been reported,[11,12] authentic samples of products were not available so that the following additional evidence was used to identify products. In eq 5, the cyclic oxonium ion that is directly produced had the following nmr: singlet at δ 2.48 (C-1 methyl), triplet at 3.53 (C-3 methylene), multiplet centered at 2.05 (C-4 and C-5 methylenes), and triplet at 5.23 (C-6 methylene), with areas within 10% of the calculated 3:2:4:2. Dilution of the reaction mixture to 20% H_2SO_4 and addition to a solution of 2,4-dinitrophenylhydrazine in 20% H_2SO_4 gave an immediate precipitate of the DNP of 6-hydroxy-2-hexanone, mp 95–96° (lit.[10] 97°).

In eq 6, the cyclic oxonium ion derived from 7-hydroxy-2-heptanone was identified on the basis of a singlet at δ 2.88 (C-1 methyl) and multiplets at 1.22–2.20 (C-4, C-5, and C-6 methylenes), 3.27 (C-3 methylene), and 4.7 (C-7 methylene) in the appropriate ratios of band areas. Both cyclic oxonium ions had nmr band positions comparable to others of this type that have been reported.[20]

In both eq 5 and 6, the absence of the characteristic band of acetic acid or methyl hydrogen sulfate was particularly definitive evidence that methyl migration had not occurred.

Registry No.—Propyl hydroperoxide, 6068-96-8; butyl hydroperoxide, 4813-50-7; 2-pentyl hydroperoxide, 14018-58-7; 2-butylhydroperoxide, 13020-06-9; 2-methyl-2-butyl hydroperoxide, 3425-61-4; 3-methyl-3-hexyl hydroperoxide, 25237-96-1; *t*-butyl hydroperoxide, 75-91-2.

Acknowledgment.—Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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Thallation and Coupling of Aromatics[1a]

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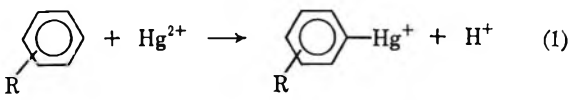
The replacement of hydrogen in aromatic compounds by thallium(III) (thallation) was found to be an electrophilic reaction by studies of the effect of aromatic structure on rate and product distribution. Furthermore, the rate of thallation was found to increase with increasing acid concentration in aqueous perchloric acid, an effect also observed with mercuration and attributed to "dehydration" of the metal ion. This result suggested that anhydrous weakly complexing acids should be good solvents for thallation and, in fact, methanesulfonic and trifluoroacetic were found to be very good solvents for the reaction. Thus, qualitatively, thallation is very similar to mercuration. Quantitatively thallation is 200–400 times slower than mercuration in aqueous perchloric acid. The main differences between the two are (1) only monothallated aromatics are formed, while polymercuration is very facile, and (2) under many reaction conditions diarylthallium(III) compounds are found. Under more severe conditions Tl^{III} couples aromatics to biphenyl derivatives. With toluene, a mixture of bitolyls consisting of mainly 3,3′, 3,4′, and 4,4′ isomers is obtained. However, the yields are low and the mechanism is uncertain.

The direct replacement of hydrogen in aromatic compounds by mercury(II) to form mercury(II) aryls (mercuration) has been known since about 1900 and



(1)

there have been numerous studies of this reaction.[1b] However, the corresponding reaction with thallium(III) (thallation) was first reported in 1943[2] and until recently there have been only two other reports of this reaction.[3,4]

In the isoelectronic series, Hg^{II}, Tl^{III}, and Pb^{IV}, the rates of electrophilic reactions, as evidenced by their reactions with olefins,[5-7] are in the order $Hg^{II} > Tl^{III} > Pb^{IV}$. The rate of reaction with aromatics, which would also most likely be an electrophilic reaction, would be expected to follow the same order. In keeping with this expectation plumbation occurs only with activated aromatics such as anisole,[8] while mercuration occurs readily even with nonactivated aromatics such as benzene.[9]

The stability of the adducts would be expected to follow the same order as the stability of their adducts with olefins.[6,7,10,11] Mercury(II) aryls are, in fact, very stable,[1] while Pb^{IV} aryls decompose to give coupled products.[8] Thallated aromatics, which would be intermediate in their stability, might thus decompose to give oxidized aromatics.

The reaction of Tl^{III} with aromatics has been studied in these laboratories for the past several years. Recent interest in thallium aryl chemistry[12-15] makes reporting of the general results of these studies timely.

Results

Thallation.—If Tl^{III} in 1 *M* H_2SO_4 is heated in the presence of benzene, solids are gradually precipitated. These solids are complex mixtures of phenylthallium(III), diphenylthallium(III), and Tl^{III} sulfates. Tl^{III} in perchloric acid did not deposit solids when heated with benzene, but treatment of the solution with sodium chloride deposited mixtures of phenylthallium dichloride and diphenylthallium chloride. From the yields of these products it was obvious that thallation was much slower than mercuration. The results of some preliminary rate measurements are listed in Table I. The results indicate that the rates of thallation increase with increasing temperature and electrolyte concentration and are faster for activated aromatics such as toluene and slower for nonactivated aromatics such as benzoic acid.

TABLE I
RATES OF THALLATION OF VARIOUS AROMATICS IN AQUEOUS PERCHLORIC ACID[a]

Aromatic	[Aromatic]	$[HClO_4]$, *M*	Temp, °C	k,[b] $sec^{-1} \times 10^6$
Benzene	Saturated	1	70	4.2
Benzene	Saturated	4	70	7
Benzene	Saturated	1	40	<0.2[c]
Benzene	Saturated	4	40	0.35
Benzene	Saturated	6	40	1.8
Benzene	Saturated	6.6	25	1.1
Toluene	Saturated	6.6	25	2.8
Benzoic acid	1 *M*	8	130	<1[d]

[a] In most runs $[Tl^{III}]$ was about 0.01 *M*. [b] First-order rate constant based on decrease of $[Tl^{III}]$. [c] No decrease in $[Tl^{III}]$ in 10 days. [d] No thallated benzoic acid in 7.5 hr.

The products themselves are of interest. Thus, at $[HClO_4] = 1$ *M*, the main species of thallated benzene present throughout the run is diphenylthallium. At higher $[HClO_4]$ the relative rate of thallation compared to diphenylthallium formation must become faster since appreciable amounts of phenylthallium are found under these conditions. Under no conditions was any evidence for dithallated aromatics found in this work.

Anhydrous or nearly anhydrous methanesulfonic acid and anhydrous trifluoracetic acid were also tried as sol-

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TABLE II

THALLATION OF AROMATICS UNDER VARIOUS REACTION CONDITIONS

Aromatic concentration	Solvent	Tl^{III} salt	Temp, °C	Time	Conversion, % aryl Tl^{III} [a]	Isomer distribution, ortho	meta	para
2 *M* benzene	90% aqueous CH_3SO_3H	0.9 *M* $Tl(CH_3SO_3)_3$	25	6 days	7			
2 *M* toluene	90% aqueous CH_3SO_3H	0.9 *M* $Tl(CH_3SO_3)_3$	25	6 days	22	3.5	18.7	77.8
2 *M* anisole	90% aqueous CH_3SO_3H	0.9 *M* $Tl(CH_3SO_3)_3$	25	6 days	1		*b*	
1 *M* benzoic acid	CH_3SO_3H	1.5 *M* $Tl(CH_3SO_3)_3$	130	1 hr	24	40	59	1
1 *M* benzoic acid	CH_3SO_3H	1.5 *M* $Tl(CH_3SO_3)_3$	130	6 hr	44	38	60	2
1 *M* benzoic acid	CH_3SO_3H	1.3 *M* $Tl(CH_3SO_3)_3$	130	2 hr	21	27	72	1
1 *M* benzoic acid	CH_3SO_3H	1.3 *M* $Tl(CH_3SO_3)_3$	130	7 hr	40	57.2	36.5	6.3
2 *M* benzene	CF_3COOH	0.8 *M* $Tl(CF_3COO)_3$	25	3 hr	99			
2 *M* toluene	CF_3COOH	0.8 *M* $Tl(CF_3COO)_3$	25	3 min	65	4.2	0.5	95.3
2 *M* anisole	CF_3COOH	0.8 *M* $Tl(CF_3COO)_3$	25	3 min	24[c]	100		

[a] Conversion of monoaryl Tl^{III} based on initial Tl^{III}; no diaryl Tl^{III} detected in any runs. [b] Distribution not determined. [c] Some black solids formed.

TABLE III

COUPLING OF AROMATICS BY THALLIC TRIACETATE AND PALLADIUM(II) ACETATE IN REFLUXING ACETIC ACID[a]

Aromatic	$[Tl(OAc)_3]$, *M*	$[CH_3SO_3H]$, *M*	$[Pd(OAc)_2]$, *M*	Yield,[b] %	Distribution, 2,2′	2,3′	2,4′	3,3′	3,4′	4,4′
Benzene	0.25	0.15		8.4						
Benzene	0.25	0.15	0.04	20						
Toluene	0.25	0.15		6.2				36	44	20
Toluene	0.25			3				42	49	9
Toluene	0.25	0.6		2.3				39	42	19
Toluene	0.25	0.15	0.01	76.4	0.4	1.7	2.1	14.8	48	33
Toluene		0.15	0.04	24.5[c]	1	11	13	16	40	19

[a] Reaction time was 24 hr. Concentration of aromatic was 2 *M*. [b] Based on one coupled aromatic per $Tl(OAc)_3$. Traces of bibenzyl detected in the toluene runs. [c] Based on one coupled aromatic per $Pd(OAc)_2$.

vents. The results of a series of such experiments are shown in Table II. The thallations were much more facile in these solvents than in aqueous perchloric acid. In fact, even benzoic acid can be thallated in methanesulfonic acid, although a temperature of 130° was required. Note that in two runs quenched at 2 and 7 hr the isomer distribution of thallated benzoic acid changes from a kinetically controlled distribution high in *meta* to an equilibrium distribution high in *ortho* and with much more *para* than in the kinetically controlled distribution. In the runs at 130° some reduction of Tl^{III} occurs, probably because of oxidation of the solvent. However, in all the runs in Table II most of the unreacted Tl^{III} was not reduced at the time of termination of reaction.

Trifluoroacetic acid was by far the best solvent for thallation. In latter work thallic triacetate was used in place of the trifluoroacetate with little loss of reactivity, and this procedure is used in these laboratories as a standard procedure for preparing phenylthallium salts. In both aqueous methanesulfonic acid and trifluoroacetic acid toluene gave predominately the *para* isomer.[16]

In none of the runs in Table II was any evidence found for diarylthallium compounds. This result is in keeping with the observation made in the perchloric acid system that diphenylthallium formation became less important as the water content of the solvent decreased.

Coupling.—In several runs in aqueous perchloric acid at 100° small amounts of organic product were detected and proved to be diphenyl. It was found that phenylthallium salts in aqueous perchloric acid at 100° were slowly decomposed to diphenyl. In subsequent studies acetic acid was used as a solvent for coupling. In a number of runs palladium(II) acetate was added to determine its effect on the coupling reaction. Typical results are listed in Table III.

In all runs more than 98% of the Tl^{III} was reduced and less than 1% thallated aromatics were detected. The main points are that yields are low in the absence of Pd^{II} and the distributions with toluene are not those expected for electrophilic attack followed by coupling from the position of Tl^{III} attachment. $Pd(OAc)_2$ gave a distribution similar to that found in the $Tl(OAc)_3$ couplings alone.

In one run phenylthallium dichloride was refluxed in acetic acid for 6 hr. Only a 1% yield of diphenyl was detected.

No coupled products were detected in the benzoic acid reaction mixtures. However, if preformed thallated benzoic acid is refluxed in acetic acid, a yield of about 50% of coupled benzoic acid is produced.

Discussion

Thallation.—The effect of aromatic structure on rate (Table I) and the product distributions found with toluene, anisole, and benzoic acid (Table II) indicate that thallation is an electrophilic reaction, in agreement with other reports on ease of thallation and product distributions.[3,12,15] The change in distribution with time for the benzoic acid runs (Table II) suggests thallation is reversible, and the increase in rate of reaction with increasing salt concentration is not surprising, since the reaction of Tl^{III} with olefins displays this same effect.[6]

(16) In a recent preliminary communication,[14] exactly the same procedure was reported to give exclusively *para* isomer. The difference may be that we isolated all the thallated toluene by precipitation with aqueous sodium chloride, while the other workers isolated only the insoluble portion.

Thus, mercuration and thallation are qualitatively very similar. Both show the characteristics of an electrophilic reaction, both are apparently reversible, and the rates of both are accelerated by lowering of water activity. Quantitatively in aqueous perchloric acid at 40°, the rates of mercuration[9] are 200–400 times as fast as thallation, a result in agreement with the relative rates of reaction with olefins.[5,6]

There are, however, differences between the two reactions. First, under many conditions Ar_2Tl^+ is the main product of thallation. With only two aromatics has this been the case with mercuration.[17,18] Secondly, only monothallation occurred with all the aromatics we studied, while polymercuration occurs very readily.[9,19,20] Thus Tl^{III} must deactivate an aromatic ring much more strongly than does Hg^{II}, a result in keeping with the higher charge of Tl^{III}.

The increase in rate of thallation with increasing acid concentration is related to decreasing water activity.[6,9] Thus, noncomplexing solvents containing little or no water should promote thallation. Indeed, thallation was much faster in methanesulfonic and trifluoroacetic acids. Trifluoroacetic acid, by far the more effective of the two, has recently been used by other workers for a variety of thallation reactions.[15] Our own choice of trifluoroacetic acid was prompted by the report that mercuration was very rapid in this solvent.[21]

The thallation of anisole in trifluoroacetic acid appears anomolous since yields are low for such an activated arene and only the *ortho* adduct is formed. However, ether linkages in the presence of strong acids are apparently strongly hydrogen bonded thus decreasing the electron releasing ability of the ether linkage.[22,23] Also, in such a poor complexing solvent as trifluoroacetic acid the ether might well be complexed to the thallic ion thus putting the thallic ion in position for an ortho attack. A similar effect has been observed for benzoic acid in trifluoroacetic acid.[15]

The formation of diarylthallium compounds must occur either by disproportionation

$$2ArTl^{2+} \longrightarrow Ar_2Tl^+ + Tl^{3+} \quad (2)$$

or by attack of the monoaryl on a second aromatic.

$$ArTl^{2+} + ArH \longrightarrow Ar_2Tl + H^+ \quad (3)$$

The fact that phenylthallium dichloride disproportionates in the absence of aromatic[24] (eq 4) suggests the

$$2ArTlCl_2 \longrightarrow Ar_2Tl + TlCl_3 \quad (4)$$

first mechanism (eq 2) is operable.

Coupling.—Thallic acetate in refluxing acetic acid reacts with benzene and toluene to give low yields of coupled aromatics (Table III). In spite of the low yields the thallic acetate is completely reduced, presumably by oxidation of the solvent, and only traces of thallated aromatics are found in the final reaction mixtures. Since thallated aromatics are formed under the reaction conditions,[12] it seems likely that they are intermediates in the reaction. In that case the thallated toluene must have arrived at an equilibrium distribution of isomers before coupling, since so large an amount of 3,3′ and 3,4′ isomers is present. Coupling of a kinetic-controlled distribution would have predicted large amounts of 4,4′ but little 3,3′ or 3,4′. The lack of 2,2′, 2,3′, and 2,4′ isomers could result from steric hindrance to coupling.

To obtain evidence for thallated aromatic intermediates, $Pd(OAc)_2$ was added to the reaction mixture. Hopefully, the initially formed intermediate would rapidly transfer aryl to Pd^{II} followed by rapid coupling. Arylmercury(II) compounds[25,26] as well as phenylboronic acids[27] transfer aryl to Pd^{II} followed by coupling of the Pd^{II} aryls. Thus a change in distribution from 3,3′ and 3,4′ to 4,4′ would be evidence for arylthallium intermediates which were coupled by $Pd(OAc)_2$. In a similar study[28] it was found that addition of Hg^{II} changed the distribution of a Pd^{II} coupling of toluene from mainly 3,4′ and 3,3′ to mainly 4,4′.

In the present case the yields were increased but the 3,4′ and 3,3′ isomers still predominated. Thus, either equilibration was occurring before transfer of aryl to Pd^{II} or else Tl^{III} was only reoxidizing the Pd^0 back to Pd^{II}.

It is possible that the interesting coupling reactions reported by McKillop, Elsom, and Taylor[14] proceed by decomposition of Tl^{III} aryls to give coupled products. However, more work is necessary to determine the mechanisms of both couplings.

Experimental Section

Reagents.—Thallic oxide was purchased from the Fairmount Chemical Company. Preparation and analysis of thallic stock solutions has been described previously.[6] Standards of phenylthallium dichloride or diphenylthallium chloride were prepared by literature procedures.[24,29] (All other chemicals were of reagent grade.)

Identification of Products.—Phenylthallium salts were precipitated as their chlorides and separated into the monophenyl and diphenyl compounds by solubility characteristics. They were identified by their X-ray powder patterns. To determine if any dithallation occurred, the phenyl thallation adducts were treated by bromine using the procedure described by Wright.[19] The presence or absence of dibromobenzenes was then determined by vapor phase chromatography (vpc) using a 20-ft 10% 4,4′-dimethoxyazoxybenzene on 45–60 mesh Chromosorb W. The temperature was 120° and the flow rate 75 ml/min.

The product distributions for the thallated toluenes, anisoles, and benzoic acids were also determined by treatment with bromine followed by vpc analysis. For the bromotoluenes the same vpc procedure was employed as was used for the bromobenzenes. The bromoanisoles were separated using a 20-ft. Ucon 75h column with a gas flow of 100 ml/min. The temperature was programmed from 130 to 205° at 4.6°/min. The bromobenzoic acids were esterified with diazomethane and the distributions of methyl esters determined using 6 ft of 5% bentone 34 + 5% didecyl phthalate on Chromosorb W. The temperature was 150° and the flow rate 80 ml/min. Identification of brominated products was determined by comparison of retention times with standards. In several cases peaks were collected from vpc and identification confirmed by infrared spectra.

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The product distributions of all the coupled products except the coupled benzoic acids were carried out using a 12-ft 15% Apiezon N column at 250°. Flow rate was 60 ml/min. The identity of the 2,2′, 3,3′, and 4,4′ bitolyls was determined from vpc by fortification with an authentic sample of each isomer. The identity of the 2,3′, 2,4′, and 3,4′ mixed bitolyls was inferred from their reported order of elution under very similar vpc conditions.[30] Further support for the assignment by vpc retention times was obtained by the ultraviolet spectra of samples collected from the vpc eluent. Because of the small samples and similarities in spectra it was difficult to make positive identification. However, the comparison of these spectra with published spectra[31] of the isomers lent support to the assignments by vpc retention time. The coupled benzoic acids were esterified by diazomethane and the esters analyzed using a 6-ft Apiezon N column at 260°. Flow rate was 60 ml/min.

Kinetic Runs.—Quantitative analyses were by polarographic analysis. The wave for monoarylthallium(III) compounds falls between the waves for Tl^{III} and diarylthallium(III) compounds. The kinetic runs were made using a soft-drink bottle stirred with a magnetic stirring bar. The bottle was capped with a metal cap having holes sealed by a rubber liner through which samples for analysis could be withdrawn using a syringe with needle attached. Two-milliliter aliquots were withdrawn and quenched by addition of 1 ml of 4 *M* NaCl. The sample was diluted to 10 ml with water for analysis. These samples were analyzed at 25° using a Sargent Model XXI polarograph. The $E_{1/2}$ for Tl^{3+} occurred at −0.1 V *vs.* a standard calomel electrode, the $E_{1/2}$ for phenyl thallium at −0.2 V, and the $E_{1/2}$ for diphenylthallium at −0.5 V. The i_d for the Tl^{3+} was directly proportional to Tl^{3+} concentration in the bulk of the solution. Control runs showed no disproportion took place in the time required for analysis.

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Registry No.—Thallic triacetate, 2570-63-0; palladium(II) diacetate, 3375-31-3.

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Substituent Effect Transmission from Heavy Atoms. Microscopic Dissociation Constants of Selenoglycolic Acid

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An unusual enhancement of the substitutent effect of a negative charge on the pK_a of a carboxyl group has been observed to be present when that charge is located on a selenium atom. A method for preparing solutions of pure selenols from the corresponding diselenides is described, and such solutions have been used in determining the extents of dissociation of the SeH groups in $HSeCH_2CO_2CH_3$ and $HSeCH_2CO_2H$ as functions of pH. Values for the microscopic dissociation constants of the latter acid have been derived from those data, and are: for the SeH groups, $pk_a = 4.7$, $pk_d = 7.3$; for the CO_2H group, $pk_b = 4.1$, $pk_c = 6.7$. Relative to the effect on the acidity of a carboxyl group which is produced by a charge located on nitrogen or oxygen, the substitutent effects of charges located on S and Se in $^-SCH_2CO_2H$ and $^-SeCH_2CO_2H$ are too large by 0.6 and 0.8 pK units, respectively. It is shown that this enhancement of the substituent effect is within the range attributable to a decrease in the effective dielectric constant arising from the increase in atomic radius in the sequence O, S, Se. An uncertain fraction of this increase in ΔpK probably arises from a decrease in the interaction between the charge on CO_2^- and the XH dipole moment as X varies through the same sequence.

The effect of charged substituents on the acidity of carboxylic acids has been studied extensively,[2-4] and for several classes of acids it has been shown[3] that such effects can be predicted from a suitably modified electrostatic model with an uncertainty not exceeding a few tenths of a pK unit. However, tests of such electrostatic predictions, as well as of purely empirical correlations of pK with the distance between the charge and the acidic site,[5-7] have been almost completely restricted to acids in which the charge is borne by a first-row atom, N or O. In connection with other work in these laboratories, it became necessary to make similar estimates for the effect of charges located on heavier atoms.

Very few pK values are available for dibasic acids in which one or both protons are bound to non-first-row atoms, and most which have been reported are apparent values measured at high or unspecified ionic strength. It is known that ΔpK for acids in which two protons are bound to the same basic atom can vary widely as that atom is changed (*e.g.*, H_3O^+ *vs.* H_2O, $\Delta pK = 17.4$; H_2S *vs.* HS^-, $\Delta pK = 7.6$,[8] in at least qualitative agreement with an electrostatic prediction based on the relative size of O and S). However, the scarcity of data makes it uncertain whether any such variation persists when the protons are not bound to the same atom and the nonelectrostatic effects which contribute[8] to those very large differences are therefore no longer operative. That changes in effective dielectric constant, D_E, arising from an increase in the radius of the atom bearing the charge might be important is suggested by the observation[4] that the acid-strengthening effect of a positive charge on quaternary nitrogen is greater than that of a charge on less highly substituted nitrogen. (*E.g.*, at 25° (a) for $H_3N^+CH_2CO_2H$ *vs.* $(CH_3)_3N^+$-CH_2CO_2H, $\Delta pK = 0.5$,[9] (b) for amine salts derived from the 1,4-diazabicyclo[2.2.2]octane ring system, $HN^+(CH_2CH_2)_3NH^+$ has $pK_a = 2.67$, $CH_3N^+(CH_2$-

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$CH_2)_3NH^+$ has $pK_a = 2.26$, and ΔpK (symmetry corrected) = 0.7.)[10]

The data reported below allow the calculation of ΔpK values for dissociation of the CO_2H groups in the acid pairs $HXCH_2CO_2H$ *vs.* $^-XCH_2CO_2H$ (X = S, Se). Earlier estimates of pK for the thiols exist, but no directly measured values for the selenols have been reported previously, presumably due to their instability and sensitivity to air.[11]

Experimental Section

Materials.—Fisher Certified thioglycolic acid was distilled *in vacuo* (20 mm) and stored under N_2 at 4° until used. Potassium selenocyanoacetate, $NCSeCH_2CO_2K$, was prepared by the method of Hofmanns[12] and was converted into diselenodiacetic acid, $(SeCH_2CO_2H)_2$, according to the procedure of Behagel and Rollmann;[13] repeated recrystallization of this diacid from ethyl acetate–toluene gave pale yellow needles, mp 104.5–105.5° (corr) (*Anal.* Calcd for $C_4H_6O_4Se_2$: C, 17.39; H, 2.19. Found: C, 17.56; H, 2.34. Mol. wt. Calcd: 276.0. Found: 276.7) The corresponding dimethyl ester, $(SeCH_2CO_2CH_3)_2$, was prepared from the reaction of the diacid in solution in diethyl ether at −10° with a 20% excess of diazomethane in ether. The resulting yellow oil was chromatographed on Florisil using *n*-hexane–benzene as eluent and the middle fraction was subjected to short-path distillation at 0.05 mm. (*Anal.* Calcd for $C_6H_{10}O_4Se_2$: C, 23.68; H, 3.32. Found: C, 23.80; H, 3.28.) All other reagents were the best available commercial grade and were used without purification.

Buffers.—All buffers used in the spectrophotometric determinations of pK had ionic strength ≤ 0.14. Their pH values were measured at 25.0 ± 0.1° with a Beckman Model 1019 pH meter equipped with Fisher full-range glass and Beckman carborundum frit junction calomel electrodes which had been standardized against NBS borax and phthalate buffers. The stock solutions of selenols used in uv measurements contained significant amounts of strong base; the increase in the pH of each buffer which resulted from addition of an aliquot of one of those solutions was calculated, either from the known concentrations of the acidic and basic component of the buffer or from the value of the van Slyke β for those buffers for which such values are tabulated.[14] These corrections were never greater than 0.04 pH unit.

Uv Spectra.—All uv spectra were obtained using a Cary 14 spectrophotometer equipped with a thermostated (25.0 ± 0.1° by measurement in the cell) cell holder. For each measurement, the cell was filled to within a few mm of the bottom of its stopper with a known volume of the buffer. The cell contents were deaerated by passing a rapid stream of Ar *via* a syringe needle through the solution for 15 min and then stoppering the cell. After scanning the "blank" spectrum of the buffer, an aliquot (10, 20, or 50 μl) of a stock solution of the acid being studied was added from a microsyringe and Ar bubbling was continued for 2 min to ensure mixing before the cell was restoppered and the spectrum recorded. The optical density (OD) values of solutions of selenols decreased with time; the spectra of such solutions were therefore scanned three times at appropriate time intervals and the OD at each wavelength of interest extrapolated back to the time of mixing. The decrease in OD was linear with time and the extrapolated value was never more than 5% higher than that observed in the first scan. Spectra of the thiols were not observed to be time dependent when oxygen was excluded by the described procedure.

Undissociated selenols and thiols show no strong absorption between 240 and 250 mμ, while their conjugate bases have maxima in that region. The following absorptions were observed: $^-SeCH_2CO_2^-$, λ_{max} 250 mμ (ϵ 6 × 10³); $^-SeCH_2CO_2CH_3$, λ_{max} 241 mμ (ϵ 5 × 10³); $^-SCH_2CO_2^-$, λ_{max} 244 mμ (ϵ 4.8 × 10³); $^-SCH_2CO_2CH_3$, no resolved maximum (ϵ_{244} = 3.8 × 10³). The ϵ values for the selenols are somewhat imprecise due to the loss by evaporation of an uncertain amount of solvent during nitrogen purging in the preparation of the stock solutions. The *OD* values used in calculating dissociation constants lay between 0.1 and 0.9.

Solutions of Selenols.—The sodium salt of selenoglycolic acid, $NaSeCH_2CO_2Na$, was prepared in solution by reduction of 0.18 mmol of $(SeCH_2CO_2Na)_2$ dissolved in 10 ml of 0.10 *F* aqueous NaOH with 0.9 mmol of $NaBH_4$. The reaction was run under N_2 at room temperature and was stirred magnetically; aliquots of solution were removed through a serum cap with a microsyringe. After 24 hr, reduction was complete; the *OD* at 250 mμ of successive aliquots (injected into deaerated 0.10 *F* NaOH) had reached its maximum value and no longer changed with increasing reaction time, and the characteristic diselenide absorption was completely absent. The continued presence of excess borohydride at this stage was demonstrated by hydrogen evolution accompanying addition of aliquots to dilute acid.

The identity of the reduction product was established by extracting the free acid into $CHCl_3$ and observing its nmr spectrum. For those experiments, the reaction flask was fitted with a breakseal tube containing excess deaerated 6 *F* HCl and a Wilmad cylindrical micro nmr tube which was separated from the flask by a medium porosity glass filter disk. After reduction was complete, the colorless reaction mixture was degassed by successive freeze–thaw cycles *in vacuo* and all subsequent operations were carried out under vacuum. The breakseal was then opened, the water and excess HCl were removed by evaporation on the vacuum line at *ca.* 0°, and a 1-ml portion of $CHCl_3$ was distilled into the flask. The solid residue was pulverized with the magnetic stirring bar and the $CHCl_3$ extract was filtered through the sintered disk into the nmr tube which was then chilled in $CHCl_3$ slush (−63°) and sealed off. The nmr spectrum remained unchanged for at least 48 hr if the sample was kept cold. The observed nmr spectrum consisted of the sum of signals attributable to the selenol and signals due to a small amount of ethanol present in the $CHCl_3$. Resonances attributed to the selenol were δ 0.32 (triplet, J = 7.5 Hz, 1.00 proton (defined)), 3.21 (doublet, J = 7.5 Hz, 2.00 protons), *ca.* 9 (broad singlet, position varying with amount of ethanol present, 0.93 proton after correction for the contribution of the ethanol OH). No other resonances were detected with intensities greater than 0.05 protons.

Solutions of the sodium salt of the methyl ester of selenoglycolic acid were prepared in a similar fashion by reduction of $(SeCH_2CO_2CH_3)_2$ using 0.1 *F* $NaOCH_3$ in CH_3OH as solvent. These solutions gave evidence of decomposition when kept at room temperature, but were stable (*i.e.*, successive aliquots gave identical uv spectra) when kept at −10°.

Results

The identification of the reduction products from the diselenides as the corresponding selenols rests on their facile oxidation by air, the analogy between their uv spectra and those of the related thiols, and the nmr spectrum of the compound assumed to be selenoglycolic acid. For comparison, benzyl selenol has been reported[15] to have an nmr spectrum with δ −0.09 (triplet, J = 7 Hz) and 3.49 (doublet, J = 7 Hz), in good agreement with the selenol and methylene proton resonances reported above for selenoglycolic acid. Both the absence of extraneous peaks in that nmr spectrum and the close agreement between the form of the pH dependence of the uv absorptions of these compounds and those expected for pure compounds suggest that the reduction to the selenol is free from side reactions.

Hydrogen ion activities, a_H, were calculated from the

(10) J. L. Kurz, unpublished observation.

(11) An indirectly measured value of K = 1.0 × 10⁻⁷ for $HSeCH_2CO^-$ has been reported [B. Nygard, *Acta Chem. Scand.*, **15**, 1039 (1961)]. That value was derived from the pH dependence of the polarographic half-wave potential for reduction of $(SeCH_2CO_2^-)_2$. However, the effective value of the ionic strength at the surface of the charged mercury drop is not known, and the direct effect of the electrostatic potential at that surface on the apparent dissociation constant is uncertain; such values are therefore not sufficiently well established to be useful in this discussion.

(12) G. H. Hofmanns, *Justus Liebigs Ann. Chem.*, **250**, 294 (1888).

(13) O. Behagel and M. Rollmann, *Ber. Bunsenges. Phys. Chem.*, **62**, 2696 (1929).

(14) R. G. Bates, "Determination of pH; Theory and Practice," Wiley, New York, N. Y., 1954, pp 157, 160.

(15) A. Merijanian, R. A. Zingaro, L. S. Sagan, and K. J. Irgolic, *Spectrochim. Acta, Part A*, **25**, 1160 (1969).

observed pH values. Molar activity coefficients, y, were estimated from the Davies equation.[16] Since these approximations were used for both the thiols and the selenols, any error arising from their use should be present for both series of acids. The value of pK found for thioglycolic acid is in good agreement with that (10.68 ±0.04) calculated by Irving, Nelander, and Wadsö[17] from measurements at much lower ionic strengths.

The ionizations of the thiols and of methyl selenoglycolate are not complicated by overlapping dissociations; the values of pK for these acids were computed from eq 1, where OD_{HA} is the optical density of a solution of the undissociated acid (solutions in 0.1 F HCl

$$pK = pH + \log \frac{OD_A - OD}{OD - OD_{HA}} + \log \frac{y_{HA}}{y_A} \quad (1)$$

of the two methyl esters and a solution in pH 6 phosphate buffer of thioglycolic acid), OD_A is the optical density of a solution of the conjugate base (solutions in 0.1 F NaOH of thioglycolic acid, in pH 11 phosphate buffer of methyl thioglycolate, and in pH 8 tris(hydroxymethyl)aminomethane buffer of methyl selenoglycolate), and OD is the optical density of a solution having the same total concentration, [HA] + [A], at the indicated pH. Corrections for small variations in the concentrations of different preparations of stock solutions of the acids were made by multiplying observed OD values by the factors which were required to bring all values of OD_A for the same acid into coincidence. Calculated pK values were not changed if the wavelength at which OD values were measured was varied over a range of 20 mμ. The results of these measurements are given in Table I. Average pK values are $^-O_2CCH_2SH$, 10.58; $CH_3O_2CCH_2SH$, 8.08; $CH_3O_2CCH_2SeH$, 4.70.

TABLE I

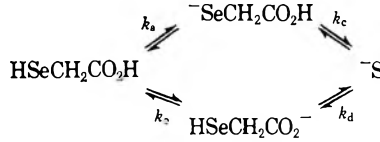
OBSERVED DISSOCIATION CONSTANTS AT 25°

Acid	pH	I[a]	pK[b]
$CH_3O_2CCH_2SH$	7.48[c]	0.04	8.09
	7.72[c]	0.04	8.08
	7.90[c]	0.03	8.05
	8.06[c]	0.03	8.09
	8.30[c]	0.02	8.08
	8.53[c]	0.02	8.12
	8.80[c]	0.01	8.07
$^-O_2CCH_2SH$	10.80[d]	0.07	10.58
	10.60[d]	0.06	10.60
	10.38[d]	0.06	10.59
	10.21[d]	0.05	10.56
$CH_3O_2CCH_2SeH$	4.33[e]	0.02	4.70
	4.42[e]	0.03	4.66
	4.66[e]	0.04	4.69
	4.87[e]	0.05	4.75
	4.96[e]	0.05	4.68

[a] Ionic strength. [b] Calcd from eq 1. [c] Tris(hydroxymethyl)-aminomethane buffer. [d] Carbonate buffer. [e] Acetate buffer.

In selenoglycolic acid, the pK values of the SeH and CO_2H groups are comparable, so that their dissociations overlap. If the extinction coefficients of $HO_2CCH_2Se^-$ and $^-O_2CCH_2Se^-$ were equal (and that of $^-O_2CCH_2SeH$ negligible), then the experimentally observed value of α (eq 2, OD_{HA} from a solution in 0.1 F HCl, OD_A from a solution in 0.1 F NaOH) would be equal to the fraction of the total selenoglycolic acid concentration which was present in those two forms. If they are not equal, then α_{obsd} would give an approximation to that fraction which became more exact as the pH increased. If the four microscopic dissociation constants are defined according to the scheme shown in eq 3, and the extinction coefficients of the two RSe^-

$$\alpha_{obs} = \frac{OD - OD_{HA}}{OD_A - OD_{HA}} \quad (2)$$



(3)

species are assumed equal, then the predicted value of α is given by eq 4, where a_H is the hydrogen ion activity and y_- and y_{2-} are the molar activity coefficients of singly and doubly charged anions.

$$\alpha_{pred} = \frac{a_H y_{2-} k_a + y_- k_a k_c}{a_H y_{2-} k_a + y_- k_a k_c + a_H y_{2-} k_b + a_H^2 y_- y_{2-}} \quad (4)$$

The value of the microscopic constant, pk_a, for dissociation of the SeH group in HO_2CCH_2SeH was assumed to be equal to that measured for the pK_a of the corresponding methyl ester (4.7). Those values of pk_b and pk_c were then selected which gave the best agreement between the values of α_{obs} and α_{pred}. In order to minimize any errors arising from inequality of the two extinction coefficients, only those eight values of α_{obs} which were measured at pH ≥ 6.7 were used in fitting eq 4 to the data; in that region, $[^-SeCH_2CO_2^-]/[^-SeCH_2CO_2H] \geq 2$. The optimum values of the microscopic constants determined by this procedure are pk_b = 4.1, pk_c = 6.7, and pk_d (= pk_a + pk_c − pk_b) = 7.3. Observed and predicted values of α are given in Table II.

TABLE II

DISSOCIATION OF $HSeCH_2CO_2H$ AT 25°

pH	I[a]	α_{obs}[b]	α_{pred}[c]
3.09[d]	0.02	0.007	0.025
3.61[d]	0.05	0.045	0.066
3.77[e]	0.03	0.045	0.082
3.98[d]	0.07	0.060	0.108
4.07[e]	0.05	0.090	0.118
4.37[e]	0.07	0.136	0.150
5.19[e]	0.20	0.196	0.202
6.70[f]	0.09	0.424	0.430
6.93[f]	0.10	0.500	0.532
7.01[g]	0.05	0.590	0.535
7.17[f]	0.12	0.621	0.647
7.38[f]	0.13	0.727	0.741
7.39[g]	0.04	0.757	0.703
7.62[f]	0.14	0.848	0.828
7.83[f]	0.14	0.878	0.885

[a] Ionic strength. [b] Equation 2. [c] Equation 4, using pk_a = 4.7, pk_b = 4.1, pk_c = 6.7. [d] Formate buffer. [e] Succinate buffer. [f] Phosphate buffer. [g] Tris(hydroxymethyl)aminomethane buffer.

The fit of eq 4 was significantly more sensitive to Δpk (defined as pk_c − pk_b) than to either pk_c or pk_b individually. For example, the root mean square (rms) differ-

(16) C. W. Davies, "Ion Association," Butterworths, London, 1962, p 41.
(17) F. R. Irving, L. Nelander, and I. Wadsö, *Acta Chem. Scand.*, **18**, 769 (1964).

ence between α_{obs} and α_{pred} which corresponds to the optimum pk values is ±0.032;[18] decreasing both pk_b and pk_c by 0.1 unit (to 4.0 and 6.6) increases the rms deviation only to ±0.034, but decreasing only pk_b by 0.1 unit (thus raising Δpk from 2.6 to 2.7) increases the rms deviation to ±0.062. It is thus possible that the individual pk values are in error by several tenths of a unit; however, the value of Δpk (which is the parameter of greatest interest) very probably lies in the range 2.6 ± 0.1.

Discussion

In a compound of the general structure $HXCH_2CO_2H$ the difference, ΔpK(CO_2H), between the pK values of the CO_2H moiety in $^-XCH_2CO_2H$ and in $HXCH_2CO_2H$ must be equal to the corresponding difference, ΔpK(XH), between the pK values of the XH moiety in $HXCH_2CO_2^-$ and ni $HXCH_2CO_2H$. It is convenient to discuss the mechanism of transmission of this substituent effect in terms of the latter difference, since the substituent change is then the same in all pairs of acids being compared. Table III lists pK values which are relevant to such a discussion.

TABLE III
VALUES OF pK AT 25° AND ZERO IONIC STRENGTH

Acid	r,[a] Å	pK[b]
HO_2CCH_2SeH	4.1	4.7,[c,d] (SeH)
$^-O_2CCH_2SeH$		7.3[c] (SeH)
HO_2CCH_2SH	4.0	8.1[c,d] (SH)
$^-O_2CCH_2SH$		10.6[c] (SH)
$HO_2CCH_2NH_3^+$	3.7	7.6[d,e] (NH_3^+)
$^-O_2CCH_2NH_3^+$		9.8[e] (NH_3^+)
HO_2CCOOH	3.4	1.6[f,g] (CO_2H)
$^-O_2CCOOH$		4.0[f,g] (CO_2H)

[a] Intercharge distance in dianion assuming the charge on X⁻ to lie at the nucleus and the charge on CO_2^- to lie 1.45 Å (ref 2c) beyond the carboxyl carbon on the extension of the carbon–carbon bond. [b] Parenthetical expression indicates group to whose ionization pK refers. [c] This work. [d] Assumed to be equal to pK for the corresponding methyl ester. [e] Reference 10. [f] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed, Butterworths, London, p 520. [g] Corrected for symmetry.

It is known[6] that a plot of log (ΔpK) for dibasic acids in which the protons are bound to first-row elements against the interchange distance, r, in ångströms gives a straight line with a slope of −0.2. This slope corresponds to McGowan's[7] empirical rule that insertion of a methylene group (*i.e.*, Δr = 1.5) between a charged substituent and an acidic proton attenuates the substituent effect on pK by a factor of 0.50 (*i.e.*, Δ log (ΔpK) = −0.3).

This correlation would predict that ΔpK(XH) should decrease from 2.2 for glycine (Table III) to 1.8 for $HSeCH_2CO_2H$ because of the increase in r from 3.7 to 4.1 Å. Instead, ΔpK(XH) increases to 2.6; ΔpK for selenoglycolic acid is thus 0.8 unit larger than is predicted from the corresponding value for glycine. Similarly, ΔpK for thioglycolic acid (2.5) is 0.6 unit larger than predicted, but pK for oxalic acid (2.4) is approximately equal to its predicted value (2.5).

This increase in ΔpK which accompanies an increase in the atomic number of X could arise from either of two effects: (a) an increase in the efficiency of transmission of the effect of the charge on X (attributable to a decrease in D_E produced by the increase in the radius of X), or (b) a decrease in the free energy of interaction between the XH dipole and the charge on CO_2^- (attributable to the decrease in the XH bond moment). Each of these effects is discussed below.

Variation in Effective Dielectric Constant.—Tanford[3] has shown that the free energy of interaction between charges in the Kirkwood–Westheimer[2] cavity model of organic acids depends critically on the depth, d, within the cavity at which the charges are placed. He has demonstrated that the observed changes in acid dissociation constants which result from the interaction of charges located on nitrogen or oxygen atoms can be predicted if the charges in the model cavity are located with d = 1.0 Å. The van der Waals radii of oxygen and nitrogen atoms are 1.4 and 1.5 Å, while those of sulfur and selenium are *ca.* 0.5 Å larger, 1.85 and 2.0 Å.[19] It would thus not be unreasonable if the correct value of d describing the interaction between the charges in $^-SeCH_2CO_2^-$ were increased to a value between 1.0 and 1.5 Å. In fact, the observed values of ΔpK for glycine and selenoglycolic acid can be accounted for if d for the latter acid is increased to 1.3 Å. Thus, using the distance parameters given in Table III, Tanford's ellipsoidal cavity model predicts for glycine (R = 3.7 Å, d = 1.0 Å) that D_E = 30 and ΔpK = 2.2, and for selenoglycolic acid (R = 4.1 Å, d = 1.3 Å) that D_E = 23 and ΔpK = 2.6.

Variation in Charge–Dipole Interaction.—When a charge is introduced into a molecule by adding or removing a proton, *two* contributions to changes in the electrostatic field of the molecule result: one arising from introduction of the charge, the other arising from creation or destruction of a dipolar bond between the proton and the basic atom to which it is bound. Although allusion has been made to the existence of this second term,[2a,20] no explicit estimation of the magnitude of its contribution is generally included in calculations of the electrostatic contribution to substituent effects on acid strength.

For the simplest case of a linear symmetric dibasic acid, HXH, the effect of the charge–dipole interaction in HX^- will be to raise the free energy of that species, thus increasing pK_1, decreasing pK_2, and decreasing ΔpK. Similarly the effect of the dipole–dipole interaction in HXH will be to increase ΔpK. More generally, if the charge–dipole interaction is dominant, the net result of electrostatic interaction involving the X–H dipole in any[21] dibasic acid will be to decrease ΔpK; the value of ΔpK calculated in the usual way from the charge–charge term is therefore an estimate of an upper limit on the total electrostatic contribution to ΔpK.

That the contribution of the charge–dipole interaction may be large is suggested by the following argument. Consider two pairs of acids into which two

(18) The quoted rms differences are based on the eight values of α_{obsd} for which pH ≥ 6.7. The validity of the assumption of equality of the extinction coefficients is implied by the agreement observed between α_{obsd} and α_{pred} at lower pH values where $^-SeCH_2CO_2H$ is the predominant absorbing species. The rms difference based on all 15 values of α_{obsd} which correspond to the quoted optimum pk values is ±0.030.

(19) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 260.

(20) H. M. Peek and T. H. Hill, *J. Amer. Chem. Soc.*, **73**, 5304 (1951).

(21) It is assumed that the molecular geometry is the common one in which both charge–dipole and dipole–dipole interactions are repulsive.

bond dipoles with approximately the same orientation are introduced at the same distance: (1) H-CH_2CH_2-CO_2H *vs.* Cl-$CH_2CH_2CO_2H$, for which $\Delta pK = 0.9$ and $\Delta\mu = \mu(CCl) - \mu(CH) \approx \mu(CH_3Cl) = 1.9$ D; (2) $NH_2CH_2CO_2H$ *vs.* H-$NH_2{}^+CH_2CO_2H$, for which $\Delta pK = 2.2$ and $\Delta\mu \approx 1.3$ D. If the value of D_E govering the charge–dipole interaction were the same in both pairs, the value of ΔpK observed for (1) would require that the charge–dipole contribution to ΔpK for (2) be 0.6 pK unit, which is 27% of the observed total ΔpK. However, this direct comparison of HN and ClC dipoles disregards the large difference in size between Cl and H. The value of Tanford's d which should be assigned to an NH dipole may be much less than the 1.5 Å which is required for halogen–carbon dipoles, and the estimate of 0.6 pK unit must be considered as an upper limit on the contribution of the NH dipole to the value of ΔpK for glycine; the actual contribution may be very much less.

In the sequence NH, SH, SeH, the magnitude of the bond dipole decreases sharply. From the dipole moments[22] and molecular geometries[23] of NH_3, H_2S, and H_2Se, these bonds moments may be estimated to be 1.3, 0.7 and 0.3 D if the contributions of lone pair moments are assumed to be negligible. These estimated bond dipole moments contain errors due to the unknown magnitudes of the lone pair moments in H_nX; the effects of such errors on estimates of the dipolar contribution to ΔpK will tend to cancel with the effects on ΔpK of the corresponding lone pair moments in the substituted carboxylic acids. This cancellation will in general, however, not be complete.

Although the magnitude of the variation in ΔpK which should result from changes in the XH bond moment (or from changes in the mean orientation of the XH dipole) cannot be quantitatively estimated, it is clear that a difference of *ca.* 1 D between the effective NH and SeH moments is probable; if the effect on ΔpK from this source had a magnitude about equal to its estimated maximum possible value, it could account for the observed total variation in ΔpK. Since that variation, however, lies well within the range which could be accounted for by changes in the value of D_E for charge–charge interactions, at least a major part of it very probably arises from an increase in the efficiency of transmission of the effect of a charge as the atom which bears that charge increases in size.

Registry No.—Selenoglycolic acid, 25244-47-7; selenoglycolic methyl ester, 25244-48-8.

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(22) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.

(23) "Table of Interatomic Distances," Special Publications No. 11 and 18, The Chemical Society, London, 1958 and 1963.

Free-Radical Bromination of Methyl Abietate by N-Bromosuccinimide and Solvolysis of the Products

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The major product from the solvolysis of the methyl bromoabietate formed by the NBS–methyl abietate reaction was methyl 12α-methoxyabietate. The structure was proved by independent synthesis from 12α-hydroxyabietic acid. Methyl 18-methoxyabietate was also formed. The three possible methyl methoxydehydroabietates were obtained as secondary reaction products from the methyl dehydroabietate formed during the NBS–abietate reaction. They have also been prepared by the solvolysis of NBS–methyl dehydroabietate reaction products. The structures of the intermediate bromo compounds have been assigned by analogy to the ethers.

As one approach to the identification of a methyl methoxyabietate obtained by photolysis of methyl neoabietate in methanol,[2] preparation of similar compounds from methyl abietate (1) by free-radical bromination followed by methanolysis of the bromides was investigated. Bromination with N-bromosuccinimide (NBS) followed by dehydrobromination[3] has been used to make dehydroabietic acid from abietic acid. In the present investigation methyl dehydroabietate (**10**) was still the major product, but a fair yield of ethers was also obtained.

On the basis of the identity of its uv spectrum with that of methyl abietate and the splitting pattern of the C_{12} proton[4] in its nmr spectrum,[5] it should be **2a**. This structure was confirmed by comparison with an authentic sample prepared from methyl 12α-hydroxyabietate[6] (**2b**). Of the minor products, only one exhibited the uv absorption characteristic of an abietate structure. Its gas chromatographic behavior was identical with that of the ether obtained by photolysis and subsequently identified as methyl 18-methoxyabietate[2] (**6a**).

The other products had uv and ir spectra which were consistent with aromatic structures, indicating that **10**

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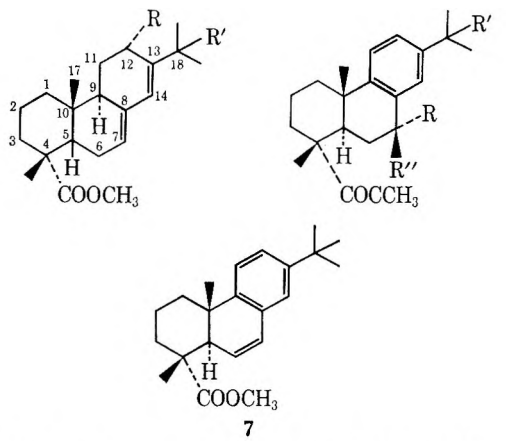
(2) J. C. Sircar and G. S. Fisher, *Chem. Ind. (London)*, 26 (1970).

(3) O. Jeger, O. Durst, and G. Buchi, *Helv. Chim. Acta*, **30**, 1853 (1947).

(4) (a) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 77. (b) J. C. Sircar and G. S. Fisher, *J. Org. Chem.*, **34**, 404 (1969).

(5) Nmr spectra were run in deuteriochloroform on a Varian A-60 spectrometer unless otherwise specified. Frequencies are given in cps with tetramethylsilane as internal standard. s = singlet, d = doublet, t = triplet, m = multiplet. The mention of firm names of trademarks does not imply that they are endorsed or recommended by the Department of Agriculture over others not mentioned.

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



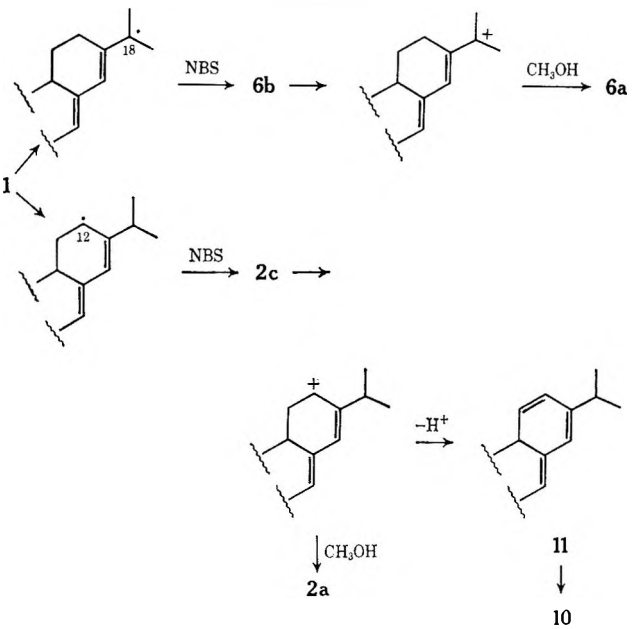
7

1, R = R′ = H
2a, R = OCH_3; R′ = H
b, R = OH; R′ = H
c, R = Br; R′ = H
6a, R = H; R′ = OCH_3
b, R = H; R′ = Br
3, R = OCH_3; R′ = R″ = H
4, R = R″ = H; R′ = OCH_3
5, R = R′ = H; R″ = OCH_3
8, R = R′ = OCH_3; R″ = H
9, R = H; R′ = R″ = OCH_3
10, R = R′ = R″ = H

formed during bromination of **1** and was also brominated by the NBS. Hence, pure **10** was brominated and solvolyzed under the same conditions. Bromination was somewhat slower than in the case of **1** and there was much less evolution of HBr. In addition to the products in question, two products with longer glpc emergence times were formed. On the basis of spectral data, the secondary products from methyl abietate, in order of emergence, were methyl Δ^6-dehydrodehydroabietate (**7**), methyl 7β-methoxydehydroabietate (**5**), methyl 7α-methoxydehydroabietate (**3**), and methyl 18-methoxydehydroabietate (**4**). One of the two additional products was isolated by column chromatography and shown to be methyl 7α,18-dimethoxydehydroabietate (**8**). On the basis of relative emergence times and yield, the other one is assumed to be the corresponding 7β isomer (**9**). The 18-methoxy derivatives accounted for only about 20% of the products. Similar selectivity for the C_7 position was observed in the autoxidation of **10**.[7]

The observed predominance of the α-quasiaxial ethers can be rationalized on the basis of a combination of steric and stereoelectronic factors. The stereoelectronic requirements for the formation of allylic radicals or ions greatly enhances the reactivity of quasiaxial allylic substituents.[8,9] Formation of axial or quasiaxial products from such ions and radicals is also favored.[8,9] Of the six allylic positions in **1**, 6α and 12β are quasiequatorial. The 6β position is synaxial to the methyl groups at C_4 and C_{10}. The 9α position is allylic to the 7 double bond, but a p orbital at C_9 cannot conjugate with the whole diene system. Hence, failure to get detectable amounts of ether formation at these four positions is reasonable. Since the abietic diene system is the most stable abietadiene system,[10] allylic rearrangement products would not be expected. The great predominance of **2a** over **6a** reflects the fact that the 12α position is quasiaxial and relatively unhindered,[6] while rotation of the isopropyl group to an H-axial conformation involves a crowding of the methyl groups,[11] which becomes more severe in the derived ion or radical. Copious evolution of HBr with formation of **10** during bromination of **1** is a further result of the stereoelectronic enhancement of the reactivity of the 12α bromine.[9] The primary product (**2c**) would aromatize immediately in the presence of acid (Scheme I).

SCHEME I



The influence of these same factors also determines the distribution of products from **10**, but compared to the vinyl group of **1**, the phenyl group of **10** is less effective in conjugating with the neighboring p orbital.[12] Hence, there is less dehydrobromination, a greater proportion of 18-methoxy products, and a significant yield of the 7β isomer. The quasiaxial 7α position is still the most reactive one. This is in accord with the observations of Meyer[11] that tetralin is more reactive than cumene and contrary to Walling's report that cumene reacts more rapidly than tetralin with NBS.[13]

Since solvolysis of the bromides is an SN1 reaction,[14,15] they would not necessarily have the same configuration as the ethers, but we consider that they do because the same steric and stereoelectronic factors which control the solvolysis steps will also govern the bromination steps.[7]

Experimental Section[16]

Bromination of Methyl Abietate (1) with NBS.—A mixture of "Vazo"[6] (AIBN) (104 mg) and N-bromosuccinimide (10.01 g,

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(14) T. I. Wrigley and W. G. Young, *ibid.*, **80**, 4604 (1958).

(15) H. L. Goering, T. D. Nevitt, and E. F. Silversmith, *ibid.*, **77**, 5026 (1955).

(16) Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. Infrared spectra were obtained with a Perkin-Elmer infrared spectrophotometer, Model 21. Ultraviolet spectra and rotations were determined in 95% ethanol. Analytical gas chromatographic analyses were performed at 245° on a Varian-Aerograph Model 1200 using a 10 ft × 3/16 in. column packed with 5% Versamid-900 on 60–80 mesh Chromosorb W. Unless otherwise mentioned, methyl arachidate was used as an internal standard for determination of relative retention times (α).

0.0568 mol) was added to a solution of methyl abietate (1) (17.93 g, 0.0568 mol) in dry carbon tetrachloride (180 ml) and the mixture heated on a steam bath for 5 min, until the reaction was complete as indicated by the disappearance of the heavy NBS. The hot solution was filtered and the solvent removed under vacuum (1 mm) at 50°. The crude bromo compound (20 g) spontaneously generated hydrogen bromide, so it was used immediately for the methanolysis.

13-Isopropyl-12α-methoxypodocarpa-7,13-dien-15-oic Acid Methyl Ester (Methyl 12α-Methoxyabietate) (2a). A. Solvolysis[17] of the Bromoabietates.—The crude bromo compounds (20 g) from above were dissolved in anhydrous methanol (1500 ml, AR) mixed with fused potassium acetate (7.40 g, 0.0644 mol), and refluxed for 8 hr. Methanol was removed by distillation under reduced pressure and the residual oil was extracted with ether as usual to give a brown oil (18.89 g). Glpc analysis showed the following composition: methyl dehydroabietate (α = 2.16), 29%; Δ^6-dehydrodehydroabietate (**7**) (α = 2.32), 5%; methyl abietate (**1**) (α = 2.51), 26%; methyl 7β-methoxydehydroabietate (**5**) (α = 2.59), methyl 7α-methoxydehydroabietate (**3**) (α = 2.89), 7%; methyl 12α-methoxyabietate (**2a**) (α = 3.38), 27%; methyl 18-methoxydehydroabietate (**4**) (α = 3.57), 1.0%; methyl 18-methoxyabietate (**6a**) (α = 4.11), 1.6%; and three other minor products, 3.5% (none of them above 2%).

The solvolysis product (9.15 g) was chromatographed over silica gel (E. Merck, 70-325 mesh ASTM, 239 g). Elution with 80% benzene–*n*-hexane mixture (700 ml) and benzene (600 ml) gave resin acid ester mixtures (3.1 g) containing methyl dehydroabietate, methyl abietate, and a little methyl palustrate. Further elution with 20–30% ether–benzene mixture (300 ml) gave semisolid mixtures of ethers, which on trituration with methanol gave white solids. Recrystallization from methanol gave methyl 12α-methoxyabietate (**2a**) (1.82 g) as white needles; mp, 113–4°. Another recrystallization from methanol gave the analytical sample: mp 115°; $[\alpha]^{26}D$ −72°; λ_{max}^{EtOH} 236, 242, and 251 mμ (ϵ_{max}^{242} 26,700); λ^{Nujol} 5.85, 8.10, 9.30, 11.40, and 12.40 μ; nmr (cps) 352 (s, 1 H, C_{14}-proton), 330 (m, 1 H, (C_7-proton), 227 (t, 1 H, $J_{a,e}$ = 2 cps, C_{12}-β-proton), 218 (s, 3 H, C_{15}-O-CH_3), 202 (s, 3 H, C_{12}-α-OCH_3), 76 (s, C_{16}-protons), 63 (d, J = 7 cps, C_{19}- or C_{20}-protons), 65 (d, J = 7 cps, C_{19}- or C_{20}-protons), 49 (s, 3 H, C_{17}-protons).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.07; H, 9.72; O, 14.05.

Mother liquor from the crude 12α-methoxyabietate (**2a**) was used to isolate methoxydehydroabietates **3**, **4**, and **5**.

B. Methylation of Methyl 12α-Hydroxyabietate (2b).—A sample of 56% sodium hydride (2.95 g) suspended in mineral oil was washed several times with dry *n*-pentane and once with 1,2-dimethoxyethane. The suspension of sodium hydride in 1,2-dimethoxyethane (15 ml) was added to a solution of methyl 12α-hydroxyabietate[6] (1.66 g) in 1,2-dimethoxyethane (40 ml). The whole mixture was refluxed for 10 min and then methyl iodide (9 ml) was added. Refluxing was continued for 5 hr. The solvent was removed under reduced pressure and the residual oil was diluted with water and extracted with ether as usual to give crude methyl 12α-methoxyabietate (**2a**) (1.91 g). The crude solid was recrystallized from methanol three times to give white crystals of **2a**: mp 111–113°; $[\alpha]^{26}D$ −71.5°; λ_{max}^{EtOH} 242 mμ (ϵ 26,000); mmp with solvolysis product (mp 115°) 113–115°. The ir and nmr spectra of the product are superimposable on those of methyl 12α-methoxyabietate (**2a**) obtained from solvolysis products. Glpc retention times and enrichment with one another also confirmed identity of the two products.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.35; H, 9.79.

13-Isopropyl-7α-methoxypodocarpa-8,11,13-trien-15-oic Acid Methyl Ester (Methyl 7α-Methoxydehydroabietate)[18] (3); 13-Isopropyl-7β-methoxypodocarpa-8,11,13-trien-15-oic Acid Methyl Ester (Methyl 7β-Methoxydehydroabietate (5); and 13-Isopropyl-18-methoxypodocarpa-8,11,13-trien-15-oic Acid Methyl Ester (Methyl 18-Methoxydehydroabietate) (4).—The mother liquor (1.9 g) from the trituration and recrystallization of **2a** was chromatographed over Woelm neutral alumina (activity I, 50 g). Elution with *n*-hexane (Fraction 1,200 ml) and benzene–hexane mixtures (each fraction 50 ml) with increasing amounts of benzene gave mixtures of ethers, partially separated from one another.

Elution with 15% benzene–*n*-hexane (50 ml) gave in Fraction 7 (and others), 18-methoxydehydroabietate (**4**) as a colorless oil (100 mg) which gave in the glpc one major peak (α = 3.57) (46%) along with five minor peaks (54%). The fraction did not have any characteristic absorption in the uv: λ^{film} 5.81 (>C=O), 6.71 (aromatic), 8.07 (ester C—O), and 9.35 (C—O—CH_3) μ; nmr (cps) 427 (m, aromatic protons), 220 (s, C_{15}-OCH_3), 184 (s, C_{18}-OCH_3), 90 (s, C_{19}- and C_{20}-protons), 77 (s, C_{16}-protons), 73 (s, C_{17}-protons).

Elution further with 30% benzene–*n*-hexane (50 ml) gave in Fraction 11 (64 mg), 7β-methoxydehydroabietate (**5**) (33%) as a colorless oil admixed with 7α-methoxydehydroabietate (**3**) (23%), 18-methoxydehydroabietate [+12α-methoxyabietate (**2a**)] (**4**) (15%), and other minor ethers (29%): no uv absorption λ^{film} 5.81, 6.71, 8.07, and 9.35 μ; nmr (cps) (after eliminating signals for known compounds), 428 (m, aromatic protons), 219 (s, C_{15}-OCH_3), 206 (s, C_7-β-OCH_3), 202 (b, $W_{1/2}$ = 11 cps, C_7 α-proton), 78 (s, C_{16}-protons), 71 (s, C_{17}-protons), 74 (d, overlapped with the C_{16}- and C_{17}-singlets, J = 7 cps, C_{19}- and C_{20}-protons).

Elution with 50% benzene–hexane mixture (250 ml) gave in Fractions 12 to 16 a white solid (250 mg) which on recrystallization afforded methyl 7α-methoxydehydroabietate (**3**); mp 98.5°; λ^{Nujol} −5.83, 6.71, 8.05, and 9.30 μ; nmr (cps) 428 (b, 3H, C_{11}-, C_{12}-, and C_{14}-protons, aromatic), 256 (t, 1 H, J = 3 cps, C_7-β-proton), 221 (s, 3 H, C_{15}-OCH_3), 205 (s, 3 H, C_7-α-OCH_3), 165 (m, C_{18}-proton), 78 (s, 6 H, C_{16}- and half of the doublet of C_{19}- and C_{20}-protons), 71 (s, 6 H, C_{17}- and half of the doublet of C_{19}- and C_{20}-protons, J = 7 cps).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.92; H, 9.49.

Intermediate fractions (50 ml each) gave mixtures of ethers as found by glpc. Methoxydehydroabietates (**3**, **4**, and **5**) have been further confirmed by synthesis from dehydroabietate (*vide infra*).

Bromination of Methyl Dehydroabietate with NBS.—Bromination of methyl dehydroabietate (1.55 g, 0.00495 mol) in carbon tetrachloride (40 ml) was carried out for 8–9 min with NBS (0.897 g, 0.00502 mol) and Vazo[5] (10 mg) as usual at reflux. Removal of solvent gave the bromides as a pale yellow oil which was used in the next step, solvolysis.

13-Isopropyl-7α-methoxypodocarpa-8,11,13-trien-15-oic Acid Methyl Ester (Methyl 7α-Methoxydehydroabietate) (3) and 13-Methoxyisopropyl-7α-methoxypodocarpa-8,11,13-trien-15-oic Acid Methyl Ester (Methyl 7α,18-Dimethoxydehydroabietate) (8).—The crude bromides (1.83 g) from above were dissolved in dry methanol (165 ml), mixed with anhydrous potassium acetate (0.879 g, 0.00762 mol), and refluxed for 8 hr. Usual work-up gave a semisolid residue (1.83 g). Glpc analysis of the crude product gave the following composition: methyl dehydroabietate (α = 2.15) (28%); methyl Δ^6-dehydrodehydroabietate (α = 2.28) (**7**) (2%); methyl 7β-methoxydehydroabietate (α = 2.59) (**5**) (15%); methyl 7α-methoxydehydroabietate (α = 2.89) (**3**) (36%); methyl 18-methoxydehydroabietate (α = 3.57) (**4**) (5%); methyl 7α-18-dimethoxydehydroabietate (α = 4.38) (**8**) (6%); and methyl 7β-18-dimethoxydehydroabietate (α = 3.98) (5%) plus one minor broad peak (2%). All the known compounds were identified by their relative retention time.

The crude solvolysis product (1.83 g) was chromatographed over silica gel (50 g) as usual. Elution with 75% benzene–*n*-hexane (225 ml) gave in Fractions 4–7 only methyl dehydroabietate (320 mg) identified by its retention time. Further elution with 20% ether–benzene mixture (200 ml) gave in Fractions 15 and 16 a solid (1.14 g) containing **3**, **4**, **5**, and **7** mainly. Recrystallization of the solid from aqueous methanol gave methyl 7α-methoxydehydroabietate (**3**) (350 mg), mp 92–5°; mixture melting point with the analytical sample (mp 98.5°) was undepressed. Ir, nmr of the sample were identical with those of **3** obtained earlier from abietate. It has been further confirmed by relative retention time. The mother liquor was used to isolate methyl Δ^6-dehydrodehydroabietate (**7**) and also identify the methyl 7β-methoxydehydroabietate (**5**) and methyl 18-methoxydehydroabietate (**4**) by their relative retention times.

(17) G. H. Whitham and J. A. F. Wickramsinghe, *J. Chem. Soc.*, 1655 (1964).

(18) One report of a methyl methoxydehydroabietate (mp 111°) was found in the literature [R. Lombard and J. P. Baltzinger, *C. R. Acad. Sci*, **236**, 1970 (1953)], but the properties fit the 7α-hydroxydehydroabietate, reported later by Dupont, *et al.*[19]

(19) G. Dupont, R. Dulou, G. Ourisson, and C. Thibault, *Bull. Soc. Chim. Fr.*, 708 (1955).

Further elution with 20% ether–benzene (100 ml) gave in Fraction 17, methyl 7α-18-dimethoxydehydroabietate (**8**) (47 mg) as a white solid, mp 129–133°. This, on recrystallization from ether, gave the analytical sample: mp 141–143°; λ^{Nujol} 5.83, 6.68, 8.05, and 9.35 μ, no λ_{max}; nmr (cps) 429 (s, 3 H, aromatic protons), 258 (t, J = 3 cps, 1 H, C_7-β-proton), 223 (s, 3 H, C_{15}-OCH_3), 206 (s, 3 H, C_7-α-OCH_3), 185 (s, 3H, C_{18}-OCH_3), 91 (s, 6 H, C_{19}- and C_{20}-protons), 79 (s, 3 H, C_{16}-protons), 71 (s, 3 H, C_{17}-protons).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.05.

13-Isopropyl-podocarpa-6,8,11,13-tetraen-15-oic Acid Methyl Ester (Methyl Δ⁶-Dehydrodehydroabietate) (7).—The mother liquor from the recrystallization of **3** above was evaporated to dryness and the residual oil (745 mg), composed of methyl Δ⁶-dehydrodehydroabietate (**7**), methyl 7β-methoxydehydroabietate (**5**), methyl 7α-methoxydehydroabietate (**3**), and methyl 18-methoxydehydroabietate (**4**) (identified **3**, **4**, and **5** by their known relative retention times) was chromatographed over alumina (25 g).

Elution with 30% benzene–hexane mixture (200 ml) (Fraction 9, 10) and 40% benzene–hexane mixture (100 ml) (Fraction 11) gave methyl Δ⁶-dehydrodehydroabietate[19] (**7**) as oil (120 mg) with 80% purity. Impurities are **3** and **5**. Further elution with 40% benzene–hexane mixture (50 ml) (Fraction 12) gave pure **7** (26 mg): λ_{max}^{EtOH} 265 and 220 mμ; λ^{neat} 3.37 (aromatic), 5.80 (>C=O), 6.25 (>C=C<), 6.42, 6.73 (aromatic), 8.06 (C–O ester), 9.27, 12.18 (aromatic), and 14.57 (*cis*-CH=CH) μ; nmr (cps) 428 (m, 34, aromatic protons), 394 (a pair of doublets, J_{AB} = 9 cps, J_{AX} = 3 cps, 1 H, C_7-proton), 346 (a pair of doublets, J_{AB} = 9 cps, J_{AX} = 2.5 cps, 1 H, C_6-proton), 220 (s, 3 H, C_{15}-OCH_3), 177 (t, J = 3 cps, C_5-proton), 166 (m, J = 7 cps, C_{18}-proton), 85 (s, 3 H, C_{16}-protons), 75 (d, J = 7 cps, C_{19}- and C_{20}-protons), 65 (s, 3 H, C_{17}-protons).

The identity was further confirmed by the relative retention time in 15% DEGS column (6 × 3/16 in.) at 230° with the known data (methyl stearate[20] as internal standard).

Further elution with benzene (100 ml) (Fraction 21) and 10% ether–benzene (200 ml) (Fraction 22, 23) gave solid **3** (131 mg) mixed with **5**.

Registry No.—**1**, 127-25-3; NBS, 128-08-5; **2a**, 25236-84-4; **3**, 25236-85-5; **4**, 25236-86-6; **7**, 18492-76-7; **8**, 25236-88-8.

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Synthesis of N,N,N′-Trifluoroamidines[1]

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The dehydrofluorination of 1,1-bis(difluoramino)alkanes yielded the corresponding N,N,N′-trifluoroalkylamidines in good yield. The geometric isomers of these compounds were separated, and conformations are proposed. The direct fluorination of fluoroalkylamidines in the solid phase produced only one isomer of the corresponding N,N,N′-trifluoroamidines, $R_fC(=NF)NF_2$. The addition of methanol to the fluorimino group followed by fluorination gave $R_fC(NF_2)_2OCH_3$.

The fluorination of nitrogen bases with elemental fluorine has received considerable attention during recent years.[2] The solution fluorination of amines[3] and N-alkylcarbamates or -ureas[4] have yielded the corresponding alkyl difluoramines, and the fluorination of nitro aromatic amines produced nitro aromatic difluoramines.[5]

The synthesis of N-haloamidines to give N-chloro-, -bromo-, and -iodoamidines has been studied extensively.[6–9] The synthesis of the first N-fluoroamidine, tetrafluoroformamidine, has been reported[10] as well as some reactions involving this compound.[2,11] Our interest in other N,N,N′-trifluoroamidines prompted us to investigate methods of preparing these compounds by two methods: (a) the dehydrofluorination of terminal geminate difluoramino compounds, and (b) the direct fluorination of amidines.

Terminal geminate difluoraminoalkanes are readily prepared by the reaction of difluoramine with aldehydes.[12] The dehydrofluorination of these compounds with base occurs rapidly to give moderate to high yields of N,N,N′-trifluoroamidines. The kinetics of the base-catalyzed dehydrofluorination of several difluoraminoalkanes has been studied previously,[13,14] but dehydrofluorination has not been applied to the synthesis of trifluoroamidines on a laboratory scale. Solution fluorination was not a practical method for the synthesis of trifluoroamidines, although trace amounts of N-fluoramino compounds were detected in the solution fluorination of acetamidine, butyramidine, and heptafluorobutyramidine.[9] The solid phase fluorination of electronegatively substituted amidines yielded the desired trifluoroamidines whereas considerable decomposition and C-fluorination resulted when unsubstituted alkyl amidines were fluorinated.

Results and Discussion

In this study the compounds prepared by dehydrofluorination were N,N,N′-trifluoropropionamidine (**1**), N,N,N′-trifluorohexanamidine (**2**), and 2-chloro-N,N,-N′-trifluoropropionamidine (**3**). The *syn* and *anti* iso-

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mers of these compounds were separated and characterized. The direct fluorination of difluoronitroacetamidine hydrochloride[15] and heptafluorobutyramidine hydrochloride[16] in the solid phase produced only one isomer of the corresponding N,N,N′-trifluoroamidines, perfluorobutyramidine (**4**), and N,N,N′-trifluorodifluoronitroacetamidine (**5**). The nucleophilic addition of methanol to **4** and **5** was demonstrated, and fluorination of the adducts produced the methyl ethers, 1,1-bis(difluoramino)heptafluorobutyl methyl ether (**6**) and 1,1-bis(difluoramino)-2,2-difluoro-2-nitroethyl methyl ether (**7**).

Trifluoroamidines by Dehydrofluorination of 1,1-Bis(difluoramino)alkanes.—The synthesis of 1,1-bis(difluoramino)alkanes was readily accomplished by the reaction of the corresponding aldehydes with difluoramine in sulfuric acid solution. These bis(difluoramino)alkanes were dissolved in methylene chloride and were treated with pyridine. Optimum yields of

$$RC(NF_2)_2H + C_5H_5N \longrightarrow RC(=NF)NF_2 + C_5H_5N\cdot HF$$

1, R = CH_3CH_2–
2, R = $CH_3(CH_2)_4$–
3, R = $ClCH_2CH_2$–

trifluoroamidines were obtained when 0.33 mol equiv of pyridine was used for the preparation of **3**, and 1 mol equiv was used for **1** and **2**. No correlation could be found between the amount of pyridine required and the bis(difluoramino)alkane used. Other bases such as piperidine, quinoline, or aqueous sodium hydroxide were used, and dehydrohalogenation of other difluoramino compounds using alkali metal fluorides have been reported,[17] but in our case pyridine gave higher yields and cleaner reaction mixtures.

The trifluoroamidines **1**, **2**, and **3** were obtained as 1:1 mixtures of the *syn* and *anti* isomers.[18] After distillation it was observed that the collected fractions contained varying amounts of the isomers. Although it may be possible to separate the isomers by distillation, the separation of small amounts of mixtures was more easily accomplished by glpc. The isomer with the shorter retention time was designated A and that with the longer retention time, B.

N,N,N′-Trifluoropropionamidine (**1**) was first prepared and its isomers were separated. Nmr analysis of the isomers gave identical proton spectra with the same splitting and chemical shifts. The ^{19}F spectra differed in that the NF_2 peak (φ^* −47.0) of isomer A was downfield from the NF_2 peak (φ^* −43.7) of isomer B. Conversely, the C=NF peak (φ^* −11.3) of isomer A was upfield from the C=NF peak (φ^* −16.2) of isomer B. These same relative shifts were observed for all of the isomeric trifluoroamidines prepared in this study. On the basis of the spectral data for **1**, no structural assignment could be made with absolute certainty. However, on the basis of volatility observed in the distillations which agreed with the relative retention times on glpc, the more volatile isomer A was assigned the *anti*-NF_2,NF structure, and the less volatile isomer B was assigned the *syn*-NF_2,NF structure.

Another trifluoroamidine, N,N,N′-trifluorohexanamidine (**2**), was also prepared in the same manner as **1**. Results of the proton and fluorine nmr analyses of **2** were essentially the same as **1**; no differences were observed in the proton spectra of the two isomers of **2**. When one considers the effect of dipole moment upon the volatility of the two isomers, the more polar isomer B should be the least volatile and *vice versa*. Distillation of 1:1 isomer mixture of **2** gave fractions enriched in each isomer. Glpc analysis showed that the first fraction was rich in isomer A and the last fraction was rich in isomer B. Comparison of this data with the molecular model of each isomer further supported the structural assignments of the isomers.

While working with the trifluoroalkylamidines it was noted that the isomers were quite stable to the conditions of glpc separation or distillation. In attempts to isomerize **2**, a 2.5:1 mixture of A:B was heated neat and in methanol solution in sealed glass tubes to 60° for 15 hr. The same 2.5:1 mixture in methanol containing *p*-toluenesulfonic acid was stirred at 60° for 15 hr; in these three cases, the ratio of isomers remained unchanged. Therefore, we conclude that the energy barrier between the less stable and the more stable isomer is sufficient to prevent isomerization under these conditions. Perhaps more severe conditions would cause isomerization, but further attempts were considered too hazardous.

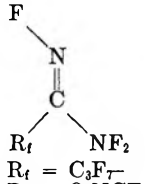
Since the nmr spectral data of **1** and **2** did not allow an assignment of isomers, a third trifluoroamidine was examined for a possible distinction of isomers. 2-Chloro-N,N,N′-trifluoropropionamidine (**3**) was prepared in the same manner as **1** and **2**, and the isomers were separated. The proton nmr spectra of the two isomers of this compound showed the same chemical shifts, and the splitting patterns of $ClCH_2$ group were identical. However, the two overlapped triplets of the CH_2C=NF group of isomer A showed a fine splitting not evident in isomer B. This result of long range H–F coupling was indicative that the structural assignment to isomer A was correct, but more supporting evidence is needed.

Trifluoroamidines by Fluorination of Amidines.—Other than tetrafluoroformamidine, pentafluoroguanidine,[10] and 1-[bis(difluoramino)fluoromethyl]-1,2,3,3-tetrafluoroguanidine,[19] the synthesis of compounds containing the trifluoroguanyl group by direct fluorination have received little attention. In order to demonstrate the feasibility of this method of synthesis, two amidines were chosen for fluorination in which the alkyl side chain would not be affected by the action of elemental fluorine. Heptafluorobutyramidine hydrochloride[16] in the solid phase was treated with fluorine diluted with nitrogen to give a liquid which was condensed from the exit gases of the reaction mixture.

(15) E. R. Bissell, *J. Org. Chem.*, **28**, 1717 (1963).
(16) W. L. Reilly and H. C. Brown, *J. Amer. Chem. Soc.*, **78**, 6032 (1956).
(17) A. L. Logothetis and G. N. Sausen, *J. Org. Chem.*, **31**, 3689 (1966).
(18) The same ratio of isomers was observed in kinetic studies when **1** was formed in 30% aqueous diglyme.[14] In this kinetic study where water acts as the base and in another study[17] in which metal fluorides were used as the base, it appeared that steric factors alone determined the stereochemistry of the final products.
(19) J. J. Hoekstra, U. S. Patent 3,361,815 (1962).

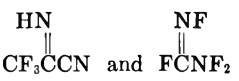
The liquid was purified and identified as perfluorobutyramidine (**4**). The major portion of the solid material remaining in the reaction was the butyramidine hydrofluoride. The use of an alkali metal fluoride as a diluent has been described.[20] By mixing the hydrochloride with sodium fluoride prior to the fluorination, less of the hydrofluoride formed and better yields of product were obtained. In contrast to the 1:1 *syn*:*anti* isomeric ratio of products observed with the hydroalkylamidines, only one isomer of **4** was obtained.[21] The ir spectrum of this compound was consistent with the assigned structure, and an nmr spectrum gave signals characteristic of the C_3F_7 group.[22,23] The NF_2 group (singlet at φ^* −42.8) was as expected, but in this instance the C=NF group occurred at φ^* −45.81.

This downfield shift is in keeping with wide variance of chemical shifts observed for the C=NF group which is strongly affected by the types of groups attached to it. For example, the C=NF group of $C_3F_7CF{=}NF$ occurs at φ^* 14.4.[23] The less sterically hindered *anti*-



4, R_f = C_3F_7–
5, R_f = O_2NCF_2–

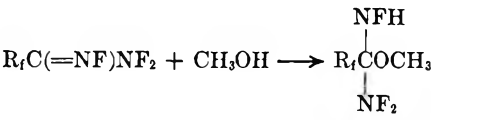
NF_2,NF structure is proposed for **4**. Other investigators[10,22] assigned the structures



to these compounds by extending the results of work on *cis* and *trans* olefin systems, and $C_3F_7CF{=}NF$ has been reported[23] but no conformation was given. Since none of these systems appeared applicable to the trifluoroamidines, the assigned configuration is preferred at this time. Other attempts to prepare **4** by the fluorination of the amidine or its hydrochloride in acetonitrile were unsuccessful. Only the hydrofluoride was obtained from these reactions due to the presence of large amounts of HF arising from the liquid-phase fluorination of acetonitrile.[24]

Difluoronitroacetamidine hydrochloride[15] was fluorinated in the same manner as heptafluorobutyramidine to give N,N,N′-trifluorodifluoronitroacetamidine (**5**). The fluorination gave a low yield mixture of five low-boiling products; nmr analysis of this mixture showed the presence of only one isomer of the desired trifluoroamidine **5**. Two of the products were separated from the mixture by glpc. One product was identified as difluoronitroacetonitrile by comparison of its ir spectrum with that of a known sample.[15] The second product was the desired trifluoroamidine **5**, whose nmr spectrum showed only one isomer with the expected singlets for the fluorimino and difluoramino groups; however, the peak at φ^* 86.1 for the O_2NCF_2 group was a quintet. Normally a 1:1:1 triplet results for the O_2NCF_2 group when no α hydrogens or fluorines are present. This type of triplet, due to coupling of fluorine (spin $^1/_2$) with nitrogen (spin 1), was shown to be characteristic of this group by obtaining the nmr spectra of $O_2NCF_2COOCH_3$, O_2NCF_2COCl, and O_2NCF_2CN.[15] Therefore, the φ^* 86.1 quintet of **5** arises from further splitting of the 1:1:1 triplet by the fluorine of either the fluorimino or the difluoramino group or both.

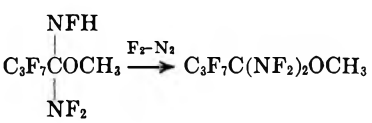
Since the cyano group of aliphatic perfluoronitriles will add ammonia, amines,[16] mercaptans,[25] and hydrogen cyanide,[22] it was of interest to determine if the trifluoroguanyl group of trifluoroamidines was sufficiently electrophilic to undergo a similar nucleophilic addition. The hydroalkyl trifluoroamidines were unreactive even in the presence of basic catalysts, but the perfluoroamidines added methanol without the aid of a catalyst.



4a, R_f = C_3F_7–
5a, R_f = O_2NCF_2–

The intermediate fluoraminodifluoraminoalkyl methyl ethers **4a** and **5a** could not be isolated from the reaction mixture without decomposition, but the presence of these compounds was shown by nmr analysis of the reaction mixtures. The ^{19}F nmr spectra of **4a** and **5a** were very characteristic, particularly the spectrum of **4a**. Since **4a** contains an asymmetric carbon, the NF_2 group occurred at φ^* −20.6 as two singlets separated by 48 Hz, and the NFH group appeared at φ^* 145.8 as two multiplets separated by 47 Hz. The pattern for the C_3F_7 group was well defined. Nmr analysis of a reaction solution containing excess methanol revealed that exchange of NF**H** with CH_3O**H** occurred to the extent that the φ^* 145.8 doublet (NF**H**) collapsed to a singlet. The proton nmr spectrum of this solution gave a singlet at τ 4.84 for NF**H** and CH_3O**H**, a singlet at τ 6.10 for $COCH_3$, and a singlet at τ 6.54 for CH_3OH. When no proton exchange can occur, CH_3O**H** is normally upfield from CH_3OH.

The presence of **4a** was further confirmed by fluorination to give the corresponding bis(difluoramino)alkyl



4a **6**

methyl ether (**6**) whose structure was confirmed by infrared, nmr, and elemental analysis.

The addition of methanol to **5** gave results similar to **4**. On the other hand, the fluorination of the methanol

(20) R. S. Koshar, D. R. Husted, and R. A. Meiklejohn, *J. Org. Chem.*, **31**, 4232 (1966).

(21) This stereospecificity was consistent with the results of others who have reported the formation of only one isomer in similar solid state fluorinations.[10] The stereospecificity in these cases is probably dependent upon the mechanism of the fluorination and may be analogous to that observed in catalytic hydrogenations in which the catalyst surface is an important factor.

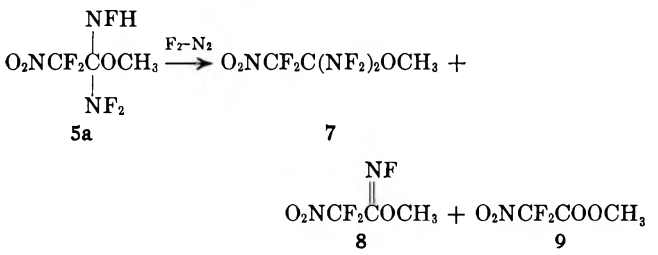
(22) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **33**, 3625 (1968).

(23) R. A. Mitsch, *J. Amer. Chem. Soc.*, **87**, 328 (1965).

(24) S. P. Makarov, I. V. Ermakova, and V. A. Shpanskii, *Zh. Obshch. Khim.*, **36** (8), 1419 (1966); *Chem. Abstr.*, **66**, 2428 (1967).

(25) H. C. Brown and R. Pater, *J. Org. Chem.*, **27**, 2858 (1962).

adduct **5a** gave three products (**7**–**9**) in equal amounts. Each compound was separated by glpc and characterized by nmr and ir analysis. The instability of the



fluoramino intermediate **5a** is demonstrated in this reaction. The desired ether **7** was obtained in addition to the fluorimino ester **8**, which likely formed before fluorination by the loss of HNF_2. Hydrolysis of **8** by water produced in the reaction of HF with glass gave **9**, methyl difluoronitroacetate;[26] the ir and nmr spectra of **9** were superimposable on those of a known sample.

Experimental Section

Caution.—It is necessary to use protective clothing and remote handling equipment when working with NF compounds. All compounds described in this work are shock sensitive and highly explosive to varying degrees. The compounds were handled and stored in dilute solutions, and only small amounts were isolated neat for characterization. Elemental analysis of some of the compounds could not be obtained owing to repeated explosions during analysis; characterization was based on ir and nmr data.

General.—Fluorine was obtained from the General Chemical Division of the Allied Chemical Corp. and was always diluted in stream with nitrogen prior to fluorination. 1,1-Bis(difluoramino)propane was supplied by Aerojet-General Corp. in Aroclor 1248 (a high-boiling polychloropolyphenyl, Monsanto Chemical Co.); other bis(difluoroamino)alkanes were prepared from their parent aldehydes using a previously reported procedure.[12]

Elemental analyses were performed by Stanford University Microanalytical Laboratory, Stanford, Calif. Infrared spectra were run on a Perkin-Elmer 137 Infracord spectrophotometer, and nmr spectra were run on a Varian HA-100 spectrometer. Values for the ^1H chemical shifts are given in τ units with respect to tetramethylsilane as an internal reference, and values for the ^{19}F chemical shifts are given in φ^* units[27] with respect to trichlorofluoromethane as an internal reference. A Varian Aerograph 1521 gas chromatograph equipped with a thermal conductivity detector was used for all glpc analyses; large amounts of mixtures were separated using an Aerograph Autoprep A-700 gas chromatograph.

N,N,N′-Trifluoropropionamidine (**1**).—To a stirred solution of 0.50 g (0.0035 mol) of 1,1-bis(difluoramino)propane in 2.63 g of Aroclor at 25° was added dropwise over 2 min a solution of 0.27 g (0.0038 mol) of pyridine in 1.0 g of Aroclor. The resulting cloudy yellow mixture was stirred for 1 hr at 25°. The desired product was evaporated from the reaction mixture using a water aspirator vacuum, and the condensate was collected in a U tube cooled to −78° to give 0.39 g (90%) of **1**. The condensate contained only the *syn* and *anti* isomers as shown by glpc and nmr analysis.

Anal. Calcd for $C_3H_5F_3N_2$: C, 28.58; H, 4.00; N, 22.23. Found: C, 28.61; H, 3.91; N, 21.92.

The isomers were separated by glpc using a 20 ft × $^3/_8$ in. column (15% Kel-F oil on 60–80 mesh Chromosorb P) at 83°. The ir (gas) spectra of the two isomers were identical: 3.31 (w), 3.35 (w), 3.42 (w), 6.80 (w) CH; 6.79 (w) CH_2; 7.25 (w) CH_3; 6.06 (w) C=N; 9.30 (w); 10.62 (w), 11.00 (s), and 11.55 μ (s) NF. Nmr: isomer A (hexachlorobutadiene), τ 8.73 (t, 3, J = 7.5 Hz, CH_3), 7.27 (two overlapped quartets, 2, J = 7.5 Hz, CH_2), φ^* −47.0 (s, 2, NF_2), −11.3 (s, 1, C=NF); isomer B, τ 8.70 (t, 3, J = 7.5 Hz, CH_3), 7.28 (two overlapped quartets, 2, J = 7.5 Hz, CH_2), φ^* −43.7 (s, 2, NF_2), −16.2 (s, 1, C=NF).

N,N,N′-Trifluorohexanamidine (**2**).—A stirred solution of 18 g (0.097 mol) of 1,1-bis(difluoramino)hexane in 50 ml of trichlorofluoromethane was cooled to 0–5°, and a solution of 8.2 g (0.098 mol) of pyridine in 20 ml of ether was added dropwise over 20 min. The mixture was stirred for 15 hr at ambient temperature and was then washed with 20 ml of water followed by 20 ml of dilute HCl and 20 ml of water. The organic phase was dried ($MgSO_4$) and evaporated to give 11.3 g (70% crude) of **2** as a light yellow liquid. Glpc and fluorine nmr analysis showed that the liquid contained the *syn* and *anti* isomers in a 1:1 ratio; distillation gave 10.01 g (62%) of **2** as a clear colorless liquid, bp 72° (80 mm), $n^{27}D$ 1.3841.

Anal. Calcd for $C_6H_{11}F_3N_2$: C, 42.85; H, 6.59; N, 16.67. Found: C, 43.54; H, 6.68; N, 16.28.

The isomers were separated by glpc using a 5 ft × 0.25 in. column (30% SE-30 on 80–100 mesh Chromosorb P) at 70°. The ir (neat) spectra of the isomers were identical: 3.38 (m) and 3.46 (w) CH; 6.10 (w) C=N; 6.86 (m) CH_2; 7.25 (w) CH_3; 10.1 (w), 10.7 (w), 11.1 (s), and 11.65 (s) NF; 13.7 μ (w). Nmr: isomer A ($CDCl_3$), τ 9.09 (t, 3, J = 7 Hz, CH_3), 8.63 (m, 4, J = 3 Hz, $CH_3CH_2CH_2$), 8.26 (t, 2, J = 7 Hz, CH_2CH_2C=NF), 7.31 (two overlapped triplets, 2, J = 7 Hz, CH_2C=NF), φ^* −45.5 (s, 2, NF_2), −9.3 (s, 1, C=NF); isomer B, τ 9.08 (t, 3, J = 7 Hz, CH_3), 8.62 (m, 4, J = 3 Hz, $CH_3CH_2CH_2$, 8.28 (m, 2, J = 7 Hz, CH_2CH_2C=NF), 7.38 (two overlapped triplets, 2, J = 7 Hz, CH_2C=NF), φ^* −42.4 (s, 2, NF_2), −15.7 (s, 1, C=NF).

2-Chloro-N,N,N′-trifluoropropionamidine (**3**).—A solution of 0.21 g (0.0026 mol) of dry pyridine in 10 ml of methylene chloride was added dropwise during 10 min to a stirred solution of 1.40 g (0.078 mol) of 1-chloro-3,3-bis(difluoramino)propane in 100 ml of methylene chloride at 5–10°. The initially colorless mixture was stirred for 15 hr at ambient temperature, the precipitate that formed was removed, and the filtrate was treated with activated charcoal and filtered. The solvent was evaporated leaving a pale yellow liquid, 0.96 g (64%) of **3**. Glpc analysis showed only two peaks, ratio 1:1, corresponding to the *syn* and *anti* isomers. The isomers were separated by glpc using a 5 ft × 0.25 in. column (15% SE-30 on 80–100 mesh Chromosorb P) at 70°. Nmr: isomer A ($CDCl_3$), τ 6.80 (two overlapped triplets, 2, J = 6 Hz, CH_2C=NF), 6.26 (t, 2, J = 7 Hz, CH_2Cl), φ^* −46.5 (s, 2, NF_2), −14.6 (s, 1, C=NF); isomer B, τ 6.89 (two overlapped triplets, 2, J = 6 Hz, CH_2C=NF), 6.25 (t, 2, J = 7 Hz, CH_2Cl), φ^* −42.8 (s, 2, NF_2), −20.9 (s, 1, C=NF).

Perfluorobutyramidine (**4**).—A 0.9-g sample (0.0036 mol) of dry powdered heptafluorobutyramidine hydrochloride[16] was mixed thoroughly with 0.9 g of powdered sodium fluoride. The mixture was placed in a U tube in alternating layers with glass wool. The tube was flushed with nitrogen, and a 1:3 mixture of fluorine–nitrogen was passed through the U tube at 20 ml/min for 4 hr. During the reaction the U tube became slightly warm, *ca.* 40°. The exit gases were passed first through a 0° trap and then through a −78° trap. The 0° trap contained mainly water, and the −78° trap contained 0.7 g (73% crude) of **4** as a clear colorless liquid that was 72% pure by glpc analysis. This liquid contained only one isomer of **4** which was isolated by glpc using a 20 ft × $^3/_8$ in. column (15% Kel-F oil on 60–80 mesh Chromosorb P) at 70°. The product was a low-boiling liquid: bp 20° (229 mm); ir (gas) 6.20 (w) C=N; 7.45 (m); 8.05 (s) CF; 8.80 (m), 9.10 (w); 10.0 (w), 10.25 (w), 11.25 (s) and 11.70 (w) NF; 13.35 (s), 13.95 μ (m); nmr (CCl_4) φ^* −45.8 (s, 1, C=NF), −42.8 (s, 2, NF_2), 80.2 (t, 3, J = 9.6 Hz, CF_3), 109.6 (m, 2, J = 9.6 Hz, CF_2C=NF), 123.9 (m, 2, J = 9.6 Hz, CF_3CF_2).

1,1-Bis(difluoramino)heptafluorobutyl Methyl Ether (**6**). (a) **Addition of Methanol to 4.**—In a glass reactor equipped with Teflon needle valves and a magnetic stirring bar was placed 1.76 g (6.6 mmol) of **4**, 0.85 g (26.4 mmol) of methanol, and 1 g of carbon tetrachloride as solvent. The vessel was sealed, and the two-phase mixture was stirred at ambient temperature for 72 hr; after 24 hr the mixture became one phase. All attempts to isolate the methanol adduct neat were unsuccessful; the adduct was stable only in solution. Nmr analysis of the reaction mixture showed that the addition of methanol was complete after 72 hr. The product, 1-fluoramino-1-difluoraminoheptafluorobutyl methyl ether (**4a**), gave the following nmr (CCl_4–CH_3OH): φ^* −20.6 (two singlets separated by 48 Hz, NF_2), 81.5 (t, 3, J = 12 Hz, CF_3), 117.8 (m, 2, CF_2CO), 126.0 (m, 2, CF_3CF_2), 145.8 (s, 1, NFH), τ 6.10 (s, $COCH_3$), 6.54 (s, CH_3OH), 4.84 (s, NFH and OH).

(b) **Fluorination of 4a.**—**4a** was not isolated but was fluorinated *in situ*. The reactor containing **4a** in the CH_3OH–CCl_4

(26) E. R. Bissell, *J. Org. Chem.*, **26**, 5100 (1961).

(27) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

solution was cooled to −35° and was flushed with nitrogen. Fluorine–nitrogen, 1:9, was passed over the stirred mixture at 20 ml/min for 4 hr while the temperature was allowed to rise slowly to −5°. During the fluorination the mixture formed two phases; the upper phase was methanol and was discarded. The lower phase contained 1,1-bis(difluoramino)heptafluorobutyl methyl ether (6) in CCl_4. 6 was separated by preparative glpc using a 20 ft × 3/8 in. column (15% SE-30 on 60–80 mesh Chromosorb P) at 100° to give 0.54 g of pure product; bp 25° (25 mm), $n^{23}D$ 1.3088; ir (gas) 3.35 (w) CH; 6.90 (w), 7.50 (w); 8.10 (s) CF; 8.82 (m) COC; 10.25 (m), 10.45 (m), 11.18 (m) and 11.70 (m) NF_2; 12.50 μ (m); nmr (CCl_4) τ 5.95 (s, 3, CH_3), φ* −21.8 (s, 4, NF_2), 81.6 (t, 3, J = 12, CF_3), 115.5 (m, 2, CF_2CO), 125.2 (m, 2, CF_3CF_2).

Anal. Calcd for $C_5H_3F_{11}N_2O$: C, 19.00; H, 0.95; N, 8.87. Found: C, 19.48; H, 0.85; N, 8.63.

N,N,N′-Trifluorodifluoronitroacetamidine (5).—A 2.5-g sample (0.014 mol) of powdered difluoronitroacetamidine hydrochloride[15] was mixed thoroughly with 7.5 g of powdered sodium fluoride. The mixture was placed in a U tube in alternating layers with glass wool, and the tube was cooled in an ice water bath. The tube was flushed with nitrogen, and a 1:9 mixture of fluorine–nitrogen was passed through the U tube at 20 ml/min for 6 hr. The condensable exit gases were collected in a 0° trap and a −78° trap; the contents of the 0° trap was mainly water and was discarded. The −78° trap contained 1.2 g of a clear colorless liquid consisting of five compounds in almost equal amounts, but only one isomer of **5** was evident. **5** was isolated by preparative glpc using a 20 ft × 3/8 in. column (15% Kel-F oil on 60–80 mesh Chromosorb P) at 40°. One of the other five compounds was also isolated and identified as difluoronitroacetonitrile by comparison of its ir spectrum with that of a known sample:[15] bp of **5** *ca.* 20°; ir (gas) 6.18 (s), 7.45 (m), 7.62 (m), and 12.25 (m) NO_2; 8.05 (s) CF; 8.70 (m), 9.60 (w); 10.10 (s), 10.70 (s), and 11.15 μ (m) NF; nmr ($CDCl_3$) φ* −45.0 (s, 2, NF_2), −42.7 (s, 1, C=NF), 86.1 (quintet, 2, J = 10 Hz, CF_2).

1,1-Bis(difluoramino)-2,2-difluoro-2-nitroethyl Methyl Ether (7). (a) **Addition of Methanol to 5.**—A 0.5-g sample (2.6 mmol) of **5** dissolved in 3 ml of acetonitrile was placed in a glass reactor equipped with Teflon needle valves and a magnetic stirring bar. Methanol (0.4 g, 12.5 mmol) was added to the solution at 0°, the reactor was sealed, and the reaction mixture was allowed to stir at 0° for 4 hr. Nmr analysis of the mixture confirmed the presence of the methanol adduct, 1-fluoramino-1-difluoramino-2,2-difluoro-2-nitroethyl methyl ether (**5a**), and showed that reaction was essentially complete; nmr (CH_3CN–CH_3OH), φ* −19.8 (s, 2, NF_2), 92.0 (broad t, CF_2), 143.1 (d of heptets, J = 49.7 and 6.5 Hz, NFH).

(b) **Fluorination of 5a.**—Since **5a** could not be isolated from the reaction mixture, the fluorination step was carried out *in situ*. The acetonitrile reaction mixture was cooled to −35°, the system was purged with nitrogen, and a mixture of 1:3 fluorine–nitrogen was passed over the stirred reaction mixture at 20 ml/min for 2 hr. The reaction mixture was warmed to ambient temperature, and the volatile products were collected in a −35° trap by vacuum transfer at 0.3 mm. Analysis of the condensate by glpc showed equivalent amounts of three main products in a large amount of acetonitrile. The three products were isolated by glpc using a 5 ft × 0.25 in. column (20% SE-30 on 80–100 mesh Chromosorb P) at 80°. In the order of increasing retention time, the compounds were identified by ir and nmr. **9**, methyl difluoronitroacetate: nmr (CCl_4) τ 5.93 (s, 3, CH_3), φ* 93.4 (t, 2, J = 9.8 Hz, CF_2); ir (neat) 3.48 (w), 6.98 (m), 7.55 (s), 9.80 (s), and 10.75 (m) CH; 5.61 (s) C=O; 6.28 (s) and 12.50 (s) NO_2; 8.10 (m), 8.35 (s), and 8.60 (s) CF; 11.82 μ (m). The ir and nmr spectra of this compound were identical with the spectra of a sample prepared by a previously reported method.[26]

8, methyl 2,2-difluoro-2-nitrofluoriminoacetate: nmr (CCl_4) φ* 40.0 (s, 1, C=NF), 92.5 (t, 2, J = 8.5 Hz, CF_2); ir (neat) 3.48 (w), 6.90 (m), 7.35 (m), 7.50 (s), and 9.72 (s) CH; 6.05 (s) C=N; 6.28 (s) and 12.35 (s) NO_2; 8.10 (s), 8.38 (s), and 8.52 (s) CF; 9.38 (m) COC; 10.40 (m) and 11.20 μ (s) NF.

7, 1,1-bis(difluoramino)-2,2-difluoro-2-nitroethyl methyl ether: nmr (CCl_4) φ* −21.9 (s, 4, NF_2), 90.4 (quintet, 2, J = 12.1 Hz, CF_2); ir (neat) 3.38 (w), 7.91 (m), and 7.48 (m) CH; 6.25 (s) and 12.18 (s) NO_2; 8.00 (s), 8.18 (s), and 8.50 (s) CF; 9.10 (m) COC; 10.60 (s), 11.25 μ (s) NF.

Registry No.—**1** (*syn*), 21372-60-1; **1** (*anti*), 21372-59-8; **2** (*syn*), 25238-00-0; **2** (*anti*), 25238-01-1; **3** (*syn*), 25238-02-2; **3** (*anti*), 25238-03-3; **4**, 25356-05-2; **4a**, 25238-04-4; **5**, 25238-05-5; **5a**, 25238-06-6; **6**, 25238-07-7; **7**, 25238-08-8; **8**, 25238-09-9.

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Synthesis and Cycloaddition Reactions of Dehydrohydantoins

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Several $\Delta^{1,5}$-imidazoline-2,5-diones (dehydrohydantoins) have been prepared and their chemistry has been examined. They are active Diels–Alder dienophiles and also react with monoolefins (ene reaction) and nucleophiles (addition across the >C=N– bond). The reactivity of the dehydrohydantoins (I) depends markedly on the substituent in the 5 position with 5-H > 5-CO_2Me > 5-Ph. The dienophilic activity of the dehydrohydantoins appears to be intermediate between those of the corresponding α-dicarbonyl azo compounds and the α-diacyl olefins. The spectra of 5-phenyl-3-methyldehydrohydantoin (Ib), which is isolable and atmospherically stable, indicate that it is a cross-conjugated system similar to 3-phenylmaleimide.

In the course of studies of the Diels–Alder reaction,[1] we have made extensive use of α-dicarbonyl azo compounds, RCON=NCOR, as dienophiles. These azo compounds are three or four orders of magnitude more reactive than the corresponding olefins,[2] and the cyclic examples such as 4-phenyl-1,2,4-triazoline-3,5-dione[2d] are among the most active dienophiles known. The reasons for the remarkable reactivity of these α-dicarbonyl azo compounds are not known. Geometric factors and polarizability are certainly important; however, we suspect that the energetics of transforming an azo ester linkage into two C–N bonds and an unusually strong N–N bond[3] may also be highly favorable.

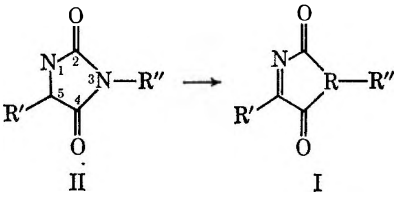
(1) (a) A. B. Evnin and D. R. Arnold, *J. Amer. Chem. Soc.*, **90**, 5330 (1968); (b) A. B. Evnin, R. D. Miller, and G. Evanega, *Tetrahedron Lett.*, 5863 (1968); (c) A. B. Evnin, A. Lam, J. Maher, and J. Blyskal, *ibid.*, 4497 (1969).

(2) (a) J. Sauer and B. Schröder, *Angew. Chem., Int. Ed. Engl.*, **4**, 711 (1965); (b) J. Sauer, *ibid.*, **6**, 16 (1967); (c) J. Sauer and B. Schröder, *Chem. Ber.*, **100**, 678 (1967); (d) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).

(3) The dissociation energy of the N–N bond in N,N-diacylhydrazines is probably >50 kcal: E. Hedaya, R. L. Hinman, V. Schomaker, S. Theodoropulos, and L. M. Kyle, *J. Amer. Chem. Soc.*, **89**, 4875 (1967).

Considerations of the differences between the azo compounds and the olefins led us to an interest in the dienophilic properties of the intermediate α-diacylimines, RCOCR′=NCOR.[4] This class of compounds was the more intriguing since no examples were, as yet, reported in the literature.[5]

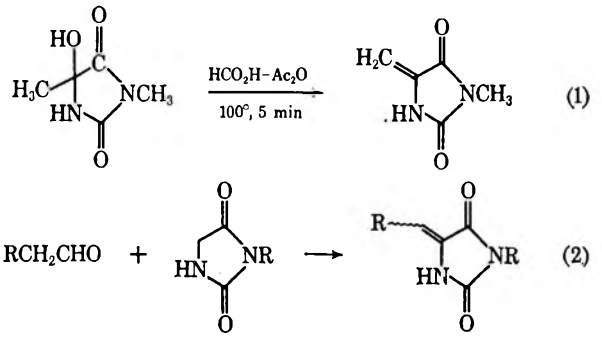
We decided upon the $\Delta^{1,5}$-imidazoline-2,5-diones (dehydrohydantoins) (I) as the starting point of this investigation. The choice was dictated by the ready availability of the precursor hydantoins (II) and by the extensive data available on the analogous C=C and N=N systems, maleimides and 1,2,4-triazoline-3,5-diones, respectively.



II I

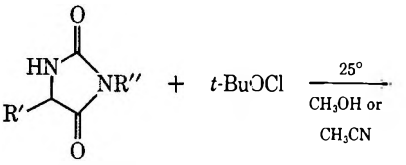
Results

Synthesis and Properties of Dehydrohydantoins.— The literature on hydantoin chemistry indicated that several approaches, which could have given 5-substituted dehydrohydantoins, resulted instead in the formation of the *exo*-methylene tautomers[6-8] (eq 1[6] and 2[8]). We accordingly chose only systems incapable of undergoing such an isomerization.

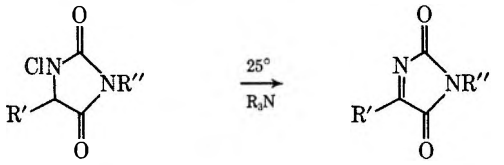


Two routes were considered for conversion of hydantoins to the corresponding dehydro form: oxidative dehydrogenation and substitution (*e.g.*, halogenation) followed by elimination. After some abortive attempts at oxidation, a halogenation–dehydrohalogenation route was developed.[9]

Treatment of the hydantoins IIa–c with *t*-butyl hypochlorite in methanol gave the N-chloro compounds III in quantitative yield. The reaction could be followed by nmr or ir spectroscopy; the N–H stretching absorptions at 3450 and 3250 cm^{-1} are especially convenient indicators of the extent of reaction. Alcoholic solvents were required for the chlorination of IIa and IIb, since there was no reaction in aprotic media;[10] IIc, however, reacted readily with *t*-butyl hypochlorite in acetonitrile.



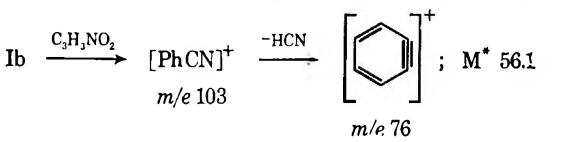
IIa, R′ = H; R″ = CH_3
b, R′ = Ph; R″ = CH_3
c, R′ = CO_2Me; R″ = CH_2Ph



IIIa, R′ = H; R″ = CH_3 Ia, R′ = H; R″ = CH_3
b, R′ = Ph; R″ = CH_3 b, R′ = Ph; R″ = CH_3
c, R′ = CO_2Me; R″ = CH_2Ph c, R′ = CO_2Me; R″ = CH_2Ph

Reaction of these N-chloro compounds (IIIa–c) with triethylamine, tetramethylethylenediamine, or 1,5-diazabicyclo[5.4.0]undec-5-ene[11] resulted in elimination of hydrogen chloride and the formation of the dehydrohydantoins Ia–c. Evidence for the formation of the dehydrohydantoins was the precipitation of the amine hydrochloride, the formation of 1,4-adducts with dienes, and, in the case of IIIb, the properties of the isolated product, Ib. All of the dehydrohydantoins are sensitive to moist air and are preferentially handled in an inert atmosphere.

5-Phenyl-3-methyldehydrohydantoin (Ib) was isolated by sublimation [60° (0.02 mm)]. It is a crystal-



line, yellow compound, mp 148–150°, with substantial atmospheric stability, once purified. The nmr spectrum ($CDCl_3$) shows only N-methyl and aryl hydrogens. The mass spectrum (70 ev) has a base peak at *m/e* 103 (PhCN) and prominent fragments at *m/e* 131 (M − 57, CH_3NCO) and *m/e* 76, in addition to a strong parent peak at *m/e* 188. The important fragment at *m/e* 76 is of interest since it is almost certainly benzyne. The presence of a metastable at *m/e* 56.1 relates this fragment to *m/e* 103 (PhCN). In the mass spectrum of benzonitrile (70 eV), *m/e* 76 is the most important fragment ion.[12] The absorption spectrum of Ic contains maxima at 284 and 325 nm, and the infrared spectrum

(4) In a recent review of heterodienes and heterodienophiles there was only one reference to acylimines and no examples of cyclic systems: J. Hamer, Ed., "1,4-Cycloaddition Reactions," Vol. 1, Academic Press, London, 1967, p 128.

(5) (a) After the completion of this work, a study of the apparent *in situ* generation of Ia was reported: E. Goldstein and D. Ben-Ishai, *Tetrahedron Lett.*, 2631 (1969). (b) Very recently, the preparation of 3-phenyl-2-azanaphthoquinone was reported: I. Felner and K. Schenker, *Helv. Chim. Acta*, **52**, 1810 (1969).

(6) S. Murahashi, H. Yuki, K. Kosai, and F. Doura, *Bull. Chem. Soc. Jap.*, **39**, 1559 (1966).

(7) E. J. McMullen, H. R. Henze, and R. W. Wyatt, *J. Amer. Chem. Soc.*, **76**, 5636 (1954).

(8) T. B. Johnson, *ibid.*, **61**, 2485 (1939).

(9) The conversion of PhCH(CN)NHCOPh to PhC(CN)=NCOPh by $SOCl_2$ in pyridine has been reported. The authors describe the reaction as an oxidation although it must involve chlorination and dehydrochlorination steps: M. Fujimori, E. Haruki, and E. Imoto, *Bull. Chem. Soc. Jap.*, **41**, 1372 (1968).

(10) Most amides can be chlorinated using *t*-BuOCl in nonpolar solvents: R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Amer. Chem. Soc.*, **88**, 3051 (1966).

(11) H. Oediger, H-J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

(12) A. Cornu and R. Massot, "Compilation of Mass Spectral Data," Heydon and Son, Ltd., London, England, 1966, p 37c.

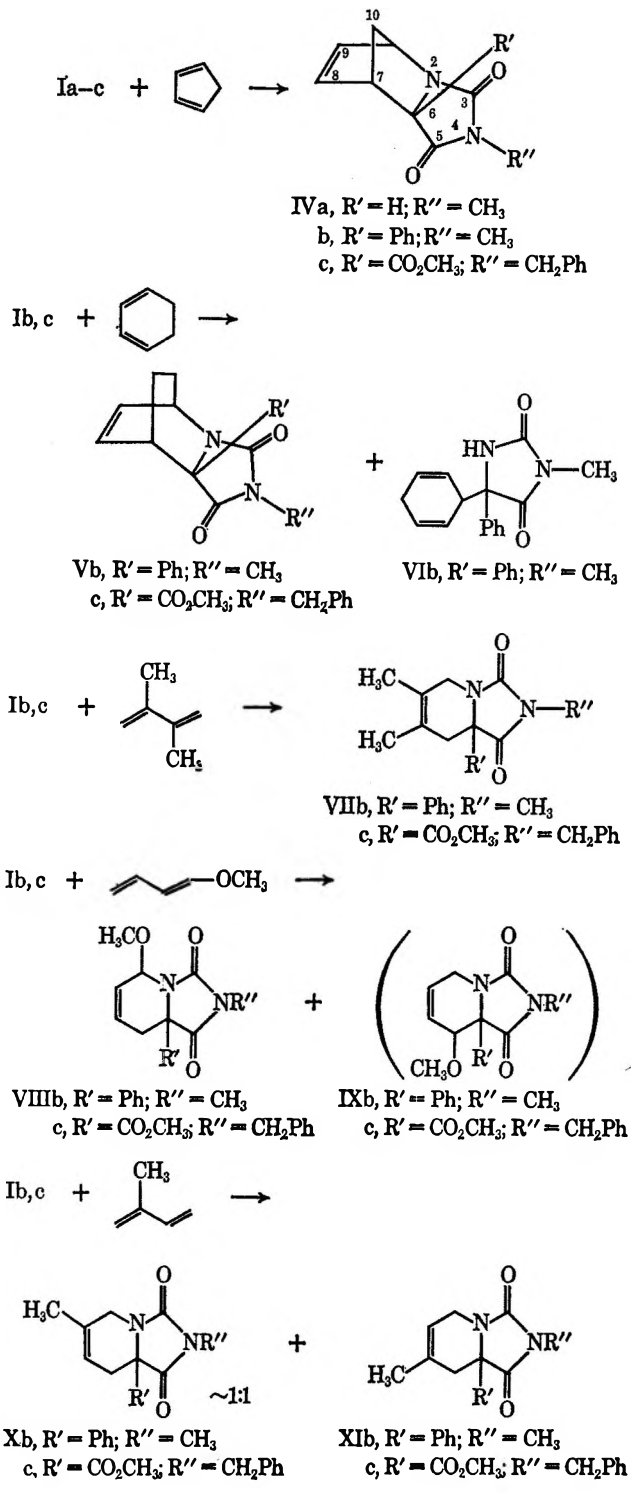
has a characteristic intense doublet at 1590 and 1563 cm^{-1}. The dehydrohydantoins Ic and Ia could not be isolated because of their instability in the atmosphere; however, they could be generated and utilized *in situ*.

Reactions of Dehydrohydantoins.—The dehydrohydantoins Ia–c are active dienophiles and undergo 4 + 2 cycloadditions under mild conditions even with dienes of modest activity. The reactivity of the dehydrohydantoin depends markedly on the substituent in the 5 position with Ic ≫ Ib. The 5-phenyl compound, Ib, reacted rapidly with cyclopentadiene and 1-methoxybutadiene and slowly with isoprene and cyclohexadiene at 25°. There was no reaction with furan or 3,5-diphenyl-4,4-dimethylisopyrazole even at 75°. Competitive experiments showed that it was substantially less reactive than N-phenylmaleimide with 2,3-dimethylbutadiene. Comparison with data in the literature suggests, however, that its reactivity is probably greater than that of phenylmaleic anhydride.[13] In contrast to Ib, Ic reacted within minutes with 1-methoxybutadiene ($k > 0.01$ l. mol^{-1} sec^{-1}), cyclohexadiene, or isoprene at 25°. The parent dehydrohydantoin, Ia, undergoes side reactions under our conditions so that yields of cycloadducts are low and irreproducible, and rates of reactions are difficult to estimate. In the reaction of its precursor IIIa, with bases, decomposition by pathways other than those leading to Ia may be important.

Only one cycloadduct was obtained by reaction of cyclopentadiene with Ia, Ib, or Ic; a second stereoisomer would have been detectable (by nmr) at concentrations of >5%. The stereochemistry of the adduct IVa was assigned by comparison of the 6-H coupling constant with those observed in analogous norbornene derivatives. In the spectra of IVa ($CDCl_3$) this proton appears as a doublet, J = 3 Hz, at δ 4.28. In norbornene derivatives the coupling between bridgehead and *exo* protons is 3–5 Hz and that between bridgehead and *endo* protons is approximately 0.[14] The cycloadducts IVb and IVc are assumed to have *endo* stereochemistry by analogy to IVa and to the adduct of cyclopentadiene and phenylmaleic anhydride, whose configuration was unambiguously established as *endo*.[15b]

Reactions of either Ib or Ic with 1-methoxybutadiene were rapid and afforded high yields, 70–85% (isolated), of the adducts VIIIb and VIIIc, respectively. None of the positionally isomeric adducts, IXb and IXc, could be detected, although 5% could have been missed. Structural assignments are based on nmr spectroscopy. The spectra of both compounds show an AB pattern (2 H) at or near δ 3.05 for the CH_2 group and a broad singlet at ~5.7 (1 H) for $CHOCH_3$. Comparison of the chemical shifts of these moieties with those of the methylene groups in VII, X, and XI indicates that the CH_2's in VIIIa and VIIIb are not adjacent to nitrogen and that the methine hydrogens must be α to both the oxygen and nitrogen.

Reactions of isoprene with Ib and Ic were not stereospecific. Approximately equal amounts of the isomeric cycloadducts X and XI were obtained. The major adduct obtained from Ib and isoprene (60% of the total) could be isolated and was assigned structure Xb. The assignment was based primarily on a double-resonance experiment. Decoupling of the C–CH_3 absorption resulted in the appearance of the highest field proton of the C(Ph)CH_2 methylene group as a doublet of doublets (J_{gem} = 17, J_{vic} = 2.7 Hz)[16] This experiment strongly implies that this methylene and the vinylic methyl group are homoallylic to one another (CH_3–C=CCH_2R) since only second-order coupling (<1 Hz) is expected from the relationship $CH_3(RCH_2)C{=}C<$.



(13) (a) L. E. Miller and D. J. Mann, *J. Amer. Chem. Soc.*, **73**, 45 (1951); (b) L. E. Miller and C. J. Strickler, *ibid.*, **76**, 698 (1954).

(14) P. Laszlo and P. von R. Schleyer, *ibid.*, **86**, 1171 (1964). The size of the coupling is directly related to the dihedral angle between vicinal hydrogens: M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

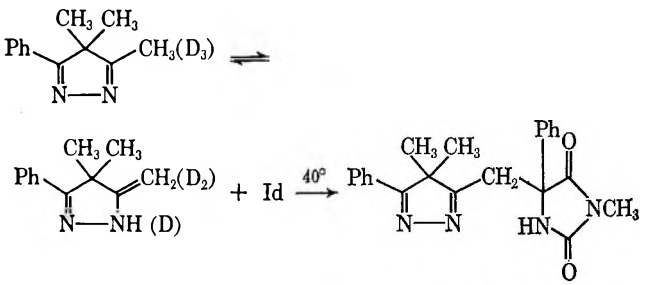
(15) (a) G. I. Poos and M. M. Lehman, *J. Org. Chem.*, **26**, 2575 (1961); (b) K. Alder, F. Brochhagen, C. Kaiser, and W. Roth, *Justus Liebigs Ann. Chem.*, **593**, 1 (1955).

(16) The vicinal coupling $=CH_a-CH_r-$ in cyclohexene is 3.1 Hz and in cyclopentene, 2.7 Hz: P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 2017 (1963).

The isomeric adducts Xc and XIc could not be separated nor could the nmr patterns be readily deciphered. Careful examination of the C–OCH_3 absorptions, however, revealed two signals of roughly equal intensity which indicated an approximately 1:1 ratio for Xc and XIc.

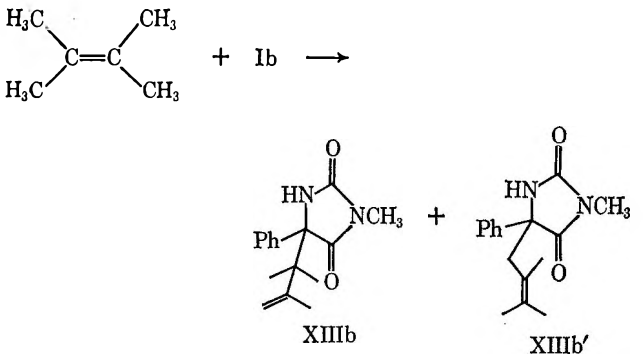
A number of attempts were made to hydrolyze the cycloadducts IV, V, VIIb, and VIIc, and their dihydro derivatives. Hydrolysis of hydantoins is a general technique for the synthesis of α-amino acids,[17] and in the case of IVb and IVc the amino acids would have been novel ones: 2-aza-3-carboxybicyclo[2.2.1]heptane derivatives. The highly substituted hydantoins IV, V, and VII and their dihydro derivatives proved exceedingly difficult to hydrolyze. They were not attacked by acids or bases under mild conditions, and even under severe conditions, 150–200° in alcoholic KOH, only partially hydrolyzed products were obtained from the hydantoins.

In addition to their dienophilic activity, the dehydrohydantoins also undergo ene-type reactions with cyclohexadiene and 3-phenyl-4,5,5-trimethylisopyrazole to afford VIb and XIIb, respectively. Simple olefins such as tetramethylethylene and cyclohexene did not react at 25°, and cyclohexene did not add even at 80° (40 hr).



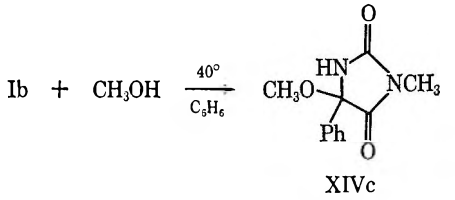
XIIIb

A photo ene reaction occurred with tetramethylethylene affording the adduct XIIIb; the double-bond isomer XIIIb was apparently present but could not be isolated. In all of these cases, the direction of addition appears to be exclusively that shown, with C–C and N–H bond formation.



XIIIb XIIIb′

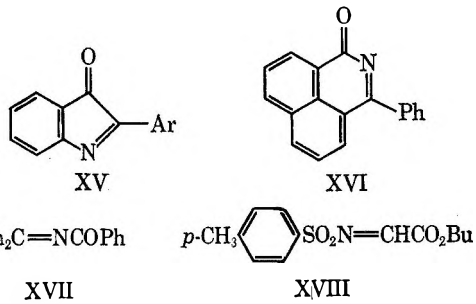
Reaction of the dehydrohydantoins Ia–c with protic reagents is rapid. The order of reactivity is Ia > Ic > Ib. Even with Ib, however, reaction with water or methanol was fast at 40°; addition of methanol to Ib in benzene was followed by nmr spectroscopy and was complete within 30 min at 39°. The dehydrohydantoins do not decompose rapidly in dry air.



XIVc

Discussion

Properties of the Dehydrohydantoins.—The dehydrohydantoins Ia–c are the first reported examples of cyclic α-diacylimines.[5] There have been, however, several studies of cyclic C- or N-monoacylimines; among the compounds studied, only the highly arylated or heteroatom-substituted examples such as XV[18] and XVI[19] were isolable. Less highly substituted derivatives were generally unstable, and only limited circumstantial evidence for their existence was available.[19,20] Several acylic N-acylimines have also been reported,[9,21] but again only specially substituted examples such as XVII[22] and XVIII[23] appear to have significant stability.



XV XVI

$Ph_2C{=}NCOPh$ $p\text{-}CH_3C_6H_4SO_2N{=}CHCO_2Bu$

XVII XVIII

We have observed that the ambient stability of the dehydrohydantoins depends significantly on the substituent on the C=N bond. The 5-phenyl derivative Ib is isolable, thermally stable, and easily handled, although retaining substantial reactivity in polar and cycloaddition reactions. The 5-carbomethoxydehydrohydantoin (Ic) and the unsubstituted compound Ia are progressively less stable. The observed trend in the stability of the dehydrohydantoins is in the direction expected from both steric and electronic considerations; bulky 5 substituents or those capable of conjugation should and do deactivate the imine linkage to attack by nucleophiles.

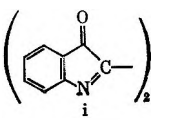
The extent of interaction of the C=N with the carbonyls in the 2 and 4 positions and with the 5 substituent was assessed by comparison of Ib's ultraviolet spectrum with those of similarly substituted maleimides.

(17) J. P. Greenstein and M. Winitz, Ed., "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961.

(18) H. S. Ch'ng and M. Hooper, *Tetrahedron Lett.*, 1527 (1969).

(19) A. Warshawsky and D. Ben-Ishai, *J. Heterocycl. Chem.*, **6**, 681 (1969).

(20) Dehydroindigo (i), a well-studied compound, is formally a C-acylimine; however, the imine moiety is part of a 1,4-diazadiene unit.



i

(21) (a) D. Pawellek, *Angew. Chem., Int. Ed. Engl.*, **5**, 845 (1966); (b) W. Lwowski and G. T. Tisue, *J. Amer. Chem. Soc.*, **87**, 4022 (1965); (c) Yu. Z. Zeifman, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. Nauk. SSSR*, 2046 (1965).

(22) G. Reddelien and H. Danilof, *Chem. Ber.*, **54**, 3132 (1921).

(23) R. Albrecht and G. Kresze, *ibid.*, **98**, 1431 (1965).

TABLE I
ULTRAVIOLET AND INFRARED ABSORPTIONS OF Ib AND ITS ANALOGS

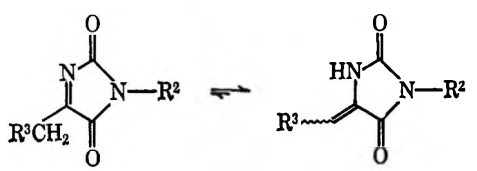
Compd	Infrared absorption: γC=N or C=C, cm⁻¹	Infrared absorption: Solvent	Ultraviolet absorption (max): nm (ε)	Ultraviolet absorption (max): Solvent
Ib	1590, 1563	$CHCl_3$	284 (9600)	CH_3CN
			325 (4925)	
3-Phenyl-2-azanaphthoquinone[a]	1660, 1572	Nujol	316 (10,200)	CH_2Cl_2
			500 (200)	
3-Phenyl-1-isopropylmaleimide			223 (12,400)[b]	95% EtOH
			270 (9400)	
			342 (3500)	
3-Phenylmaleic anhydride			216 (9600)[b]	Isooctane
			240 (3200)	
			312 (10,200)	
1-Isopropylmaleimide			217 (12,300)[b]	Isooctane
			223 (10,800)	
			301 (520)	
5-Benzylidenehydantoin[c]			255 (3400)	
			320 (23,400)	
XVI	1640[d]	$CHCl_3$		
XVIII	1625[e]			
2-Phenylpyrazoline-1	1615[f]	Film		

[a] Reference 5b. [b] C. S. Rondestvedt, Jr., M. J. Kalm, and O. Vogl, *J. Amer. Chem. Soc.*, 78, 6115 (1956). [c] Reference 7. [d] Reference 19. [e] Reference 23. [f] M. C. Kloetzel, J. L. Pinkus, and R. M. Washburn, *J. Amer. Chem. Soc.*, 79, 4222 (1957).

The data in Table I indicate that Ib is a cross-conjugated system identical with its olefinic analogs. Both Ia and Ic appear to be colorless, as are their olefinic analogs.

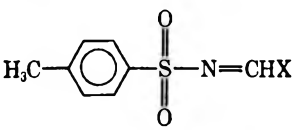
Infrared spectroscopy provides further evidence of conjugation between the imine carbonyls and the 5 substituent. The intense doublet at 1590 and 1563 cm^{-1} can be assigned to the C=N stretch by virtue of its position and the absence of such absorptions in the spectra of IIb–XIIIb. Both the unusually low frequency and the high intensity of these bands are indicative of resonance interactions.

It is of interest at this point to comment on the position of the equilibrium between 5-alkyldehydrohydantoins and the 5-methylene (enamide) tautomers.[5] The isolation of the 5-methylene isomers exclusively under

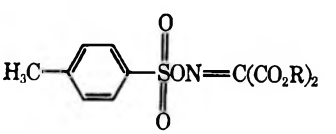


what must have been equilibrating conditions indicate that the equilibrium lies very far to the right.[5,6,8] Our results, which indicate that 5-alkyldehydrohydantoins should have limited atomospheric stability, support this since reaction of the 5-alkyldehydrohydantoin tautomer would lead to rapid deterioration of the samples. In most monounsaturated five-membered rings, the isomer with the double bond exocyclic to the ring has substantial stability;[24] however, in the hydantoin series the equilibrium lies far in this direction. The most important factors in driving this equilibrium toward the enamide are probably the energy gained by delocalization of the nonbonding electrons on the 1-N into the adjacent carbonyl and the formation of an N–H bond; this and the delocalization energy of the α,β-unsaturated amide must be large enough to counterbalance any benefit due to delocalization of the π electrons in the cross conjugated dehydrohydantoin.

Cycloaddition Reactions.—There are two reports in the literature of acylic imines with dienophilic reactivity. Kresze and Albrecht observed in 1964[23,25] that N-trichloro-, N-trifluoro- and N-carbobutyloxylethylidene *p*-toluenesulfonamides



where X = CCl_3, CF_3, or CO_2Bu, underwent the Diels–Alder reaction with various dienes at 80°. From their data one can estimate that these are active dienophiles. Sometime after our researches in the area had begun, Biehler, *et al.*,[26] reported that certain derivatives of isonitrosomalonic esters, *e.g.*



reacted with cyclopentadiene at 25°. This work unfortunately does not give a good indication of dienophilic activity since cyclopentadiene is the most reactive simple diene by several orders of magnitude.[3] The study is of considerable interest, however, since the cycloadducts should be readily hydrolyzable to amino acids.

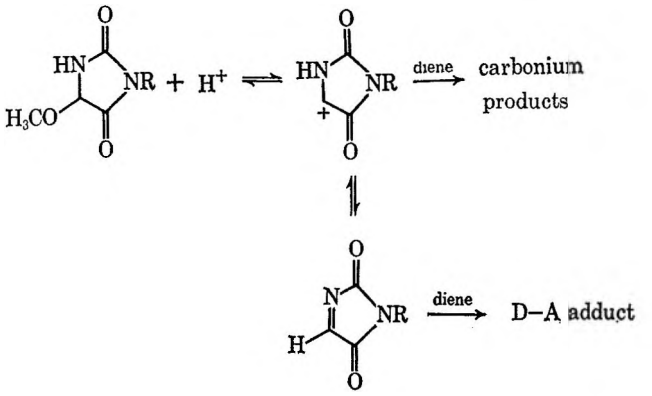
Very recently Goldstein and Ben-Ishai[5a] communicated that reaction of various 3-substituted 5-methoxyhydantoins at 80° with acids in the presence of dienes affords satisfactory yields of Diels–Alder adduct. In certain cases products of carbonium ion reactions between the hydantoin and diene were also observed. Their results can be interpreted, in the light of our data, as due to the reversible formation of the 3-substituted dehydrohydantoins by way of the 5-carbonium ions.

(24) Itaconic anhydride is stable at ambient temperatures but under equilibrating conditions is converted to citraconic anhydride: R. L. Shriner, S. G. Ford, and L. J. Roll, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 368; W. G. Barb, *J. Chem. Soc.*, 1647 (1955).

(25) G. Kresze and R. Albrecht, *Chem. Ber.*, 97, 490 (1964).

(26) J.-M. Biehler, J.-P. Fleury, J. Perchais, and A. Regent, *Tetrahedron Lett.*, 4227 (1968).

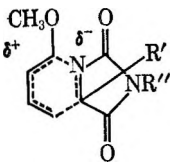
Reaction of the dehydrohydantoins or the ions with dienes are slower than reaction with methanol but are irreversible. This system is useful for the preparation



of certain cycloadducts of dehydrohydantoins. Its limitations result from the presence of methanol and acid which preclude observation or isolation of the dehydrohydantoin and the utilization of most heteroatom-substituted dienes.

The dehydrohydantoins Ia–c are reactive dienophiles, surpassing the previously reported acyclic imines and the cyclic monoacylimines in their activity. This appears to be true even for Ib in which the phenyl group affords a substantial steric hindrance to cycloaddition. The increase in activity obtained by incorporation of the imine moiety into a five-membered ring is consistent with results obtained with olefins and azo systems.[2] Attempts to compare the activity of comparably substituted C=C, C=N, N=N dienophiles are not wholly successful owing to the difficulty of evaluating the parent dehydrohydantoin system, Ia. The 5-phenyl-3-methyldehydrohydantoin appears to be more reactive with isoprene than 3-phenylmaleic anhydride by a factor of 5–10 and less reactive than N-phenylmaleimide by a similar amount. The 5-carbomethoxy-3-benzylhydantoin is substantially more reactive with isoprene and 1-methoxybutadiene than is maleic anhydride or N-phenylmaleimide and appears to be comparable in reactivity to an extremely active diene such as tricyanoethylene.[27] The high reactivity of Ic is, in part, accounted for by the presence of three electron-withdrawing substituents. Observations made by Sauer and coworkers[2] indicate that a 1,1,2 arrangement of cyano groups on an olefin is much more strongly activating ($>10^3$ times) for Diels–Alder addition than is a 1,2 arrangement. Quantitative data on triacyl olefins are not available for comparison with Ic; however, Russian work indicates that ethylidenemalonate is more reactive than maleic anhydride.[28] Unfortunately, data on Ib and Ic cannot be extrapolated with much confidence to the case of Ia, although our feeling is that Ia's activity is intermediate between that of N-phenylmaleimide and 4-phenyl-1,2,4-triazoline-3,5-dione, but closer to the former.

Reaction of 1-methoxybutadiene with either Ib or Ic affords only the cycloadduct with the methoxyl group α to nitrogen and probably *trans* to the phenyl or carbomethoxyl substituent. The observed regioselectivity has an analogy in the reports that 1-substituted butadienes (both electron-donating and -withdrawing substituents) react with monoacyl ethylenes to form primarily the 1,2-disubstituted cyclohex-3-enes.[29] The explanation for the orientational selectivity in the carbocyclic systems is not known. In our reactions the preference is consistent with the contribution of polar structures to the transition state since charge delocalization is most favorable for XIXc. Other evidence (*vide infra*) indicates that the transition and ground



XIXb, R′ = Ph; R″ = CH_3
c, R′ = CO_2CH_3; R″ = CH_2Ph

states have similar polarities; however, the reactants used in these studies have dipoles and so a transition structure with some small amount of polar character is possible. The stereochemical relationship of the methoxyl and R′ groups cannot be rigorously deduced from the nmr spectrum; however, a *trans* relationship is predicted by the Woodward–Hoffmann rules[30] and is expected from the earlier empirical correlations of Alder.[29a]

Reactions of isoprene with either Ib or Ic show little selectivity and afford roughly equal amounts of the two positional isomers. In contrast, the reaction of isoprene with either 3-phenyl- or 3-*p*-nitrophenylmaleic anhydride[13] or with N-carbobutyloxyethylidene-*p*-toluenesulfonamide[25] is highly stereospecific affording the isomer with methyl and aryl groups in a *para* relationship. Consideration of the various alignments of isoprene with Ib, Ic, and the dienophiles cited above does not reveal a single transition state that is as highly favored by electronic considerations as is XIX.

A perturbational MO method has recently been applied with some success to the prediction of isomer mixtures from the reaction of unsymmetrical dienes and dienophiles.[31] However, the technique was utilized for substantially simpler systems. The complexity of the dienophiles considered here makes the contradictions between our results and those of Miller[13] and of Kresze[23,25] unexceptional.

The rates of reaction of Ib and 1-methoxybutadiene in solvents with very different dielectric constants (CD_3CN and C_6D_6–$CDCl_3$) were essentially the same. A more detailed investigation of solvent effects was not made because of the anticipation of severe problems due to reaction of Ib with the solvents. The indication is, however, that there is little charge separation in the transition state.

The characteristic features of the reaction between dehydrohydantoins and dienes are the regiospecificity of product formation (in nearly all cases), the apparent absence of solvent effects, and the rate enhancement caused by electron-donating groups on the diene.

(27) Reaction rate of tricyanoethylene with cyclopentadiene is fast: $k = 4.8$ l. mol^{-1} sec^{-1}.[2b]

(28) B. A. Arbusov and E. G. Kataev, *Zh. Org. Khim.*, **20**, 68 (1950).

(29) (a) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937); (b) M. G. Ettlinger and E. S. Lewis, *Tex. J. Sci.*, **14**, 58 (1962); (c) J. C. Martin and R. K. Hall, *Chem. Rev.*, **61**, 537 (1961).

(30) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965); *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

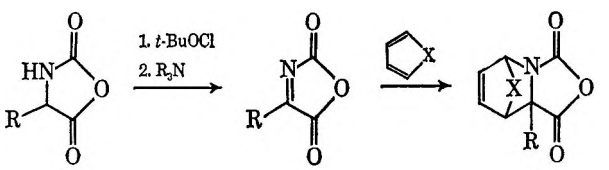
(31) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968).

These same phenomena are prominent in the concerted 4 + 2 cycloaddition[30] of olefins to dienes, and the two reactions appear to have the same mechanism.[32]

The ene-type additions of Ib with cyclohexadiene, 3-phenyl-4,4,5-trimethylisopyrazole, and tetramethylethylene (photochemically) are among the first examples of this reaction with imines.[33] The activity of α-diacylimines in the ene reaction appears to be intermediate between that of the olefinic[34] and azo analogs.[35] Neither cyclohexadiene nor 3-phenyl-4,5,5-trimethylisopyrazole form ene adducts with maleic anhydride under conditions close to those at which Ib reacts. On the other hand, 4-phenyl-1,2,4-triazoline-3,5-dione reacts with simple olefins even at −78°,[35b] although no ene products are formed with dienes capable of undergoing 4 + 2 cycloadditions.[2] A higher ratio of k(ene)/k(cycloaddition) for diacylimines than for diacyl olefins or azo compounds is reasonable since the transition state for the ene reaction is unsymmetrical. The higher absolute rate of ene addition for Ib than for maleic anhydride is explicable in terms of the favorable energetics of formation of an NH bond in the case of Ib.

The inability to hydrolyze the Diels–Alder adducts IV–VII or their dihydro derivatives to the amino acids was a disappointment. Numerous techniques successful for less highly substituted hydantoins were useless here.[36] We attribute the unusual solvolytic behavior of the compounds in this study to the complex and bulky substituents which inhibit the approach of nucleophiles to the carbonyl groups.

Several attempts were made to synthesize derivatives of the anhydride XX by a halogenation–dehydrohalogenation sequence starting from Leuch's anhydrides. Cycloadducts of XX are expected to be readily hydrolyzable. However, all attempts to prepare XX were unsuccessful. The recent work of Biehler, *et al.*, provides an amine dienophile that is more convenient for cases where the amino acid derivable from the cycloadduct is of interest.



The addition of nucleophiles to simple imines are facile reactions,[37] and, as expected, the presence of electron-withdrawing groups accelerates the rate of such additions substantially. There have been several studies of the reaction of nucleophiles with acyl- and sulfonylimines.[19,21c,23,38] We have, accordingly, not studied the addition of nucleophiles to dehydrohydantoins in detail. The mild conditions under which methanol adds to even Ib and the atmospheric instability of Ia and Ic indicates the ease with which such reactions occur. The reactivity of Ia–c should be similar to that of N-acylimines since attack of nucleophiles occurs on the carbon end of the imine bond affording the stabilized amide anion. The reactivities of Ib, 3-phenyl-2-azanapthoquinone,[5b] and XVI[19] toward methanol appear to be comparable.

(32) For recent discussions of the mechanism of the Diels–Alder reaction, see ref 2 and 30, and also A. Wasserman, "Diels–Alder Reactions," Elsevier, Amsterdam, 1965.

(33) After the completion of this manuscript, a report appeared of the reaction of 3-benzyl-5-methoxyhydantoin with olefins at 80° in the presence of acids. The results suggest that the 5-carbonium ion and the dehydrohydantoin have both been generated and have reacted with the olefin present. Some of the additions are probably by an ene mechanism: D. Ben-Ishai and G. Ben-Et, *Chem. Commun.*, 1399 (1969).

(34) K. Alder and M. Schumacher, "Fortschritte der Chemie Organishen," Part I, W. Forest, Ed., Verlag Chemie, Berlin, 1943, p 251.

(35) (a) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962); (b) W. H. Pirkle and J. C. Stickler, *Chem. Commun.*, 760 (1967).

(36) Hydantoins are easily hydrolyzed when lightly substituted; however, highly substituted systems resist hydrolysis: H. Aspelund and P. Waselius, *Acta Acad. Abo., Math. Phys.*, **27**, 18 (1967); *Chem. Abstr.*, **68**, 49512M (1968); M. Lora-Tamayo, R. Madronero, and C. Ochoa, *An. Quim.*, **64**, 591 (1968); *Chem. Abstr.*, **69**, 106154 (1968).

(37) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

Experimental Section

All experiments were carried out in a moisture-free, nitrogen atmosphere, unless otherwise indicated. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or ERA, Brussels, Belgium. Mass spectra were obtained by I. R. Ladd, Union Carbide Research Institute, Tarrytown, N. Y. Nmr studies at 220 Hz and decoupling studies at 60 Hz were carried out by Dr. E. B. Whipple and M. Ruta of the Union Carbide Research Institute.

Hydantoins IIa, b.—3-Methylhydantoin (IIa) was prepared by reaction of methyl isocyanate and glycine ethyl ester to form the ethyl ester of methylhydantoic acid, followed by cyclization in hot hydrochloric acid.[39] Yields based on the glycine ethyl ester were 40–50%. Methylation of hydantoin (Eastman) with methyl sulfate in aqueous sodium hydroxide[40] afforded IIa in 20–30% yield.

Reaction of 5-phenylhydantoin (K and K) with methyl sulfate in aqueous base afforded 5-phenyl-3-methylhydantoin (IIb) in 50–65% yields.

3-Benzyl-5-carbomethoxyhydantoin (IIc).—A solution of 100 g of hydantoin in 500 ml of 2 *M* NaOH was treated in a dropwise fashion with 220 ml of benzyl chloride. The reaction mixture was then heated at reflux for 20 hr. Cooling and pouring onto ice afforded 40 g of crystalline material. Drying and recrystallization from benzene gave 35 g of 3-benzylhydantoin.

Addition of 9.5 g of the 3-benzylhydantoin to 50 ml of a 2 *M* solution of $MgCO_3$ in dimethylformamide saturated with CO_2[41] and heated for 3 hr at 80° afforded a gelatinous, crystalline precipitate. This was poured into 250 ml of dry ether, the ether was decanted from the crystals, and 200 ml of cold methanol (−78°) saturated with HCl was added. The reaction mixture was then stirred overnight. Filtration yielded 4.3 g of colorless crystals, mp 137–141°. Recrystallization from benzene gave 3.7 g (38%) of 3-benzyl-5-carbomethoxyhydantoin as colorless crystals, mp 140–142° (lit.[41a] mp 134–136°).

Attempts to prepare 3-benzyl-5-acetylhydantoin by a similar technique[41a] were unsuccessful.

1-Chlorohydantoins IIIa–d.—Compounds IIa–c were chlorinated in an identical manner except that acetonitrile was utilized as the solvent with IIc. The reactions were run in the atmosphere. A solution of 1.00 g (5.3 mmol) of IIb was slurried in 25 ml of methanol and 0.6 g of *t*-BuOCl (K and K) diluted to 5 ml with benzene added dropwise. Removal of a sample of the reaction mixture after 2 hr and examination by infrared spectroscopy ($CHCl_3$) indicated the absence of N–H bonds (no absorption at 3450 and 3250 cm^{-1}). The nmr spectra ($CDCl_3$) contained a singlet at δ 5.3 (CH–N) establishing that chlorination had occurred at the 1 position (on N). Removal of the volatiles on a rotary evaporator afforded IIIb as colorless crystals, mp 122–124°, which were dried *in vacuo* [50° (0.02 mm)] prior to use.

Reaction of Ia and Cyclopentadiene.—A solution of 0.5 g (4.3 mmol) of IIIa in 10 ml of benzene was added dropwise to a solution of 6 ml of cyclopentadiene (freshly cracked), 0.5 ml of triethylamine, and a few milligrams of hydroquinone in 10 ml of benzene at 25°. The solution remained clear throughout most of the addition, but after a further 2 hr it turned yellow and a precipitate formed. Removal of the solvent *in vacuo* and ex-

(38) R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, **97**, 483 (1964).

(39) J. R. Bailey, *J. Amer. Chem. Soc.*, **26**, 1006 (1904).

(40) A. Kjaer, *Acta Chem. Scand.*, **4**, 893 (1950).

(41) (a) H. Finkbeiner, *J. Org. Chem.*, **30**, 3414 (1965); (b) French Patent 1,389,841 (Feb 19, 1965); *Chem. Abstr.*, **62**, 16258 (1965).

amination of the residue by nmr ($CDCl_3$) revealed two singlets in the N-CH_3 region, at δ 3.03 and 2.91. Chromatography of the residue on Florisil using benzene–chloroform as the eluent afforded 0.075 g of colorless oil, which was homogeneous by tlc (silica gel; $CHCl_3$–CH_3OH). Attempts to crystallize the oil were unsuccessful. The nmr spectrum ($CDCl_3$) of the material had absorption at 1.88 (m, CH_2), 2.90 (s, NCH_3), 3.58 (m, =C—CH), 4.28 (d, J = 3.1 Hz, NCHCO), 4.75 (m, =CCHN), 6.34 (m, CH=CH). The infrared spectrum ($CHCl_3$) had bands at 1780 and 1710 cm^{-1}. The spectral data are in agreement with the structure IVa: 4-methyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione.

The yield was not improved by variation in the reaction conditions. Reaction with other dienes were unsuccessful.

5-Phenyl-3-methyldehydrohydantoin (Ib).—A well-stirred suspension of 1.15 g (5.3 mmol) of 1-chloro-5-phenyl-3-methylhydrohydantoin (IIIb) in 25 ml of benzene (dried over sodium wire) was treated in a dropwise fashion with a solution of 0.59 g (5.1 mmol) of tetramethylethylenediamine in benzene. A yellow color was observed after the first drop and became increasingly more intense. After the completion of addition, the reaction mixture was stirred for an additional 30 min and the yellow solution decanted into a second flask *via* a Tygon tube fitted with a glass wool plug. The solution of Ib was either utilized directly or was worked up. Isolation of Ib was accomplished by removal of the volatiles *in vacuo* [25° (0.02 mm)], insertion of a cold finger into the flask, and sublimation [60° (0.02 mm)]. The isolated yield of yellow, crystalline Ib, mp 148–150°, was 0.65 g (66%). The melting point was not changed by repeated sublimation. The product could be handled and even stored for several days in the atmosphere.

Reaction of Ib with Cyclopentadiene.—A slurry of IIIb (prepared from 51.5 mmol of IIb) in 50 ml of benzene was added dropwise to a solution of 3.24 ml of tetramethylethylenediamine, 20 ml of freshly distilled cyclopentadiene, and a trace of hydroquinone in benzene. The solution became yellow-brown and was stirred overnight. After removal of the volatiles the reaction mixture was worked up by column chromatography (Florisil, hexane–chloroform) and afforded 9.1 g (68%) of crystalline material, mp 115–118°. Recrystallization from ether–hexane afforded 8.8 g of colorless crystals, mp 118–119°, which were identified as 6-phenyl-4-methyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (IVb).

Hydrogenation of IVb in EtOAc over Adams catalyst (1 atm of H_2) afforded the dihydro derivative of IVb, 6-phenyl-4-methyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-3,5-dione, in quantitative yield, mp 157–158°.

Reaction of Ib with Cyclohexadiene.—A solution of 0.100 g (0.53 mmol) of Ib and 1 ml of cyclohexadiene was stirred at 40° for 10 hr. Removal of the solvent *in vacuo* and examination of the residue by nmr spectroscopy ($CDCl_3$) indicated the presence of two products (two N-methyls, at δ 2.88 and 3.0) in the ratio of 4.5:1. The minor product, mp 216–218°, was isolated by column chromatography and recrystallized from $CHCl_3$; it was identified (see Table II) as 5-(cyclohexa-2,5-dienyl)-5-phenyl-3-methylhydantoin (VIb). The major product crystallized from hexane–chloroform, mp 210–211°, and was identified as the cycloadduct, 6-phenyl-4-methyl-2,4-diazatricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (Vb).

Reaction of Ib and 2,3-Dimethylbutadiene.—The reaction was carried out as described for cyclopentadiene except that the starting material was 25.6 mmol of IIb and the reaction mixture was heated overnight at 60°. The yield of crude 6-phenyl-3,4,8-trimethyl-1,8-diazabicyclo[4.3.0]non-3-ene-7,9-dione (VIIb) was 4.34 g (60%). Recrystallization from ether–hexane afforded 3.8 g of colorless crystals, mp 159.5–162°.

1-Methoxybutadiene and Ib.—To a solution of 5.0 ml of 1-methoxybutadiene and a few milligrams of hydroquinone in 10 ml of dry benzene at 25° was added 0.450 g (2.4 mmol) of sublimed Ib. The yellow color of the solution faded rapidly and a precipitate formed. The reaction was complete within 90 min. The initial precipitate was 0.280 g of crystalline material, mp 147–150°. Removal of the volatiles on a rotary evaporator left a yellow oil. Trituration with ether–pentane afforded an additional 0.305 g. The combined precipitate, 0.585 g (86%), showed a single spot in tlc (silica gel; benzene–2-propanol, 9:1). Recrystallization afforded colorless crystals, mp 157–159.5°. The infrared ($CHCl_3$) had bands at 1775, and 1715 and 1070 cm^{-1}, among others. The nmr spectrum ($CDCl_3$) had absorptions at δ 3.02 (s, NCH_3), 3.51 (s, OCH_3), 5.72 (m, $CHOCH_3$), 5.75–6.1 (m, 2 CH=), and 7.43 (m, 5) as well as an AB pattern centered at δ 3.0. The 220-MHz spectrum resolved the AB pattern and permitted determination of the couplings; the geminal coupling is 16 Hz and the low-field AB proton is coupled, J_{vic} = 7 Hz, to the low-field vinylic hydrogen while the high-field AB proton and the $CHOCH_3$ show only small coupling (1–2.5 Hz) with the vinylic hydrogens.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.95; N, 10.29; O, 17.83. Found: C, 66.32; H, 5.86; N, 10.17.

A solution of 0.063 g (0.33 mmol) of Ib and 0.020 g (0.24 mmol) of 1-methoxybutadiene in 0.50 ml of benzene-d_6 and $CDCl_3$ (1:1) was placed in the probe of the A-60 mass spectrometer (39°), and the disappearance of Ib and the formation of VIIIb were followed by repeated integration of the OCH_3 and NCH_3 absorptions. After 35 min, 50% of Ib had reacted. The rate of disappearance of 0.064 g of Ib in the presence of 0.020 g of 1-methoxybutadiene in 0.5 ml of CD_3CN was followed similarly; 50% of Ib had reacted at the end of 30 min. In neither case were products other than VIIIb formed in observable concentrations.

Isoprene and Ib.—A solution of 0.100 g (0.53 mmol) of Ib and 2 ml of isoprene in 10 ml of dry benzene was heated at 40° for 12 hr. The yellow color of the solution gradually faded and a fine white precipitate (polymer) formed. After removal of the volatiles, the crude reaction mixture was examined by nmr spectroscopy. The spectrum ($CDCl_3$) contained, among other signals, absorptions at δ 1.66 and 1.47 (=CCH_3) with an area ratio of 3:2. The reaction mixture was chromatographed on Florisil and a homogeneous, crystalline fraction, 0.102 g (75%), obtained. Crystallization from chloroform–hexane resulted in the selective precipitation of the major isomer, mp 131–133°. The infrared spectrum had bands at 1770 and 1710 cm^{-1}. The nmr spectrum ($CDCl_3$) had absorptions at δ 1.73 (m, =CCH_3), 3.07 (s, NCH_3), 5.42 (m, 1), and 7.42 (m, 5) in addition to AB patterns centered at δ 2.77 and 4.12. The protons of the high-field AB pattern absorb at δ 2.54 and 2.95 with J_{gem} = 16 Hz while in the low-field pattern the protons absorb at δ 4.54 and 3.62 and J_{gem} = 19 Hz. Decoupling of the C-methyl group led to sharpening of the proton at δ 2.54 into a doublet, J = 2.7 Hz, due to coupling with the vinylic hydrogen. The major isomer is accordingly assigned structure Xb, 5-phenyl-3,7-dimethyl-1,8-diazabicyclo[4.3.0]non-3-ene-7,9-dione. Subsequent crystalline fractions contained a mixture of both isomers.

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.11; H, 6.21; N, 10.89.

Competition between Ib and N-Phenylmaleimide for 2,3-Dimethylbutadiene.—A solution of 0.100 g (0.53 mmol) of Ib, 0.0935 g (0.54 mmol) of N-phenylmaleimide, and 45 μl (0.40 mmol) of 2,3-dimethylbutadiene was stirred for 16 hr at 25°. Removal of the solvent *in vacuo* and examination of the residue by nmr spectroscopy ($CDCl_3$) revealed absorptions at δ 1.73 (s, CH_3) and 2.48 (m, CH_2) due to 8-phenyl-3,4-dimethyl-8-azabicyclo[4.3.0]non-3-ene-7,9-dione and minor absorptions at δ 1.58 and 3.07 assignable to VIIb. Resonances due to the starting materials were present at δ 3.07 (s, NCH_3) and 6.88 (s, CH=CH). Comparison of the integrals indicates that the ratio of VIIb to the adduct of N-phenylmaleimide and 2,3-dimethylbutadiene is no more than 1:10 and possibly less.

Reaction of Ic and Cyclopentadiene.—A solution of IIIc (prepared from 1.0 g of IIc) in 20 ml of dry benzene was added dropwise at 25° to a solution of 10 ml of cyclopentadiene (freshly distilled), 0.65 ml of triethylamine, and a trace of hydroquinone. The solution became yellow and then tan and a precipitate formed. After 2 hr, the volatiles were removed and the oily residue purified by column filtration (Florisil; hexane–$CHCl_3$ eluent). The crude yield of cycloadduct (homogeneous by tlc on silica gel with chloroform–methanol, 9:1) was 0.98 g (79%). Crystallization from hexane afforded 0.85 g (69%) of colorless crystals, mp 111.5–113.5°, which were identified as 6-carbomethoxy-4-benzyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (IVc) (see Table II).

Reaction of Ic with Cyclohexadiene.—The reaction was carried out exactly as described above except that the reaction mixture was stirred overnight prior to work-up. The crude yield of cycloadduct, mp 107–111°, was 0.580 (60%). Recrystallized material (ether–hexane) had mp 110–111° and was shown to be 6-carbomethoxy-4-benzyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]undec-8-ene-3,5-dione (Vc) (see Table II).

Reaction of Ic with Isoprene.—The reaction was carried out and worked up as above except that 0.320 g (1.15 mmol) of

TABLE II

Compd	Mp, C°	Ir,[a] cm^{-1}	Nmr,[b] δ
IIb	163	3460, 3250 1780, 1720	3.05 (s, 3)[c] 5.28 (m, 1); 7.53 (m, 5)
IIIb	123–125[d]	1795, 1730	
Ib	148–150[e]	1800, 1730 1590, 1563	3.18 (s, 3) 7.3–7.8 (m, 5)
IVb[f]	118–119[g]	1775, 1710	1.25–1.9 (m, 2) (s, 3) 3.63 (m, CHC═), 4.85 (m, NCHC═) 5.92 (m, CH═) 6.52 (m, CH═) 7.27–7.9 (m, 5)
6-Phenyl-4-methyl-2,4-diazatricyclo-[5.2.1.0^{2,6}]deca-3,5-dione[g]	156–158	1775, 1715	1.2–2.2 (7); 3.00 (s, 3) 4.36 (m, 1) 7.3–7.85 (m, 5)
Vb[g]	210–211[h]	1780, 1720	1.1–2.1 (m, 4) 2.85 (s, NCH_3) 3.52 (m, CHC═) 4.98 (m, NCH═) 6.5 (m, 2CH═) 7.3–7.9 (m, 5)
6-Phenyl-4-methyl-2,4-diazatricyclo-[5.2.2.0^{2,6}]undeca-3,5-dione[f]	134–135	1780, 1715	1.1–2.3 (m, 8); 2.78 (m, 1) 4.25 (m, CHN) 2.97 (s, NCH_3) 7.3–7.9 (m, 5)
VIb[f]	216–218[i]	3460, 3300 1775, 1700[j]	2.7 (m, 2) 3.02 (s, NCH_3) 3.8 (m, 1) 5.1–6.1 (m, 4) 7.3–7.9 (m, 5)
VIIb[f]	159.5–162.5[k]	1770, 1710	1.58 (s, 3); 1.7 (s, 3) 2.5–2.9 (m, 2) 3.08 (s, 3) 3.25–3.8 (m, 2) 7.42 (3, Ph)
XIIb[f]	208.5–210[l]	3400, 1785 1715	1.05 (s, 3) 1.38 (s, 3) 3.08 (s, NCH_3) 3.10 (d, 1; J = 17 Hz) 3.62 (d, 1; J = 17 Hz) 7.2–8.2 (m, 11)
XIIb-d_3			1.05 (s, 3); 1.38 (s, 3) 3.08 (s, NCH_3) 7.2–8.2 (10)
XIIIb	206–208[m]	3440, 3240 1770, 1708	1.27 (s, 6) 1.47 (s, 3); 3.01 (s, 3) 5.04 (m, 2) 7.25–7.9 (m, 5)
XIVb[f]	134.5–136[d]	3440, 3250 1790, 1730	3.08 (s, NCH_3) 3.52 (s, OCH_3) 6.6 (m, NH) 7.35–7.9 (m, 5)
IIIc[f]	142–143	3460, 3250 1780, 1720	3.82 (s, 3)[c] 4.67 (m, CHN, NCH_2Ph) 6.7 (m, NH); 7.34 (m, 5)
IVc[f]	111.5–113.5[l]	1790, 1750 1720	1.88 (m, 2) 3.76 (s, 3) 3.9 (m, CH—C═) 4.57 (s, CH_2N) 4.76 (m, NCHC═) 6.35 (m, 2)
Vc[f]	110–111[n]	1790, 1745	1.3–2.1 (m, 4) 3.58 (m, CH—C═) 3.8 (s, OCH_3); 4.61 (s, CH_2N) 4.82 (N—CH═C) 6.37 (m, 2)

[a] In $CHCl_3$ unless otherwise indicated. [b] In $CDCl_3$ unless otherwise indicated. [c] In $(CD_3)_2CO$. [d] Yield 95–100%. [e] Yield 60–70%; mass spectral analysis (70 eV): 188 (36; pp); 131 (17), 103 (100), 77 (6), 76 (14). [g] Yield 70%. [f] Satisfactory combustion analyses (±0.4%) have been obtained for these compounds (Ed.). [h] Yield 53%. [i] Yield, 10%. [j] KBr pellet. [k] Yield 50%. [l] Yield 80%. [m] Yield 20%. *Anal.* Calcd: C, 70.55; H, 7.40. Found: C, 69.95; H, 7.13. [n] Yield 60%.

IIIc, 0.20 ml of tetramethylethylenediamine, and 5 ml of isoprene were employed. The reaction required less than 1 hr at 25°. The cycloaddition products Xc and XIc were obtained after chromatography in a combined yield of 0.167 g (55%). The mixture was a colorless oil which was homogeneous by tlc (silica gel, benzene–2-propanol, 9:1). It could not be crystallized or sublimed.

The nmr spectrum ($CDCl_3$) of the mixture was extremely complex; there were absorptions at δ 1.67 (m, C-CH_3), 3.79 and 3.80 (s, OCH_3), 4.73 (s, CH_2Ph), and 5.49 (m, =CH), in addition to ill-defined multiplets (AB patterns by analogy to Xb and XIb) centered at δ 2.67 and 4.0. The observation of two CO_2CH_3 absorptions of roughly equal intensity at δ 3.80 indicates that the two isomers are present in approximately equal amounts. The infrared spectrum ($CHCl_3$) had absorptions at 1790, 1750, and 1725 cm^{-1}, among others. The mass spectrum (70 eV) had *m/e* 314 (23; pp), 256 (15), 255 (38), 91 (100), and 66 (14) as major fragments.

Reaction of Ic with 1-Methoxybutadiene.—The cycloaddition was carried out as described for isoprene. The reaction was over within 10 min of the completion of addition of IIIc. The yield of chromatographed material (homogeneous by tlc) was 72%, mp 115–118°. The nmr spectrum ($CDCl_3$) of the crude chromatographic residue indicated that a single product was formed; the spectrum ($CDCl_3$) had absorptions at δ 3.41 (s, OCH_3), 3.84 (s, CO_2CH_3), 4.73 (s, NCH_2Ph), 5.67 (m, $CHOCH_3$), 5.83 (m, 1, =CH), and 7.40 (m, 5) as well as an AB pattern whose two protons absorb at δ 2.51 and 3.26. The AB protons are coupled to each other by 16 Hz and the proton at δ 3.26 is split by the lowest field vinylic hydrogen, J = 6 Hz. Recrystallization from methylene chloride–hexane afforded colorless crystals, mp 117–118.5°, identified as 6-carbomethoxy-2-methoxy-4-benzyl-2,4-diazabicyclo[4.3.0]non-3-ene-7,9-dione (VIIIc).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.22; H, 5.47; N, 8.22.

Attempted Hydrolysis of IV, V, VI, and Their Hydrolysis Derivatives.—Various conditions were utilized in an attempt to hydrolyze the Diels–Alder adducts and their dihydro derivatives. The experiments described here are representative. A solution of 1.0 g (3.7 mmol) of Vb and 1.2 g (2.1 mmol) of potassium hydroxide in 20 ml of ethylene glycol was heated under reflux for 70 hr. Removal of the alcohol *in vacuo*, addition of water, and extraction with ether afforded, after removal of the ether solvent, 0.75 g of Vb. Analysis of the residue by tlc (silica gel–10% methanol in chloroform) indicated that several products had been formed but in amounts too small to isolate.

A mixture of 0.50 g of 6-phenyl-4-methyl-2,4-diazatricyclo-[5.2.1.$0^{2,5}$]deca-3,5-dione (IVb-H_2) and 0.6 g (11 mmol) of potassium hydroxide in 20 ml of water was heated at 150° for 2 hr in a bomb. The reaction mixture was extracted with ether and the ethereal solution dried over KOH and evaporated. Examination of the residue by tlc showed a major product in addition to small amounts of starting material. The product's nmr spectrum ($CDCl_3$) had absorption at δ 1.53 (m, ~6), 2.3 (m, 1), 2.78 (d, J = 5 Hz, $NHCH_3$), 3.28 (m, 1), 3.58 (m, 1), 7.36 (m, 5), and 8.1 (br, NHCO). The mass spectrum (70 eV) had *m/e* 230 (0.2; pp), 229 (0.2), 172 (100), 144 (58), 143 (11), 115 (5), 104 (11), 91 (3), and 77 (3), among others. The spectral results indicate partial hydrolysis of the hydantoin and formation of 3-(N-methylcarbamido)-3-phenyl-2-azabicyclo[2.2.1]heptane.

Anal. Calcd for $C_{14}H_{19}N_3O$: C, 73.01; H, 7.88; N, 12.16; O, 6.95. Found: C, 72.69; H, 8.03; N, 12.28; O, 6.99.

Attempts to further hydrolyze the product with aqueous base were unsuccessful; intractable tars were formed. Reaction of IVb-H_2 with aqueous barium hydroxide at 100–150° or with ethylene glycol–potassium hydroxide afforded identical results.

Attempted Preparation of XX.—Under rigorously moisture-free conditions, 2.0 g of carbobenzyloxyphenylglycine (7 mmol) and 1.5 g (7 mmol) of PCl_5 were allowed to react in ether for 40 min at 0°.[42] The reaction mixture was then decanted and the solvent removed *in vacuo*, affording a residue which melted at around room temperature. The residue was dissolved in 20 ml of acetonitrile and then treated with 0.88 g (8 mmol) of *t*-butyl hypochlorite in 5 ml of CH_3CN and stirred overnight. The solvents were removed *in vacuo;* the residue was dissolved in 10 ml of dry benzene and added to 1 ml of cyclopentadiene and 1.1 ml (8 mmol) of triethylamine in benzene. After 3 hr the reaction mixture was poured into ice. Work-up by ether extraction followed by removal of volatiles *in vacuo* afforded an oily residue which was examined by tlc and nmr. The residue contained no adducts of cyclopentadiene and XX or hydrolysis products thereof.

When the chlorination was carried out in *t*-BuOH, polymerization of the Leuch's anhydride was observed.

Attempted Reaction of Ib with Cyclohexene.—A solution of 0.100 g (0.53 mmol) of Ib and 1 ml of cyclohexene (freshly distilled from $LiAlH_4$) in 10 ml of benzene was stirred for 16 hr at 25°. Examination of the infrared spectra of the solution showed that the imine absorptions at 1590 and 1560 cm^{-1} were undiminished. Heating for 60 hr at reflux also failed to effect reaction; the concentration of Ib was unchanged. Examination of the reaction mixture by tlc did not reveal the presence of any products.

Reaction of Ib with 3-Phenyl-4,5,5-trimethylisopyrazole.—A solution of 0.100 g of 3-phenyl-4,5,5-trimethylisopyrazole in 5 ml of benzene was heated at 55°. After 2 hr the reaction mixture contained a new component, on the basis of tlc. The reaction was complete after 16 hr and a crystalline material was present in the flask. Removal of the solvent *in vacuo* and recrystallization of the total residue afforded 0.156 g of colorless crystals, mp 208.5–210°. The structure XIIb was assigned from elemental and spectral analyses (Table II).

Attempted Reaction of Ib with 3,5-Diphenyl-4,4-dimethylisopyrazole.—A solution of 0.100 g (0.053 mmol) of Ib and 0.125 g (0.50 mmol) of 3,5-diphenyl-4,4-dimethylisopyrazole was heated for 72 hr at 60°. Careful examination of the reaction mixture by tlc and infrared spectroscopy (benzene–2-propanol, 9:1) indicated that no reaction had occurred.

Photochemical Reaction of Ib with Tetramethylethylene.—A solution of Ib (prepared from 0.3 g of IIb) and 5 ml of tetramethylethylene (purified by passage through active alumina) in 10 ml of benzene in a quartz tube was irradiated at 10° with an Hanovia high-pressure mercury lamp. The reaction was complete within 12 hr. Examination of the crude reaction mixture by tlc (silica gel; chloroform–methanol, 9:1) revealed a major product with an R_f greater than that of starting material. Column chromatography on Florisil afforded 0.205 g of viscous oil homogeneous by tlc. Fractional crystallization from chloroform–hexane afforded 0.065 g of crystalline material, mp 195–198°. Two recrystallizations from chloroform–hexane gave colorless crystals, mp 206–208°, which were identified by nmr spectroscopy (Table II) as 5-(1,1,2-trimethylprop-2-enyl)-5-phenyl-3-methylhydantoin (XIIIb). The mother liquors could not be induced to crystallize; the nmr spectrum ($CDCl_3$) had absorptions at δ 1.25, 1.40, 1.55, and 2.97 and 7.1–7.8, in addition to bands due to XIIIb.

A control reaction run with identical concentrations of the reactants but in the dark (16 hr at 25°) did not afford an observable concentration of product(s).

Reaction of Ic with Methanol.—A solution of 0.025 g (0.13 mmol) of sublimed Ib in 350 ml of benzene-d_6 was placed in an nmr tube. The solution was then treated with 0.20 ml of methanol and the reaction followed in the nmr cavity (39°). Within minutes two new singlets (other than those for CH_3OH) appeared; one was 2.5 Hz above the CH_3OH and the other was 2 Hz to higher field than the N-CH_3 absorption of Ib. The reaction was complete within 30 min. Removal of the solvent *in vacuo* and crystallization from ether–hexane afforded colorless crystals, mp 134.5–136°. The product was identified as 5-methoxy-5-phenyl-3-methylhydantoin (XIVb).

Registry No.—Ib, 25370-99-4; IIb, 6846-11-3; IIIb, 25371-01-1; IIIc, 25371-02-2; IVa, 25336-83-8; IVb, 25371-03-3; IVb (dihydro deriv), 25371-04-4; IVc, 25371-05-5; Vb, 25336-84-9; Vc, 25371-06-6; VIb, 25371-07-7; VIIb, 25371-08-8; VIIIb, 25371-09-9; VIIIc, 25371-10-2; Xb, 25371-11-3; XIIb, 25371-12-4; XIIb-d_3, 25371-13-5; XIIIb, 25371-14-6; XIVb, 25371-15-7; 3-phenyl-2-azanapthoquinone, 23994-23-2; 5-benzylidenehydantoin, 3775-01-7; 3-(N-methylcarbamido)-3-phenyl-2-azabicyclo[2.2.1]heptane, 25371-18-0; 6-phenyl-4-methyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-3,5-dione, 25371-19-1; 6-phenyl-4-methyl-2,4-diazatricyclo[5.2.2.$0^{2,6}$]undec-3,5-dione, 25371-20-4.

(42) M. Bergmann, L. Zervas, and W. F. Ross, *J. Biol. Chem.*, **111**, 245 (1935).

Alkaline Decomposition of Nitrosohydroxylamine Derivatives[1]

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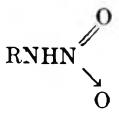
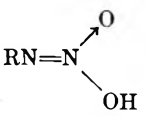
Nitrosohydroxylamine tosylates, $R_2CHN(O)NOSO_2C_7H_7$, are decomposed by potassium *t*-butoxide to the corresponding aldehyde or ketone. They also decompose thermally to olefins. Atempts to prepare analogous acyl derivatives resulted in cleavage to the corresponding esters, $R_2CHOC(O)R'$, and nitrous oxide. Esters also were obtained from nitrosation of O-acyl- or O-sulfonylhydroxylamines.

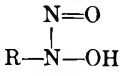
There are five constitutional isomers of compounds with the molecular formula RN_2O_2H.



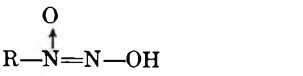
1
(nitramines)



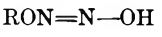
2
(*aci*-nitramines)



3
(nitrosohydroxylamines)



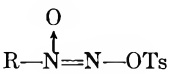
4
(N′-hydroxydiimide N-oxides)



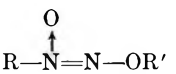
5
(monoalkyl hyponitrite)

Alkyl derivatives of all these isomers are also known.[2] The highlights of the chemistry of nitramines and their *aci* derivatives have been reviewed,[3] but considerably less is known about nitrosohydroxylamines and their tautomers.

Recently it was found that nitrosohydroxylamines could be converted to the tosyl derivatives of **4**.[4] The decomposition of N-alkyl-N′-tosyloxydiimide N-oxides (**6**) by Grignard reagents[4] prompted an investigation of the action of bases on these compounds and also the N′-alkoxy derivatives **7**.

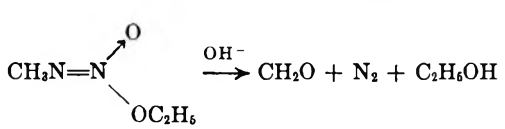


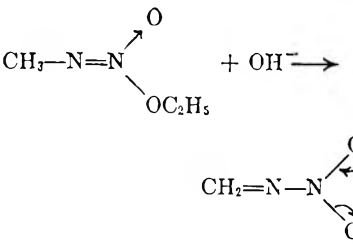
6



7

For comparison with the present results it should be recalled that alkyl derivatives of **1**, secondary nitramines, undergo elimination of nitrous acid when treated with base to yield imines which are hydrolyzed to a mixture of primary amine and aldehyde or ketone.[5] Alkyl "esters" of *aci*-nitramines (**2**) undergo an elimination reaction in base to produce aldehydes, nitrogen, and alcohol.[6] A mechanism for this somewhat unusual reaction[7] was not postulated, but it seems reasonable that nitrosimines, compounds known[10] to decompose to aldehydes and nitrogen, are involved.

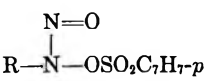




The elimination of the elements of carboxylic acid from a postulated O-acyl derivative of **2** to form a nitrosimine has been suggested,[11] although that intermediate was postulated to yield esters in one case[11a] and carbonyl compounds in another.[11b] Some differences between the chemistry of postulated nitramine derivatives and that observed in this investigation will be pointed out in the discussion.

Structure of Starting Materials.—The structure of the alkylation products of nitrosohydroxylamines has been a subject of some controversy, but it is assumed in this investigation that structure **7** has been established by recent nmr[12] and chemical[13] studies.

The structure of the tosylates **6** had not been established rigorously but was inferred from the structure of the azoxy compounds obtained from their reaction with Grignard reagents.[4] The ultraviolet spectra of the N-phenyl (λ_{max} 222 mμ, ϵ_{max} 32,200; λ_{max} 251 mμ, ϵ_{max} 20,100) and the N-*p*-chlorophenyl (λ_{max} 223 mμ, ϵ_{max} 25,900; λ_{max} 262 mμ, ϵ_{max} 17,400) derivatives are compatible with structure **6**. The alternative structure **8** (tosyl derivative of **3**) would not be expected to show the long-wavelength band. In addition an attempt to prepare **8**, R = CH_3, by the nitrosation of O-tosyl-N-



8

(1) This research was supported under Grant No. 5256 from the National Science Foundation and is based upon the Ph.D. Thesis of L. D. Lillwitz.

(2) Hyponitrous acid derivatives, **5**, are not of interest in this investigation and will not be discussed further. For leading references to their chemistry, see T. Koenig and M. Deniger, *J. Amer. Chem. Soc.*, **90**, 7014 (1968).

(3) (a) A. Lamberton, *Quart. Rev. Chem. Soc.*, **5**, 75 (1951); (b) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, p 490.

(4) T. E. Stevens, *J. Org. Chem.*, **29**, 311 (1964).

(5) W. H. Jones, *Science*, **118**, 387 (1953).

(6) A. H. Lamberton and G. Newton, *J. Chem. Soc.*, 1791 (1961).

(7) It might have been anticipated that the aldehyde would be derived from the O-alkyl group in analogy with similar eliminations of nitrate esters[8] to aldehyde and nitrite ion and nitronate esters[9] to aldehyde and oxime.

(8) J. W. Baker and D. M. Easty, *J. Chem. Soc.*, 1208 (1952).

(9) N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, **86**, 2681 (1964).

(10) C. J. Thoman and I. M. Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968).

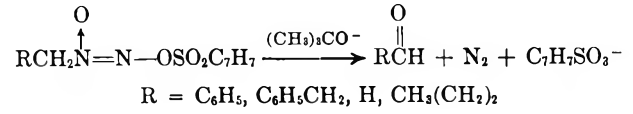
(11) (a) E. H. White and C. A. Aufdermarsh, *J. Amer. Chem. Soc.*, **83**, 1174 (1961); (b) E. H. White and R. J. Baumgarten, *J. Org. Chem.*, **29**, 3636 (1964). A major product of reaction, ethyl pyruvate, is said to originate from the nitrosimine [$Me(CO_2Et)C{=}N{-}N{=}O$].

(12) J. P. Freeman, *ibid.*, **28**, 2508 (1963).

(13) R. B. Woodward and C. E. Wintner, *Tetrahedron Lett.*, 2689 (1969).

methylhydroxylamine yielded only methyl tosylate and nitrous oxide.[14]

Alkaline Decomposition.—Treatment of a series of primary alkyl derivatives of **6** with potassium *t*-butoxide in *t*-butyl alcohol produced the corresponding aldehyde, nitrogen, and tosylate ion.



$$RCH_2\overset{\uparrow}{N}{=}N{-}OSO_2C_7H_7 \xrightarrow{(CH_3)_3CO^-} R\overset{\|}{C}H + N_2 + C_7H_7SO_3^-$$

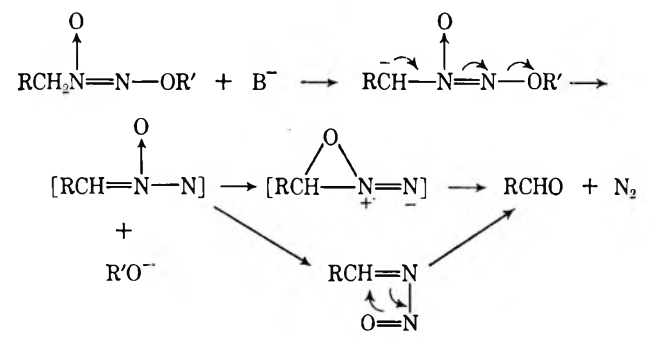
$$R = C_6H_5,\ C_6H_5CH_2,\ H,\ CH_3(CH_2)_2$$

The corresponding O-alkyl derivatives **7** also decomposed but much more slowly and only when the α-methylene group was suitably activated. For example, N-benzyl-N′-methoxydiimide N-oxide (**7**, R = $C_6H_5CH_2$; R′ = CH_3) decomposed during a 6-day period to benzaldehyde and nitrogen. However, N-methyl-N′-ethoxydiimide N-oxide was reported recently[15] to be stable to base. It is of some interest that the presence of two N′-methoxydiimide N-oxide (methoxazonyl)[13] groups so stabilizes the resultant carbanion that no decomposition occurs.[13] The limits of groups that activate α-hydrogen abstraction but do not sufficiently stabilize the resultant carbanion have not been established.

A thorough investigation of other alkyl groups was not made but the secondary derivatives examined, RCH_2 = isopropyl and cyclohexyl, behaved in a similar manner yielding the corresponding ketones. The reactions were more sluggish and the yields lower indicating the incursion of side reactions which were not investigated.

A reasonable path for these decompositions is shown in Scheme I. In an effort to determine if the first step

SCHEME I

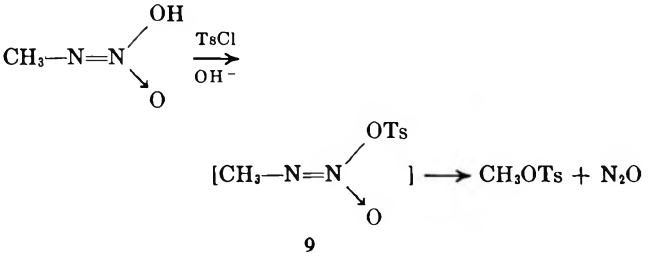


was reversible or possibly concerted with loss of the anion, exchange studies in methanol-O-*d* were carried out with **7** (R = $C_6H_5CH_2$, R′ = CH_3) and in *t*-butyl alcohol-O-*d* with **6** (R = $C_6H_5CH_2$ and $(CH_3)_2CH$). In the former case complete exchange of the benzylic protons was achieved in the presence of sodium methoxide without decomposition. In the latter, using potassium *t*-butoxide, decomposition was apparently faster than exchange as no deuterated material could be recovered.

The oxygen-transfer step is completely speculative, but it appears to be intramolecular since aldehyde formation is not dependent upon a hydrolysis step. Two possible modes of transfer are envisioned. The first is through oxaziridine formation, a common isomerization process for nitrones,[16] followed by nitrogen elimination from a type of intermediate expected to easily lose nitrogen. The second involves isomerization to a nitrosimine, compounds known to decompose readily to aldehydes and nitrogen.[10] The latter intermediate may well be involved since the intense color associated with nitrosimines was observed in several of these reactions. Oxygen transfer from one nitrogen to another has been proposed to account for the formation of N-nitroimines in the nitrosation of many oximes.[17]

In none of the reactions of the tosyloxydiimide N-oxides was there any indication of the solvolysis reactions reported for the corresponding acyloxydiimide N′-oxides.[14a] In the absence of base no decomposition occurred until temperatures of 180° were reached, whereupon thermal elimination of nitrous oxide and toluenesulfonic acid led to the corresponding olefin (when a β-hydrogen was present). Similar thermal decompositions of analogous azoxy compounds have been noted previously.[13,20]

In an attempted synthesis of the tosyl derivative of **2**, **9**, to determine if it were a possible intermediate in the decomposition of the alkyl-N′-tosyloxydiimide N-oxides, only the alkyl tosylate was isolated as expected on the basis of the previous studies of analogous acyl derivatives.[14a] The azoxy tosylates **6** also decomposed



$$CH_3{-}N{=}N(OH)(O) \xrightarrow[OH^-]{TsCl}$$

$$[CH_3{-}N{=}N(OTs)(O)] \longrightarrow CH_3OTs + N_2O$$

9

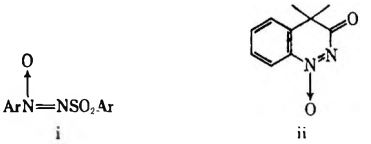
photochemically to yield alkyl tosylate and nitrous oxide. It is tempting to speculate that photochemical isomerization to compounds like **9** is involved in this decomposition. One is tempted to generalize that acyl derivatives of **2** undergo ready solvolysis *via* an oxydiazonium ion while derivatives of the type **6** cannot ionize in this way. The difference is probably associated with the position of the leaving group with respect to the nitrogen atom having the unshared pair of electrons.[21]

(14) (a) This decomposition is reminiscent of the decomposition of N-nitro amides to esters and nitrous oxide [E. H. White and D. G. Grisley, Jr., *J. Amer. Chem. Soc.*, **83**, 1191 (1961)], and (b) of the decomposition of O,N-dibenzoylhydroxylamines upon nitrosation to benzoic anhydride and nitrous oxide [T. Koenig, T. Fithian, M. Tolela, S. Markwell, and D. Rogers, *J. Org. Chem.*, **34**, 952 (1969)].

(15) A. H. Lamberton and H. M. Yusuf, *J. Chem. Soc.*, 397 (1969).

(16) G. R. Delpierre and M. Lamchen, *Quart. Rev. Chem. Soc.*, **19**, 329 (1965).

(17) J. P. Freeman, *J. Org. Chem.*, **26**, 4190 (1961). Oxygen transfer must also be involved in the formation of diazotate ions from azoxy sulfones[18] (i) and azoxycarbonyl derivatives[19] (*e.g.*, ii).



i ii

(18) W. V. Farrar and J. Masson Gulland, *J. Chem. Soc.*, 368 (1944).

(19) R. J. Sundberg and D. E. Blackburn, *J. Org. Chem.*, **34**, 2799 (1969).

(20) T. E. Stevens and J. P. Freeman, *ibid.*, **29**, 2280 (1964).

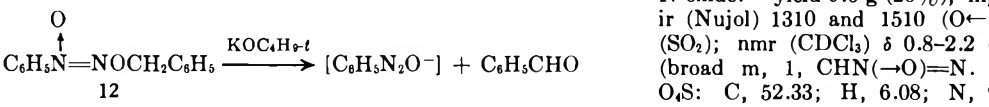
(21) This generalization suggests that the unstable product obtained by the treatment of isobutylnitrosohydroxylamine with 3,5-dinitrobenzoyl chloride was not the derivative of **4** claimed[14a] but rather a derivative of **3** similar to **8**. This point is under investigation.

In connection with this investigation it was of interest to examine the reactivity in base of derivatives of **7** in which the group R did not bear a hydrogen on the N-oxide carbon.[22] Previously it has been reported that N-phenyl-N′-methoxydiimide N-oxide (**10**) (**7**, R = C_6H_5; R′ = CH_3) possessed active hydrogen in the Zerewitinoff determination.[23] This result led to an erroneous structure assignment.

Wintner[24] later challenged the validity of this result and attributed the active hydrogen to N-phenyl-N′-methyldiimide N-oxide (**11**), a possibility explicitly excluded by the previous workers. It was suggested by Stevens[4] that base-catalyzed elimination of diazotic

10 **11**

acid to yield an aldehyde might be involved. It has now been found that treatment of N-phenyl-N′-benzyloxydiimide N-oxide (**12**) with potassium *t*-butoxide indeed produces benzaldehyde. The corresponding methoxy compound **10** was inert to potassium *t*-butoxide, however. These compounds thus bear some similarity to nitronate esters and nitrate esters in their behavior toward bases although they are much more resistant.



12

Efforts to prepare derivatives of **6** in which R was a tertiary alkyl group were frustrated by the instability of both the nitrosohydroxlamines themselves and of their tosylates. In the case of the *t*-octyl derivative, for example, attempts to recrystallize the solid tosylate led to spontaneous evolution of gas and toluenesulfonic acid. Apparently in this case solvolysis is possible. *t*-Octylnitrosohydroxylamine was very labile and gradually decomposed to *t*-nitrosooctane.

Experimental Section

N-Benzyl-N′-tosyloxydiimide N-Oxide.—A stream of nitrogen-diluted nitric oxide was bubbled through the solution of the benzyl Grignard reagent prepared from 11.7 g of magnesium and 57.7 ml (63.8 g) of benzyl chloride in 11 of dry ether for 50 min. The solution was hydrolyzed with 400 ml of 2 *N* HCl and the ether layer was extracted with 1.5 *N* NaOH. These basic extracts were acidified, reextracted with ether, dried ($MgSO_4$), and concentrated. The crude residue (*ca.* 13.0 g) was dissolved in a solution of 8.4 g of *p*-toluenesulfonyl chloride in 100 ml of acetone. At ice-bath temperature 25 ml of 1.5 *N* NaOH was added over a period of 45 min with stirring. The solution was stirred for an additional 30 min; water was added and the product oiled out. Upon cooling 6.6 g (4.5%, based on benzyl chloride) of N-benzyl-N′-tosyloxydiimide N-oxide crystallized. Recrystallization was effected from chloroform–hexane: mp 90–92° (lit.[4] mp 92°); ir (KBr) 1300 and 1510 (O←N=N), 1185 and 1200 cm^{-1} (SO_2).

N-Phenethyl-N′-tosyloxydiimide N-Oxide.—The procedure used was the same as that for N-benzyl-N′-tosyloxydiimide N-oxide;[4] yield 7.3 g (8.5%): mp 121.5–122°; ir (Nujol) 1305 and 1520 (O←N=N), 1190 and 1205 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.45 (s, 3, $C_6H_4CH_3$), 3.14 (t, 2, *J* = 7 Hz, $C_6H_5CH_2CH_2$), 4.29 (t, 2, *J* = 7 Hz, $C_6H_5CH_2CH_2$), 7.48 (m, 9, C_6H_5, C_6H_4). *Anal.* Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.2; H, 5.0; N, 8.8; S, 10.0. Found: C, 56.27; H, 5.05; N, 9.30; S, 10.01.

N-Methyl-N′-tosyloxydiimide N-Oxide.—A stream of nitrogen-diluted nitric oxide was bubbled through the solution of the methyl Grignard reagent prepared from 4.22 g of magnesium and 25 g methyl iodide in 400 ml of dry ether for 45 min. The solution was hydrolyzed with 2 *N* HCl and the ether layer was extracted with 1.5 *N* NaOH. To the basic extracts was added 12.0 g of *p*-toluenesulfonyl chloride in one portion and the mixture was stirred for 4 hr. The solution was then filtered to yield a white solid which was recrystallized from chloroform–hexane to give 3 g (7.5%): mp 83–84° (lit.[4] mp 86°); ir (Nujol) 1320 and 1495 O←N=N), 1185 and 1195 cm^{-1} (SO_2).

N-*n*-Butyl-N′-tosyloxydiimide N-Oxide.—The procedure used was the same as that for N-benzyl-N′-tosyloxydiimide N-oxide.[4] After tosylation, the solution was stirred for an additional 1.5 hr, extracted with methylene chloride, and dried ($CaCl_2$). The oil obtained was chromatographed on silica gel. The hexane eluate contained only tosyl chloride. Methylene chloride was used to elute N-*n*-butyl-N′-tosyloxydiimide N-oxide as a light yellow oil: nmr ($CDCl_3$) δ 7.70 (q, 4, C_6H_4), 4.12 (t, 2, CH_2N=N), 2.45 (s, 3, $C_6H_4CH_3$), 2.3–0.5 (m, 7, $CH_3CH_2CH_2$); ir (neat) 1310 and 1510 (O←N=N), 1185 and 1200 cm^{-1} (SO_2). *Anal.*[25] Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.92; N, 10.29. Found: C, 48.71; H, 5.98; N, 11.11.

N-Cyclohexyl-N′-tosyloxydiimide N-Oxide.—The procedure used was the same as that for N-benzyl-N′-tosyloxydiimide N-oxide:[4] yield 9.0 g (20%); mp 93–94.5° (lit.[25] mp 93–94.5°); ir (Nujol) 1310 and 1510 (O←N=N), 1185 and 1200 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 0.8–2.2 (broad m, 10, C_6H_{10}), 3.9–4.6 (broad m, 1, CHN(→O)=N. *Anal.*[25] Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 51.91; H, 6.18; N, 9.61.

N-Benzyl-N′-methoxydiimide N-Oxide.—This compound was prepared by Wright's procedure[23] using the *sodium* salt of N-benzyl-N-nitrosohydroxylamine: mp 28–29°; bp 104° (0.2 mm); ir (neat) 1295 and 1500 cm^{-1} (O←N=N); nmr ($CDCl_3$) δ 4.06 (s, 3, CH_3), 5.12 (s, 2, CH_2), 7.43 (s, 5, C_6H_5). *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 59.28; H, 6.09; N, 16.43.

Decomposition of N-Benzyl-N′-tosyloxydiimide N-Oxide.—Into a three-necked 250-ml pear-shaped flask, equipped with thermometer, equilibrating addition funnel, and magnetic stirrer and attached to a vacuum rack, was placed 1.22 g (4.0 mm) of N-benzyl-N′-tosyloxydiimide N-oxide dissolved in 45 ml of *t*-butyl alcohol.

In the addition funnel was placed 0.46 g (4.0 mm) of potassium *t*-butoxide. The N-benzyl-N′-tosyloxydiimide N-oxide solution was frozen out with liquid N_2, and the potassium *t*-butoxide solution dripped onto the frozen solution. The pressure was reduced to 0.001 mm and the frozen mixture warmed to 50° with vigorous stirring. The gas collected proved to be N_2 by mass spectral analysis and the amount indicated 70% decomposition of the starting material. A 2,4-DNP derivative of the remaining (filtered to remove potassium tosylate) neutralized *t*-butyl alcohol solution yielded the benzaldehyde derivative: mp 239–240° (lit.[26] mp 237°).

Decomposition of N-Primary Alkyl-N′-tosyloxydiimide N-Oxides with Potassium *t*-Butoxide.—The following general procedure was used for the decomposition of the N-alkyl-N′-tosyloxydiimide N-oxides. The diimide N-oxide was dissolved in the least amount of *t*-butyl alcohol and an equimolar amount of potassium *t*-butoxide in *t*-butyl alcohol was added slowly with stirring. After 1 hr the reaction mixture (a slurry in some cases) was filtered to remove potassium tosylate and neutralized with HCl if necessary. In all cases a strong odor of the aldehyde appeared except in the case of formaldehyde; these were isolated as the 2,4-DNP derivatives from the neutral solution. Phenylacetaldehyde was identified by comparison of its glpc retention time on a silicone column at 135° with that of authentic material. The yields (%) of aldehyde (based upon 2,4-DNP's isolated) were as follows: C_6H_5CHO (61), $C_6H_5CH_2CHO$ (47), CH_2O (54), and C_3H_7CHO (52).

Decomposition of N-Benzyl-N′-methoxydiimide N-Oxide with Potassium *t*-Butoxide.—The procedure was the same as that for

(22) The corresponding derivatives of **2**, *e.g.*, R = aryl, were found to be essentially inert to base.[6]

(23) M. V. George, R. W. Kierstead, and G. F. Wright, *Can. J. Chem.*, **37**, 679 (1959).

(24) C. Wintner, Ph.D. Thesis, Harvard University, 1963.

(25) These analyses were obtained by T. E. Stevens, Rohm and Haas Co., Huntsville, Ala.

(26) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 320.

N-alkyl-N′-tosyloxydiimides N-oxides. The solution was stirred for 6 days until the reaction was complete (no more precipitate formed and solution was neutral to litmus). The 2,4-DNP derivative of benzaldehyde, mp 237–239° (lit.[26] mp 237°), was isolated; yield (calcd as C_6H_5CHO), 57%.

Decomposition of N-Phenyl-N′-benzyloxydiimide N-Oxide with Potassium *t*-Butoxide.—The diimide N-oxide[23] (1.0 g) and potassium *t*-butoxide (0.5 g) were dissolved in *t*-butyl alcohol (10 ml) and the mixture was refluxed for 3 hr. The reaction mixture was cooled and filtered. The 2,4-DNP derivative of benzaldehyde was isolated from the solution; yield (calcd as C_6H_5CHO), 42%.

Deuterium Exchange of N-Benzyl-N′-methoxydiimide N-Oxide.—To a solution of 0.02 g of sodium in 5 ml of CH_3OD (99%) was added 0.3 g of N-benzyl-N′-methoxydiimide N-oxide, and the mixture was stirred for 3 hr. The CH_3OD was evaporated, deuterium oxide added, and the solution extracted with chloroform. Nmr analysis showed 95% exchange of the methylene protons at δ 5.12. Medium intensity C–D stretching at 4.44 μ was detected in the infrared spectrum of this material.

Decomposition of N-Cyclohexyl-N′-tosyloxydiimide N-Oxide. (a) **Potassium *t*-Butoxide.**—The procedure used was the same as that for the decomposition of the primary alkyldiimide N-oxide derivatives except ether was employed as the solvent. During the *rapid* addition of base the solution turned deep raspberry in color. After the precipitate was filtered, the ether evaporated, and the residue taken up in ethanol, a 2,4-DNP derivative of cyclohexanone, mp 160–161° (lit.[26] mp 162°), was obtained in 45% yield by the usual procedure. Nitrogen, by mass spectral analysis, proved to be the only gas collected when the decomposition was carried out by the procedure used for the potassium *t*-butoxide decomposition of 6, R = $C_6H_5CH_2$.

(b) **Thermal Decomposition.**—The diimide N-oxide was dissolved in o-dichlorobenzene and the solution was heated at 180° for 30 min. Vpc analysis on a silicone column at 25° of the solution indicated a nearly quantitative yield of cyclohexene.

(c) **Photolysis.**—The diimide N-oxide (0.90 g) was dissolved in 400 ml of cyclohexane and irradiated with a Hanovia high-pressure submersion lamp with a Pyrex filter for 22 hr while stirring. The brownish residue obtained was chromatographed on silica gel with hexane, yield 0.45 g (50%) of cyclohexyl *p*-toluenesulfonate, identified by comparison with an authentic sample.[27]

N-*t*-Octyl-N′-tosyloxydiimide N-Oxide.—Nitrosation[28] of 29 g of *t*-octylhydroxylamine[29] with 13.8 g of sodium nitrite yielded, upon recrystallization from chloroform–pentane, 12.0 g (31%) of the ammonium salt: mp 55–60°; sublimes 55° (0.3 mm); ir 1320 and 1500 (O←N=N), 3300 cm^{-1} (NH_4^+). *Anal.* Calcd for $C_8H_{21}N_3O_2$: C, 50.3; H, 11.0; N, 22.0. Found: C, 50.17; H, 11.05; N, 21.88.

The method of Stevens[4] using 7.5 g of the ammonium salt of *t*-octylnitrosohydroxylamine and 7.5 g of *p*-toluenesulfonyl chloride yielded 11.0 g (86%) of the tosylate. Decomposition occurred upon attempts to make Nujol mulls for ir and upon attempted recrystallization from chloroform–hexane.

Decomposition.—A small amount of the diimide N-oxide was dissolved in chloroform and warmed for a few minutes. The nmr spectrum of the solution showed diisobutylene (by comparison with the spectrum of authentic material) and *p*-toluenesulfonic acid to be present.

N-*t*-Octyl-N′-methoxydiimide N-Oxide.—The method of Wright[23] using 1.7 g of the ammonium salt of *t*-octylnitrosohydroxylamine and 1.7 g of dimethyl sulfate was employed. The crude oil was chromatographed on silica gel and eluted with 1:1 methylene chloride–hexane yielding 0.1 g (7%) of light brown oil; ir (neat) 1360 and 1485 cm^{-1} (O←N=N); nmr (neat) δ 0.95 (s, 9, $(CH_3)_3C$), 1.5 (s, 6, $(CH_3)_2C$), 1.88 (s, 2, CH_2), 3.90 (s, 8, OCH_3). *Anal.* Calcd for $C_9H_{20}N_2O_2$: C, 57.4; H, 10.6; N, 15.0. Found: C, 56.44; H, 10.32; N, 15.30.

Attempted Solvolysis.—A small amount of the diimide N-oxide was dissolved in 95% ethanol and refluxed on a steam bath for 0.5 hr; it was recovered unchanged.

Decomposition of N-Phenyl-N′-methoxydiimide N-Oxide with Potassium *t*-Butoxide.—The diimide N-oxide[23] (3.1 g) and potassium *t*-butoxide (2.25 g) were dissolved in 25 ml of *t*-butyl alcohol and the mixture was refluxed overnight. The precipitate was filtered and identified as the potassium salt of N-phenyl-N-nitrosohydroxylamine (by ir, nmr, and reaction with dimethyl sulfate to yield starting material). No 2,4-DNP derivative of formaldehyde could be obtained from the solution.

Preparation of *t*-Butyl N-Methyl-N-hydroxycarbamate.—The method of Carpino[30] using methylhydroxylamine hydrochloride (15.7 g) was employed. The light yellow oil obtained (19.1 g, 92%) was chromatographed on silica gel with 1:1 chloroform–methylene chloride: ir (neat) 1670 (C=O) and 3300 cm^{-1} (OH); nmr (neat) δ 1.46 (s, 9, $C(CH_3)_3$), 3.11 (s, CH_3–N). *Anal.* Calcd for $C_6H_{13}NO_3$: C, 49.0; H, 8.8; N, 9.5. Found: C, 48.80; H, 8.47; N, 9.55.

Preparation of *t*-Butyl N-Methyl-N-*p*-toluenesulfonoxycarbamate.—The method of Carpino[30] using *t*-butyl N-methyl-N-hydroxycarbamate (4.80 g) was employed. Recrystallization from benzene–petroleum ether yielded 7.2 g (70%), mp 67–68°; ir (Nujol) 1740 (C=O), 1175 and 1185 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 1.24 (s, 9, $C(CH_3)_3$), 2.46 (s, 3, C_6H_4–CH_3), 3.25 (s, 3, CH_3–N), 7.65 (q, 4, C_6H_4). *Anal.* Calcd for $C_{13}H_{19}NO_5S$: C, 51.8; H, 6.3; N, 4.7; S, 10.6. Found: C, 51.83; H, 6.38; N, 4.71; S, 10.82.

N-Methyl-O-(*p*-toluenesulfonyl)hydroxylamine.—The method of Carpino[31] using *t*-butyl N-methyl-*p*-toluenesulfonoxycarbamate (7.2 g) was employed: yield of crude product, 4.7 g (100%); mp 47–50°; ir (Nujol) 3330 (NH), 1170 and 1185 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.55 (s, C_6H_4–CH_3), 2.72 (s, CH_3–N), 6.45 (broad s, NH), 7.63 (q, C_6H_4). Because of the sensitivity of this compound to solvolytic decomposition, it was not further purified. Its spectral properties are consistent with the structure assigned.

Attempted Preparation of N-Methyl-N-nitroso-O-(*p*-toluenesulfonyl)hydroxylamine.—Nitrosation by the method of Paskovich and Zimmerman[32] using 4.1 g of N-methyl-O-(*p*-toluenesulfonyl)hydroxylamine was carried out with N_2O_4 in CCl_4. The only organic product isolated was methyl *p*-toluenesulfonate: yield 1.70 g (45%); bp 124° (1 mm).

Attempted Synthesis of N-Methyl-N′-tosyloxydiimide N′-Oxide.—The silver salt of methylnitramine[33] (6.67 g) was stirred in 50 ml of acetonitrile (cooled to 0°) while tosyl chloride (7.0 g) in 25 ml of acetonitrile was added slowly. The solution was stirred overnight, the silver chloride filtered off, and the acetonitrile evaporated. The residue was chromatographed on silica gel. The column was first eluted with hexane and then methylene chloride. The first fraction contained tosyl chloride (by ir); the second contained methyl tosylate (by ir, nmr, and Sadtler's Index), 2.5 g (37%).

Registry No.—N-Phenethyl-N′-tosyloxydiimide N-oxide, 25370-87-0; N-*n*-butyl-N′-tosyloxydiimide N-oxide, 25370-88-1; N-cyclohexyl-N′-tosyloxydiimide N-oxide, 25370-89-2; N-benzyl-N′-methosydiimide N-oxide, 25370-90-5; N-benzyl-N′-tosyloxydiimide N-oxide, 25370-91-6; N-phenyl-N′-benzyloxydiimide N-oxide, 25370-92-7; *t*-octylnitrosohydroxylamine ammonium salt, 25370-98-3; N-*t*-octyl-N′-methoxydiimide N-oxide, 25370-93-8; N-phenyl-N-methoxydiimide N-oxide, 25370-94-9; *t*-butyl N-methyl-N-hydroxycarbamate, 19689-97-5; *t*-butyl N-methyl-N-*p*-toluenesulfonoxycarbamate, 25370-96-1; N-methyl-O-(*p*-toluenesulfonyl)hydroxylamine, 25730-97-2.

Acknowledgment.—We are indebted to the National Science Foundation for a grant in support of this research and for an equipment grant for the purchase of the A-60A nmr instrument used in this investigation.

(27) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).
(28) British Patent 815,537 (1959).
(29) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(30) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959).
(31) L. A. Carpino, *ibid.*, **82**, 3133 (1960).
(32) H. Zimmerman and D. H. Paskovich, *ibid.*, **86**, 2149 (1964).
(33) M. I. Gillibrand and A. H. Lamberton, *J. Chem. Soc.*, 1883 (1949).

Gas-Phase Reaction of Chloramine with Olefins and Saturated Hydrocarbons

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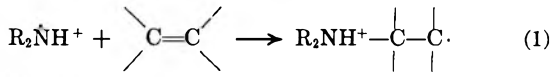
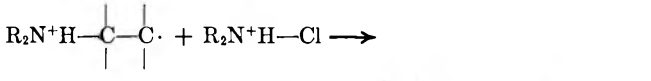
The gas-phase reactions of chloramine with 2-methylpropene, ethylene, neopentane, and isobutane under the influence of ultraviolet radiation and heat have been shown to yield chlorinated products. Substitution as well as addition products have been isolated in the case of 2-methylpropene. The results of this study appear to support the implications in the literature that free neutral amino radicals possess a strong tendency to abstract hydrogen from olefins, rather than to add to the olefinic bond.

The dialkyl chloramines have been shown[1-5] to undergo free-radical addition to dienes, olefins, allenes, and acetylenes dissolved in a sulfuric acid–acetic acid mixture to give the corresponding β-chloroamines. All these reactions were represented as a sequence of free-radical chain reactions of the type represented by eq 1 and 2, in which the key propagation step is the addition of a protonated dialkylamino (*i.e.*, dialkylaminium) radical to a carbon–carbon multiple bond.

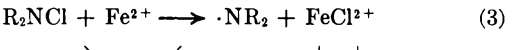


(1)



(2)

Minisci and Galli[6,7] have recently pointed out that dialkylamino radicals, produced by the redox system, N-chloramine/ferrous or cuprous salts, easily added to the olefinic bond according to the following steps.



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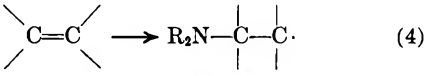

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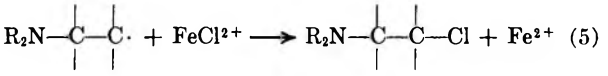
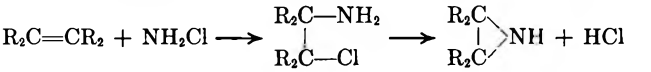


(5)

However, electrophilic chlorination can sometimes compete with radical addition of dialkylchloramines to allenes and olefins. Thus, chlorinated products, rather than β-chloroamines (chloraminated products), were also obtained in some cases.[1,2,6]

We were interested in investigating the utility of chloramine with respect to the conversion of olefins to the corresponding chloroamino or imino derivatives.



(6)

There was a possibility that the direct addition of chloramine across the double bond in olefins, a source of electrons for the electrophilic chloramine, might result in a more direct route for the synthesis of β-chloroamines. No specific mode, radical or ionic, was proposed for the addition of chloramine to the olefins. However, we believed that the electrophilic chloramine might polarize the π-electron cloud in the olefins and consequently add to the double bond, probably in an ionic manner analogous to the addition of other electrophilic reagents such as halogens and hydrogen halides.

Several olefins were exposed to chloramine in a solution phase under various reaction conditions, but no definite evidence was found for the addition of chloramine to the olefinic bond. Chloramine does not add to cyclohexene, 2-methylpropene, and 2-methyl-1-butene when ethereal solutions are exposed to either uv radiation or reacted in a strongly acidic medium such as a mixture of sulfuric acid with glacial acetic acid. Allylbenzene and 2-methyl-1-butene do not add chloramine in ether in the presence of a Fe^{2+}/Fe^{3+} redox couple. Allylbenzene, styrene, and cyclohexene do not react with chloramine in ether solutions when exposed to the emergent gases from the chloramine generator. Other unsuccessful attempts have also been made by Coleman and Patterson[8] to add chloramine to olefins.

However, we have demonstrated that when a mixture of the gaseous chloramine and olefins is exposed to uv radiation or high temperature, chlorination of the olefin occurs. Similarly, isobutane and neopentane are chlorinated by chloramine under these conditions.

Experimental Section

Materials.—Isobutane, ethylene, 2-methylpropene, and neopentane were obtained from Matheson Company, Inc. Chloramine was produced from the gas phase reaction of ammonia with chlorine as described by Mattair and Sisler.[9]

A modified reactor design[9a] which produces virtually quantitative yields of chloramine, even at ammonia to chlorine mole ratios almost as low as 2.0:1, was used in this study.

Nuclear Magnetic Resonance Spectra.—^1H nmr spectra were determined using a Varian Model A-60-A nuclear magnetic resonance spectrometer. The spectra of the liquids were determined as neat liquids using tetramethylsilane as an external reference.

Procedure for Gas Phase Reactions.—A typical experiment was carried out as follows: The gaseous hydrocarbon metered with the flowmeter (Tube No. 600, Tube Size R-2-15-AAA) obtained from Matheson Co., Inc., was introduced along with the effluent gases from the chloramine generator. This mixture was then passed through either a Pyrex glass tube heated to the desired temperature, or through a three-necked Pyrex glass vessel which is exposed to ultraviolet radiation (using Hanovia mercury arc lamp, 654A36, 420342). The uv source was contained in a quartz tube. The quartz tube was suspended in the Pyrex glass vessel through the middle neck. The resulting gaseous mixture was condensed in a trap chilled by a Dry Ice–acetone bath. The reaction time varied from two to several hours to obtain a sizable

(1) R. S. Neale and R. L. Hinman, *J. Amer. Chem. Soc.*, **85**, 2666 (1963).
(2) R. S. Neale, *ibid.*, **86**, 5340 (1964).
(3) R. S. Neale, *Tetrahedron Lett.*, 483 (1966).
(4) R. S. Neale, *J. Org. Chem.*, **32**, 3263 (1967).
(5) R. S. Neale and N. L. Marcus, *ibid.*, **32**, 3273 (1967).
(6) F. Minisci and R. Galli, *Tetrahedron Lett.*, 167 (1964).
(7) F. Minisci and R. Galli, *ibid.*, 3197 (1964).
(8) G. H. Coleman and R. L. Patterson, *Proc. Iowa Acad. Sci.*, **42**, 122 (1935); *Chem. Abstr.*, **30**, 8156 (1936).
(9) R. Mattair and H. H. Sisler, *J. Amer. Chem. Soc.*, **73**, 1619 (1951).
(9a) NOTE ADDED IN PROOF.—H. Prakash and H. H. Sisler, *Allg. Prakt. Chem.*, **21** (4), 123 (1970).

TABLE I

GAS PHASE REACTION OF CHLORAMINE WITH OLEFINS AND SATURATED HYDROCARBONS

Entry no.	$Cl_2/NH_3/N_2$/hydrocarbon mole ratio	Hydrocarbon	Conditions	Products	Bp, °C	% yield based on NH_2Cl	^1H nmr data area ratios Found	Calcd
1	1/2.10/5.33/0.90	$CH_2=CH_2$	Uv	CH_2ClCH_2Cl	83.5	35.5		
2	1/2.09/3.06/0.55	$(CH_3)_3CH$	Uv	$(CH_3)_3CCl$	51.5	2.8		
				$(CH_3)_2CHCH_2Cl$	68.5	7.6	1/2/6	1/2/6
3	1/2.09/3.13/1.35	$(CH_3)_4C$	Uv	$(CH_3)_3CCH_2Cl$	84.5–85	14.8	1/4.64	1/4.5
4	1/2.50/2.48/0.73	$(CH_3)_4C$	Uv	$(CH_3)_3CCH_2Cl$	84	10.0	1/4.6	1/4.5
5	1/3.26/2.93/1.35	$(CH_3)_4C$	Uv	No liquid product				
6	1/2.10/9.33/0.87	$(CH_3)_2C=CH_2$	425°	$(CH_3)_3CCl$		0.8		
				$(CH_3)_2C(Cl)CH_2Cl$	104	5.9	1/2.91	1/3
				$(CH_3)CCH_2Cl$ ‖ CH_2	72	8.6	1/1.07/1.38	1/1/1.5
7	1/2.07/6.62/0.87	$(CH_3)_2C=CH_2$	Uv	$(CH_3)_3CCl$		0.7		
				$(CH_3)_2C(Cl)CH_2Cl$	107	24.7	1/3.12	1/3
				$(CH_3)CCH_2Cl$ ‖ CH_2	71.8	6.4		
8	1/3.15/3.09/0.92	$(CH_3)_2C=CH_2$	450°	No liquid product				
9	1/5.39/2.30/0.92	$(CH_3)_2C=CH_2$	450°	No liquid product				
10	1/2.51/3.31/0.96	$(CH_3)_2C=CH_2$	425°	$(CH_3)_2CCl$[a]				
				$(CH_3)_2C(Cl)CH_2Cl$[a]				
				$(CH_3)CCH_2Cl$ ‖ CH_2[a]				

[a] Identified by vapor phase chromatography.

amount of products in order to make their separation and identification convenient. At the conclusion of the experiment, the trap was removed from the Dry Ice–acetone bath and allowed to slowly warm to room temperature. Volatile materials were evaporated from the solution. The liquid products remaining in the trap were separated into individual components on a vapor phase chromatographic preparative column packed with silicone elastomer, 20% by weight on Chromosorb P. The products were identified by their boiling points and characteristic ^1H nmr spectra.

The solid observed in almost all the cases in the receiver, in the tubes leading from the hot tube to the receiver, and in the uv reaction vessel was found to be ammonium chloride. The results of the reactions with various hydrocarbons are summarized in Table I.

Discussion and Conclusion

An examination of Table I reveals that the gas phase reaction of chloramine with ethylene and 2-methylpropene results in the chlorination of these molecules. No addition of chloramine across the double bond in ethylene to give the β-chloroamine or imine was observed. No polymeric materials were found in the cold trap. The small amounts of the solid recovered were shown by infrared spectroscopy to be principally ammonium chloride. The isolation of brown and black polymeric materials containing carbon, hydrogen, nitrogen, and chlorine in the reaction of 2-methylpropene with chloramine at 425° indicates that some addition of chloramine across the double bond may have occurred, but, if so, the resulting products probably underwent further reaction to give highly polymerized products which were not characterized. The amount of these polymeric materials was relatively very small and they were not titrated for the number of base equivalents.

The chlorination of ethylene and 2-methylpropene by chloramine raised an interesting possibility that the saturated hydrocarbons could also be chlorinated by chloramine. The experimental data (entries 2, 3, and 4) in Table I demonstrate that such is the case. These data show that chloramine reacts with isobutane to give *t*-butyl chloride and isobutyl chloride. Neopentane yields neopentyl chloride.

The fact that ammonium chloride and no liquid chlorinated product was obtained when neopentane was chloraminated at a $Cl_2/NH_3/N_2$/neopentane mole ratio of 1/3.26/2.93/1.35 (entry 5) was interesting to note. Similar experiments with 2-methylpropene at 450° at $Cl_2/NH_3/N_2$/2-methylpropene mole ratios of 1/5.39/2.30/0.92 and 1/3.15/3.09/0.92 (entires 8 and 9) yielded ammonium chloride and no chlorinated liquid product. The possibility that some unreacted chlorine coming from the generator might be responsible for giving the chlorinated products when the reactions were run at Cl_2/NH_3 mole ratio of 1/2.00 to 1/2.10 was considered. However, when neopentane was chloraminated at a $Cl_2/NH_3/N_2$/neopentane mole ratio of 1/2.50/2.48/0.73, a 10% yield of neopentyl chloride was again obtained (entry 4). Similarly, 2-methylpropene at a $Cl_2/NH_3/N_2$/2-methylpropene mole ratio of 1/2.51/3.31/0.96 (entry 10) reacts with chloramine at 425° to yield the chlorinated products. Furthermore, ultraviolet spectrophotometric measurements on the ether solutions of the emergent gases from the chloramine generator, when NH_3–Cl_2 gas phase reaction was carried out at Cl_2/NH_3 mole ratio ranging from 1.00/2.04 to 1.00/2.53, demonstrated that the only chlorine-containing product in the emergent gases was chloramine.

In all these chloramination reactions at a Cl_2/NH_3 mole ratios of 1/2.00 to 1/2.10, the delivery tube leading to the cold trap stayed relatively clean and little ammonium chloride was found in the cold trap. As the NH_3 to Cl_2 mole ratio was increased, more ammonium chloride was observed in the delivery tube and the cold trap. The increasing mole ratio of ammonia to chlorine resulted in a decrease in the yield of the chlorinated products. This is supported by entries 3, 4,

and 5 in Table I. It was observed that the yield of neopentyl chloride decreases from 14.8% to 0% when the Cl_2/NH_3 ratio was changed from 1/2.09 to 1/3.26. Similarly, no chlorinated product was isolated when 2-methylpropene was chloraminated at Cl_2/NH_3 mole ratios of 1/3.15 and 1/5.39. It is, thus, highly probable that the chlorinated products come from the reaction of chloramine with the hydrocarbon in the absence of excess ammonia.

The relatively low energy of the N–Cl bond (47.7 kcal/mol)[10] and the chlorinating ability of chloramine, as demonstrated in the case of isobutane and neopentane, suggests the possible initial formation of amino ($NH_2\cdot$) and chlorine ($Cl\cdot$) radicals under the influence of uv radiation or heat. If such radical formation is assumed, the chlorination of isbutane, neopentane, and 2-methylpropene could then be realized in terms of the following reactions where R = $(CH_3)_3CCH_2$ (neopentyl), $(CH_3)_3C$ (*t*-butyl), $(CH_3)_2CHCH_3$ (isobutyl), and $CH_3(CH_2)C{=}CH_2$ (isobutenyl) groups. Equation 7 is the chain-initiating step and equations 8 and 9 are the chain-propagating steps. The proposal of chain reaction is again speculative, since no experimental evidence has been obtained. An alternative route by which the alkyl radical ($R\cdot$) could lead to the chlorinated product is to combine with the chlorine ($Cl\cdot$) radical generated in equation 7.

$$NH_2Cl \xrightarrow{\text{uv or heat}} NH_2\cdot + Cl\cdot \quad (7)$$

$$RH + NH_2\cdot \longrightarrow R\cdot + NH_3 \quad (8)$$

$$R\cdot + NH_2Cl \longrightarrow RCl + NH_2\cdot \quad (9)$$

$$R\cdot + Cl\cdot \longrightarrow RCl \quad (10)$$

Equation 8 which assumes the hydrogen abstraction from the hydrocarbon by the amino radical to yield alkyl radical and ammonia, is reasonable. In many cases, the neutral amino radicals preferred to abstract hydrogen from the olefin rather than add to the olefinic bond. This strong tendency toward hydrogen abstraction by the amino radicals, and their relative inability to add to the olefinic bond, has been supported by many researchers. Cowley and Waters[11] carried out the liquid phase thermal decomposition of tetramethyltetrazene in the presence of 1-octene and failed to observe amination products. The postulated dimethylamino radical usually appeared as dimethylamine. This indicates hydrogen abstraction and not addition. Amino radicals from the photolyzed amines failed to add to propylene in the gas phase.[12] Propylene was converted to propane and hexane by adding hydrogen atoms resulting from the photolyzed amines according to the following reactions.

$$R_2NH \longrightarrow R_2N\cdot + H\cdot \quad (11)$$

$$C_3H_6 + 2H\cdot \longrightarrow C_3H_8 \quad (12)$$

$$C_3H_6 + H\cdot \longrightarrow C_3H_7\cdot \quad (13)$$

$$C_3H_7\cdot + C_3H_7\cdot \longrightarrow C_6H_{14} \quad (14)$$

(10) L. Pauling "Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 85.

(11) B. R. Cowley and W. A. Waters, *J. Chem. Soc.*, 1228 (1961).

(12) C. H. Bamford, *ibid.*, 17 (1939).

Neale and Hinman[1] found that strong irradiation of carbon tetrachloride solutions of alkyl substituted chloramines containing butadiene failed to result in the addition of the chloramine to the unsaturated substrate. This is in contrast with the smooth addition occurring with aminium radicals ($R_2\dot{N}H^+$). The conclusion was reached that either the neutral amino radicals do not form, or if they do form, they do not add to the diene. Paquette and Farley[13] did not observe any chlorinated or chloraminated product of 1-octene when an ethereal solution of chloramine was added to solutions of various phenols in 1-octene. The phenols were dimerized. These reactions are believed to be initiated *via* the aminium radical formation ($\cdot\dot{N}H_3^+$). In fact the observation that in our studies, in the presence of a considerable excess of ammonia, chlorination of the hydrocarbons by chloramine did not occur would be understandable if a mechanism involving NH_3Cl^+ and its breaking into $\dot{N}H_3^+$ and $\cdot Cl$ radicals is assumed. It is, however, not readily apparent where the protons to form the NH_3Cl^+ would come from. Furthermore, Paquette's and Farley's results were obtained in a highly acidic liquid phase molten phenols or solutions of phenols in hydrocarbons.

The suggestion in the literature that amino radicals have little tendency to add to the olefinic bond is in accord with the experimental results obtained in this study. The formation of 1,2-dichloroethane from ethylene and chloramine (entry 1) and 1,2-dichloro-2-methylpropane from 2-methylpropene and chloramine (entries 6, 7, and 10) can be accounted according to the following sequence of reactions.

$$NH_2Cl \xrightarrow{\text{uv or heat}} NH_2\cdot + Cl\cdot \quad (7)$$

$$CH_2{=}CH_2 + Cl\cdot \longrightarrow \cdot CH_2{-}CH_2Cl \quad (15)$$

$$\cdot CH_2{-}CH_2Cl + NH_2Cl \longrightarrow ClCH_2{-}CH_2Cl + NH_2\cdot \quad (16)$$

or

$$\cdot CH_2{-}CH_2Cl + Cl\cdot \longrightarrow CH_2Cl{-}CH_2Cl \quad (17)$$

Similarly, with 2-methylpropene

$$(CH_3)_2C{=}CH_2 + Cl\cdot \longrightarrow (CH_3)_2\dot{C}{-}CH_2Cl \quad (18)$$

$$(CH_3)_2\dot{C}CH_2Cl + NH_2Cl \longrightarrow (CH_3)_2C(Cl)CH_2Cl + NH_2\cdot \quad (19)$$

or

$$(CH_3)_2\dot{C}{-}CH_2Cl + Cl\cdot \longrightarrow (CH_3)_2\underset{\displaystyle Cl}{\underset{|}{C}}{-}CH_2Cl \quad (20)$$

The amino radicals produced in equations 7, 9, 16, and 19 may couple to produce hydrazine.

$$NH_2\cdot + NH_2\cdot \longrightarrow NH_2{-}NH_2 \quad (21)$$

Any hydrazine formed would probably react with chloramine to yield nitrogen and ammonium chloride.

$$NH_2{-}NH_2 + 2NH_2Cl \longrightarrow N_2 + 2NH_4Cl \quad (22)$$

(13) L. A. Paquette and W. C. Farley, *J. Org. Chem.*, **32**, 2718 (1967).

Reaction 22, which is the important yield reducing reaction in the synthesis of hydrazine, has been postulated to proceed *via* a free radical mechanism,[14] indicating that chloramine is capable of undergoing this type of reaction.

(14) F. N. Collier, Jr., H. H. Sisler, J. G. Calvert, and F. R. Hurley, *J. Amer. Chem. Soc.*, **81**, 6177 (1959).

Registry No.—Chloramine, 55-86-7; 2-methylpropene, 115-11-7; ethylene, 74-85-1; neopentane, 463-82-1; isobutane, 75-28-5.

Acknowledgments.—We gratefully acknowledge the generous support of the research reported in this paper by W. R. Grace and Company through a contract with the University of Florida.

Heterocyclic Synthesis with 2-Benzimidazoleacetic Acid Derivatives

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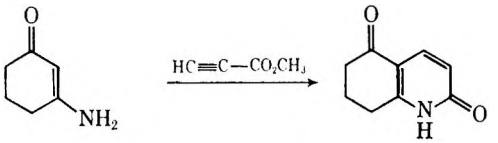
Ethyl 2-benzimidazoleacetic ester (**2**) reacted with diethyl azodicarboxylate and oxidative cyclization of the adduct yielded ethyl 1-hydroxy-*as*-triazino[4,5,*a*]benzimidazole-4-carboxylate (**13**). The chemistry of this new heterocycle and the mechanism of its formation are discussed. Reactions of **2** and 2-benzimidazoleacetonitrile (**1**) with dimethyl acetylenedicarboxylate are described.

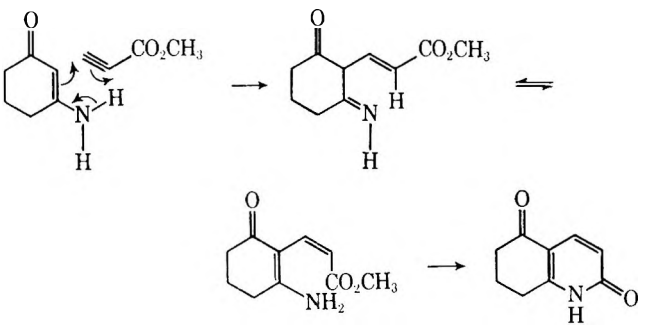
One of the most commonly employed procedures for the construction of new heterocyclic systems is cycloaddition.[1] This process has been well investigated mechanistically, and the factors determining the orientation of addition and the stereochemistry of the product are relatively well understood.

Alternative procedures involving construction of heterocycles by condensation processes have been subject to less mechanistic scrutiny. One such process is the reaction of an electrophilic multiple bond with enamino ketones and esters, where the amine is not fully substituted, followed by acylation of the amine by a substituent on the multiple bond, *e.g.*[2]



Many examples of this type of process are extant and they have usually been described as Michael additions by the nucleophilic carbon atom of the enamino carbonyl compound.[3] There is however a high degree of selectivity in the orientation of the electrophilic multiple bond. While addition by the nitrogen atom is in principle reversible, this requires more vigorous conditions than are normally employed in such processes.[4] This suggests that there is an additional factor operating which favors addition of the olefin to carbon rather than nitrogen. We would like to consider this to be the intramolecular transfer of a proton from nitrogen, *i.e.*, a hetero example of the ene reaction,[5] which may be represented by the sequence shown in Scheme I. The exclusive carbon alkylation of enamines by electrophilic olefins, where this mechanism cannot operate, is due to the more facile reversibility of N-alkylation in such cases.[6]

SCHEME I



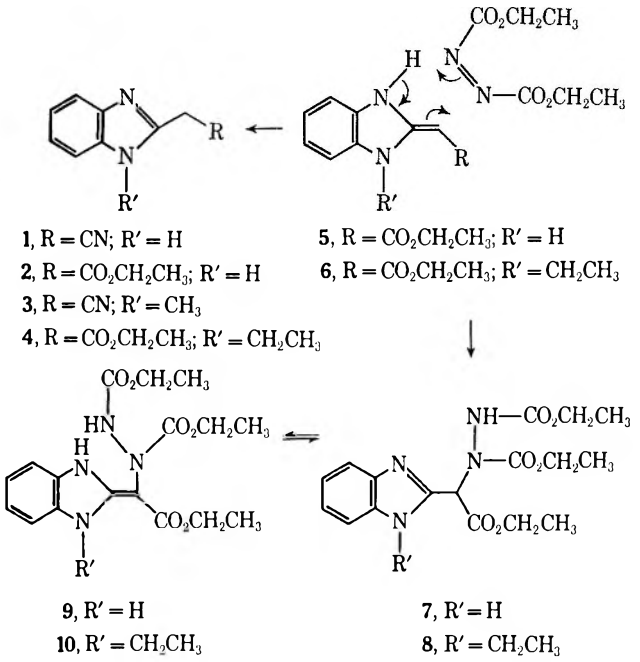
2-Benzimidazoleacetonitrile (**1**) is readily accessible by condensation of *o*-phenylenediamine with cyano acetic ester.[7] Ethyl 2-benzimidazole acetic ester (**2**) is available by ethanolysis of this nitrile (**1**).[7] The chemistry of neither substance has been well investigated but it might be anticipated that they would react with electrophilic multiple bonds to give new heterocycles. In particular with diethyl azodicarboxylate they might react to give an *as*-triazinobenzimidazole system reminiscent of the *as*-triazinoindoles for which good antiviral properties have been claimed.[8]

The reaction may be envisioned as proceeding *via* the tautomers **5** and **6** (Scheme II).

Equimolar mixtures of diethyl azodicarboxylate with **2** and with **4** in refluxing methylene chloride rapidly gave good yields of the adducts **9** and **8**, respectively. The interesting observation that the position of tautomeric equilibrium between **9** and **7**, and between **10** and **8**, was sensitive to substitution on the imidazole nitrogen atom has been commented on previously.[9] There was, however, no evidence to suggest that the cyclized forms were present to any extent. (The three O-ethyl resonances in the nmr spectra were very similar in both compounds.) This was not unexpected; however, it was hoped that oxidation would yield a cyclized product as

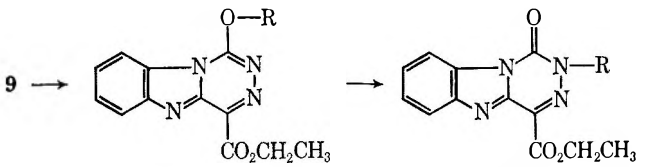
(1) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(2) M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 87 (1966).
(3) L. Paquette "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y. 1968, p 354.
(4) Z. Horii, C. Iwata, Y. Tamura, N. A. Nelson, and G. H. Rasmusson, *J. Org. Chem.*, **29**, 2768 (1964).
(5) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(7) R. A. B. Copeland and A. R. Day, *ibid.*, **65**, 1072 (1943).
(8) J. M. Z. Gladyck, J. H. Hunt, D. Jack, R. F. Hagg, J. J. Boyle, R. C. Stewart, and R. J. Ferlanto, *Nature*, **221**, 286 (1969).
(9) In a preliminary report of some of this work: N. Finch and C. W. Gemenden, *Tetrahedron Lett.*, 1203 (1969).

Scheme II



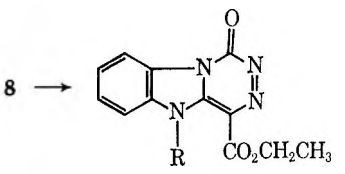
1, R = CN; R′ = H
2, R = $CO_2CH_2CH_3$; R′ = H
3, R = CN; R′ = CH_3
4, R = $CO_2CH_2CH_3$; R′ = CH_2CH_3
5, R = $CO_2CH_2CH_3$; R′ = H
6, R = $CO_2CH_2CH_3$; R′ = CH_2CH_3
9, R′ = H
10, R′ = CH_2CH_3
7, R′ = H
8, R′ = CH_2CH_3

this would now be aromatic. Treatment of **9** in methylene chloride containing 2 molar equiv of the Hünig base (diisopropylethylamine) with 1 molar equiv of bromine in the cold gave in moderate yield (40%) a new compound (**11**). This substance had a simple nmr spectrum, two different types of O-ethyl function and four aromatic protons. Warming **11** in 50% aqueous acetic acid transformed it into **12**. The tautomerism between **12** and **13** has been discussed in our preliminary report[9] and has been observed in related heterocycles.[10]



11, R = CH_2CH_3
13, R = H
14, R = -$COCH_3$
15, R = -$COCH_2Cl$
12, R = H
16, R = CH_2CH_3

Compound **12** could also be obtained directly by oxidizing crude **9** at room temperature. Application of several variations of oxidizing conditions to **8** gave no improvement of the tiny yield obtained by the usual method. Sufficient amounts of the product **17** were, however, available for complete characterization.



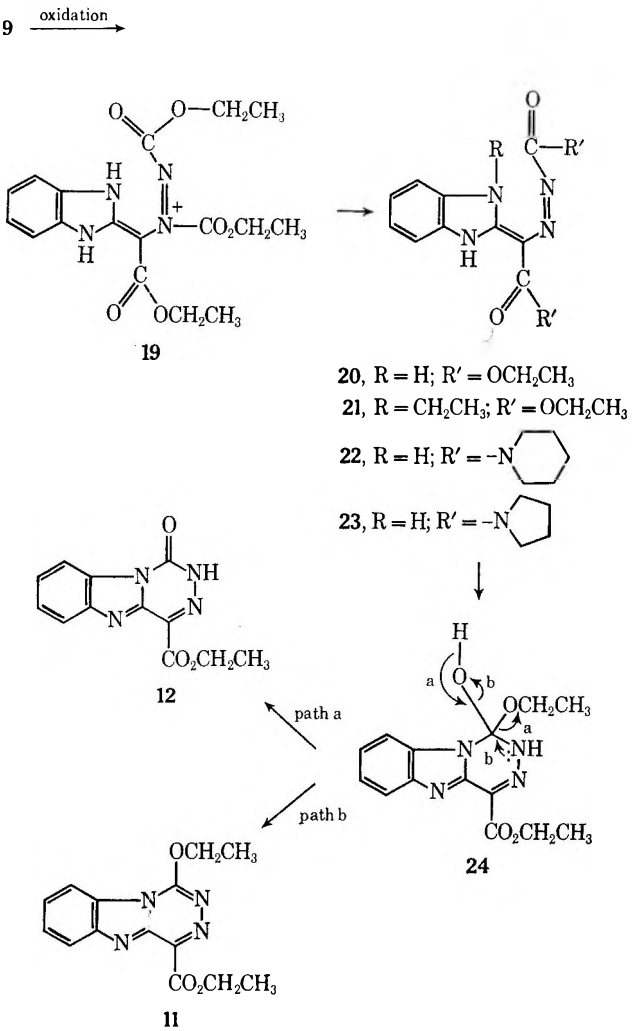
17, R = CH_2CH_3
18, R = H

Assignment of structure **12** rather than the tautomer **18** to our new heterocycle, ethyl 1-hydroxy-*as*-triazino[4,5,*a*]benzimidazole-4-carboxylate, is based on the spectral similarities between this substance and the N-ethyl derivative obtained by direct ethylation [EtI–DMF–NaH]. This N-ethyl compound is assigned structure **16**, because it is different from the other two ethyl compounds **11** and **17**, whose structures are unambiguous. At the time this work was performed the ring system, such as **12** possesses, was unknown. A publication by Slouka on another derivative of this system prompted our preliminary communication and subsequently a full report of Slouka's work has appeared.[11]

While attempts at O-ethylation of **13** were unsuccessful in regenerating **11** the presence of a readily enolizable amide function was further demonstrated by O-acylation in high yield to give **14** and **15**. The presence of a strong band at 1800 cm^{-1} in the ir spectra was regarded as convincing evidence for O- rather than N-acylation. This propensity for enolization in amides which have a heteroatom bonded to the nitrogen atom[10,12] may be the result of lone pair interaction between the adjacent heteroatoms.

The formation of **11** in the oxidative cyclization of **9** rather than **12**, which would be expected by analogy with related processes, can be discussed on the basis of our proposed mechanism (Scheme III). The expected

Scheme III



19
20, R = H; R′ = OCH_2CH_3
21, R = CH_2CH_3; R′ = OCH_2CH_3
22, R = H; R′ = -N⟨ ⟩
23, R = H; R′ = -N⟨ ⟩
12
24
11

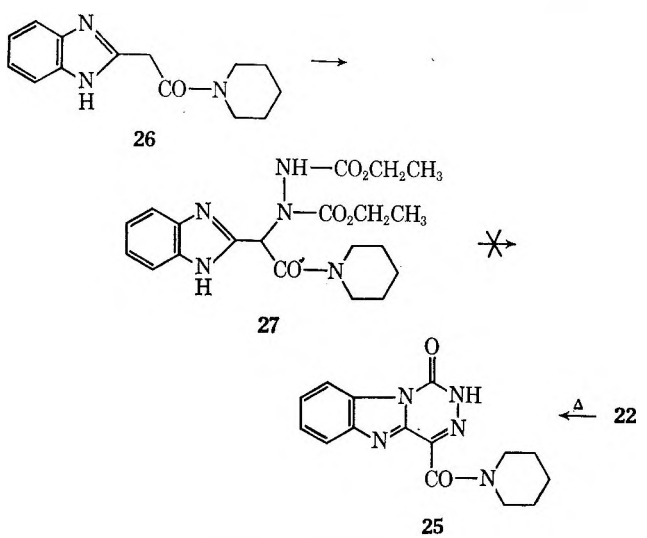
(10) A. A. Gordon, A. R. Katritsky, and F. D. Popp, *Tetrahedron, Suppl.*, **7**, 213 (1966).

(11) J. Slouka, *Tetrahedron Lett.*, 4007 (1968); *Monatsh. Chem.*, **100**, 91 (1969).

(12) A. R. Katritsky and F. W. Maine, *Tetrahedron*, **20**, 315 (1964).

reaction for an intermediate such as compound **24**, or its deprotonated form, would be that in path a to **12**. We suggest that the enhanced electron donation from the neighboring nitrogen atom permits departure of either hydroxy or ethoxy (path b). The choice is then determined by stereo electronic considerations. It is not unreasonable to assume that in **24** the OH group is principally axial, thus giving good overlap of the rupturing C—O bond with the neighboring nitrogen lone pair. This assumption about the configuration of **24** is based on ΔG values derived from cyclohexane cases. In nonpolar solvents, such as methylene chloride, hydroxyl is a small group relative to an ethyl ether.[13] The failure of the N-ethyl compound **8** to undergo the oxidative cyclization in good yield can be attributed to the intermediacy of **21**, where one NH is involved in a strong intramolecular hydrogen bond and the other is alkylated, thus providing an impediment to ring closure and an alternate reaction path (or paths) is followed.

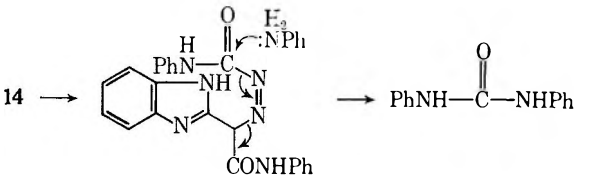
Support for the mechanism outlined above is provided by reaction of the O-acetyl derivative with other nucleophiles. Refluxing in piperidine converted **14** in good yield to a compound which was clearly an analog **22** of the proposed intermediate **20**. The long wavelength absorption in the uv spectrum suggested extended linear conjugation. The nmr spectrum showed essentially an A^2B^2 pattern for the aromatic protons, none of which were at unusually low field. Furthermore two types of NH were seen, one being at lower field and slower to exchange with D_2O than the other. Heating **22** in ethanol during an attempt at recrystallization partially converted it to a new compound **25**; this transformation could be effected quantitatively by melting **22**. Compound **25** is the piperamide of **12**. This was evident by the similarities in the nmr spectra of **25** and **12**, particularly the aromatic protons, one being at low field with both *ortho* and *meta* couplings. This is characteristic of N-acylbenzimidazoles. An attempt was made to confirm this assignment by synthesis, but this was thwarted by the failure of **27** to undergo the oxidative cyclization to give compound **25**.



26 **27** **22** **25**

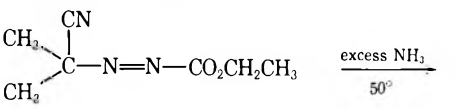
The formation of **25** from **22**, rather than the amidine, which would arise by loss of water from a cyclic intermediate, analogous to **24**, is perhaps attributable to the autocatalytic effect of the piperidine formed. This would assist proton removal in such an intermediate thus favoring path a. The failure of **27** to undergo oxidative cyclization to **25** is less readily explicable, although it may be relevant that, unlike **9**, **27** exists as the benzimidazole tautomer.

The reaction of **14** with other amines was explored. Refluxing in pyrrolidine gave an analogous and somewhat more stable compound **23**. Refluxing in aniline however gave diphenylurea as the only recognizable product. This may be a result of fragmentation of the product **28** at the higher reaction temperature.

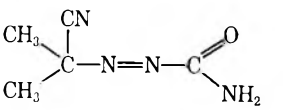


28

The stability of compounds **23** and **22** in the presence of excess amine is perhaps surprising but analogous processes are known, *e.g.*



29

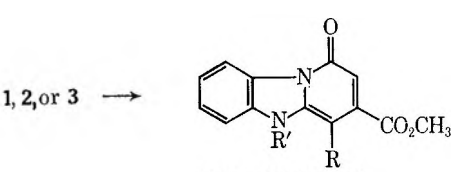


30

and no instability of the product **30** is mentioned (*i.e.*, mp 81° without decomposition).[14]

With stronger bases, *e.g.*, ethoxide, fragmentation of this type of compound is of course observed.[15]

Before concluding our study of 2-benzimidazoleacetic acid derivatives a further heterocycle was constructed. Experience with diethyl azodicarboxylic ester suggested that an adduct which would cyclize directly to a new aromatic system might be preferable. A dimethyl acetylenedicarboxylate adduct meets this requirement. Reaction occurred spontaneously with this ester and **1**, **2**, and **3** in DMF gave directly the tricyclic systems **31**, **32**, and **33** in moderate yield. Compound **33** could



31, R = CN; R′ = H
32, R = $CO_2CH_2CH_3$; R′ = H
33, R = CN; R′ = CH_3
34, R = CN; R′ = $COCH_3$
35, R = $CO_2CH_2CH_3$; R′ = $COCH_3$

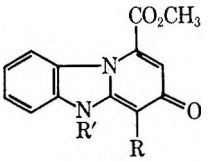
also be obtained by methylation of compound **31**. Acylation also occurred on the imidazole nitrogen atom to give **34** and **35**. There was no evidence of any O-acyla-

(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and A. G. Morrison, "Conformational Analysis," 1st ed, Interscience, New York, N. Y., 1965, p 437.

(14) E. Müller, French Patent 1,433,719 (1966); *Chem. Abstr.*, **65**, 16879c (1966).

(15) R. W. Hoffmann, *Chem. Ber.*, **97**, 2763 (1964).

tion in this series. The orientation of the addition of the acetylene follows from Scheme I; support for this assignment comes from the nmr spectrum of **31** which shows a low field single-proton multiplet characteristic of one benzimidazole nitrogen being acylated. This speaks against an alternative formulation of **36**.



36

These substances were however of less interest chemically and pharmacologically than the *as*-triazinobenzimidazoles; so their chemistry was not further investigated.

Experimental Section[16]

Formation of 9 from Ethyl 2-Benzimidazoleacetic Ester (2).—Ethyl 2-benzimidazoleacetic ester[7] (2.04 g) was dissolved in methylene chloride (20 ml) and the mixture refluxed with diethyl azodicarboxylate (1.742 g) for 1 hr. The solution was cooled and added directly to a silica gel column (150 g) made up in methylene chloride. The main band (3.60 g) was eluted by 5% methanol in methylene chloride. This was crystallized from ether; three crops were collected (2.62 g, 69%, mp 126–130°). The first crop (1.10 g) was recrystallized (ether) to mp 128–130°, (**9**): uv λ_{max} [MeOH] 254 (7120), 267 (7590), 274 (6840), 282 (6360), 323 mμ (14,450); ir (Nujol) 3240, 1642, 1622 cm^{-1}; nmr [$CDCl_3$] δ 10.6 (s, 2, exchangeable NH), 4.22 [q, 6].

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81. Found: C, 53.66; H, 5.79; N, 14.87.

Oxidative Cyclization of 9 to 11.—Compound **9** (9.45 g) was dissolved in methylene chloride (150 ml) containing 3.23 g of Hünig base (diisopropylethylamine); bromine (4.0 g) in methylene chloride (20 ml) was added dropwise to the well cooled and stirred solution. The ice bath was removed after the addition and the mixture stirred for 10 min at room temperature (starch, iodide test negative), then washed water, and dried ($MgSO_4$). The methylene chloride was removed and the residue dissolved in ethanol; on cooling and concentrating three crops of crystals were obtained (3.70 g, 50%, mp 136–149°). Recrystallization (ethanol) gave **11**: mp 154–155°; uv λ_{max} [MeOH], 227 (16,210), 250 (30,550), 320 mμ (5920); ir (Nujol), 1735, 1568 cm^{-1}; nmr [$(CD_3)_2SO$] δ 4.72 [q, 2], 4.32 [q, 2].

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.57; H, 4.67; N, 19.48.

Hydrolysis of 11 to 12 and 13.—Compound **11** (500 mg) was dissolved in glacial acetic acid (2 ml); water (2 ml) was added and the mixture heated on a steam bath for 4 hr. On cooling crystals (**12**) were deposited [293 mg, 65%, mp 240–242°]: uv λ_{max} (MeOH), 218 [23,450], 244 [23,550], 326 mμ [8550]; ir (Nujol), 3180, 1735, 1720; ir (CH_3CN), 1730 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.44 [q, 2].

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.50; H, 3.87; N, 21.94.

Recrystallization from DMF gave material **13**, mp 243–244°, whose ir (Nujol) was different [ν_{max} 3240, 1725 cm^{-1}]. The solution spectra, ir (CH_3CN), nmr [$(CD_3)_2SO$], were identical with those of the material crystallized from protic solvents. Recrystallization of this sample from ethanol gave material with an ir spectrum showing bands at 1735, 1720 cm^{-1}, identical with that of the analytical sample.

Direct Conversion of Ethyl 2-Benzimidazoleacetic Ester to 12.—Ethyl 2-benzimidazoleacetic ester[7] (122 g) was dissolved in methylene chloride (700 ml) and diethyl azodicarboxylate (117 g) added slowly to reflux the reaction gently. After addition was completed the mixture was refluxed for 1 hr more. Hünig base (85 g) was added, and then bromine (32 ml) without cooling but with stirring. After addition was completed the mixture was stirred at room temperature for 15 min, then washed with water and dried ($MgSO_4$). The methylene chloride was removed and the residue dissolved in ethanol. On standing overnight crystals separated (**12**) [50 g, 32% overall, mp 236–240°]. These were recrystallized from ethanol to mp 240–242°. This material was identical [spectra and mixture melting point] with **12** obtained by hydrolysis.

Acetylation of 12 to 14.—Compound **12** [6.45 g] was slurried in methylene chloride [250 ml]. Hünig base [3.57 g] was added and then acetyl chloride [2.20 g] slowly. The solid rapidly dissolved. After stirring for 2 hr at room temperature the reaction was washed with water, dried ($MgSO_4$), and concentrated on a steam bath after addition of ethanol. When the solution became turbid it was set aside. The product (5.67 g, 76%, mp 149–151°) was collected. Recrystallization from DMF–ethanol gave **14**: mp 150–151°; uv λ_{max} (MeOH), 243 (21,630), 324 mμ (8300); ir [Nujol], 1800, 1740 cm^{-1}; nmr [$(CD_3)_2NCDO$], δ 4.16 (q, 2), 2.40 (s, 3).

Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.67; H, 3.89; N, 18.36.

Chloroacetylation of 12 to 15.—In an analogous manner the chloroacetyl derivative **15** was prepared: mp 188–190° [EtOH/DMF]; uv λ_{max} [MeOH], 243 mμ [22,080], 326 mμ [8220]; ir [Nujol], 1800 cm^{-1}, 1730 cm^{-1}; nmr [$(CD_3)_2NCDO$] δ 5.24 [s, 2, $-OC(=O)CH_2Cl$].

Anal. Calcd for $C_{14}H_{11}ClN_4O_4$: C, 50.24; H, 3.31; N, 16.75. Found: C, 50.07; H, 3.33; N, 16.83.

Ethylation of 12 to 16.—Compound **12** (1.29 g) was dissolved in DMF (25 ml) and NaH (240 mg, 50% in mineral oil) added. The mixture was warmed on a steam bath for 15 min. Ethyl iodide (excess, approximately 2 molar equiv) was added in DMF. The reaction was heated 18 hr on the steam bath; dilution with water gave a solid, mp 159–160°. This was recrystallized from ethanol to give **16** (943 mg, 66%, mp 161–162°): uv λ_{max} [MeOH], 247 [24,300], 332 mμ [9220]; ir [Nujol], 1734, 1710; ir [CH_3CN], 1734 ,1712 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.32 [q, 2], 4.10 [q, 2].

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.60; H, 4.84; N, 19.54.

N-Ethyl-2-benzimidazoleacetonitrile.—2-Benzimidazoleacetonitrile[7] (15.7 g) was slurried in 0.33 *N* NaOH (300 ml). Some insoluble material was removed by filtration. To the orange filtrate was added dropwise ethyl sulfate (19.56 g). This was stirred at room temperature. After a short time a heavy oily precipitate separated. After stirring for 8 hr this had solidified and the pH fell to 7. The solid (12.185 g, 66%, mp 135–145°) was collected, and recrystallized from aqueous ethanol to mp 156–157°: uv λ_{max} [MeOH], 253 [6480], 267 [4700], 274 [5690], 282 mμ [5900]; ir [$CHCl_3$], 2260 cm^{-1}; nmr [$CDCl_3$], δ 4.03 [s, 2, $-CH_2CN$].

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.31; H, 5.95; N, 22.49.

Ethanolysis of N-Ethyl-2-benzimidazoleacetonitrile to 4.—N-Ethyl-2-benzimidazoleacetonitrile [8.77 g] was refluxed in ethanolic HCl [100 ml] for 2 hr. The solvent was removed, the residue dissolved in water, made basic with aqueous 10% K_2CO_3, and extracted with methylene chloride. The extract was dried ($MgSO_4$) concentrated and the residue distilled. The center cut, **4** [6.03 g, 55%, bp 151–153° (0.4 mm)], had uv λ_{max} [MeOH], 253 [7180], 267 [5390], 275 [6620], 282 mμ [7080]; ir [film], 1735, 1620 cm^{-1}; nmr [$CDCl_3$], δ 3.96 [s, 2, $-CH_2CO_2Et$].

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.21; H, 6.94.

The known 1-methyl-2-cyanomethylbenzimidazole reacted in an analogous manner to give ethyl 1-methyl-2-benzimidazoleacetic ester: mp 63–64°; uv λ_{max} (MeOH), 253 [7250], 267 [5430], 275 [6790], 282 mμ [7250]: ir [Nujol], 1732 cm^{-1}; nmr [$CDCl_3$], δ 3.92 [s, 2 $-CH_2CO_2Et$), 3.58 [s, 3, $N-CH_3$].

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.35; H, 6.54; N, 13.03.

Formation of 8 from N-Ethyl-2-benzimidazoleacetic Ester (4).—Compound **4** [19.42 g] was dissolved in methylene chloride [200 ml] and diethyl azodicarboxylate [16.0 g] added. The mixture was refluxed overnight. The solvent was removed. The residue crystallized and was recrystallized from ether–petroleum ether [27.7 g, 81%, mp 78–81°]. A further recrystallization gave the analytical sample (**8**): mp 82–83°, uv λ_{max} (MeOH),

(16) Melting points were obtained in a Thomas–Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument.

258 [7700], 270 [7010], 277 [8040], 285 mμ [6980]; ir (Nujol), 1735, 1705 cm^{-1}; nmr ($CDCl_3$), 6.36 δ (s, 1 ).

Anal. Calcd for $C_{19}H_{26}N_4O_6$: C, 56.14; H, 6.45; N, 13.79. Found: C, 55.95; H, 6.48; N, 13.76.

Ethyl 1-methyl-2-benzimidazoleacetic ester reacted in an analogous manner to give the triester: mp 84–85°; uv λ_{max} (MeOH), 257 mμ [7670], 270 [6860], 277 [7900], 285 mμ [6970]; ir [Nujol], 1750, 1735, 1708 cm^{-1}; nmr [$CDCl_3$], 6.40 δ [s, 1 ], 3.85 δ [s, 3, N-CH_3].

Anal. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.88; H, 6.14; N, 13.91.

Oxidative Cyclization of 8 to 17.—Compound **8** (4.06 g) was dissolved in methylene chloride (60 ml). Hünig base (1.42 g) was added. Bromine (0.54 ml) in methylene chloride (5 ml) was then poured into the well stirred solution at room temperature. After 15 min the solution was well washed with water, dried ($MgSO_4$), and concentrated. The residue (4.0 g) was dissolved in ethanol; on standing, some crystalline material (100 mg) separated, mp 214–218°. This was recrystallized from DMSO–ethanol (**17**): mp 224–225°; uv λ_{max} [MeOH], 245 [17,550], 265 [18,310], 359 mμ [11,750]; ir (Nujol), 1700, 1676 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.43 (q, 2), 4.16 (q, 2).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.75; H, 4.91; N, 19.60.

Reaction of 14 with Piperidine to 22 and 25.—Compound **14** (500 mg) was refluxed in piperidine overnight. The piperidine was removed and the residue dissolved in ether and allowed to stand. Crystals [357 mg, 56%, mp 194–198°] were deposited. Attempts to recrystallize from ethanol caused partial transformation to a faster moving material (tlc, silica gel–ethyl acetate). Purification was effected by preparative tlc (silica gel GF–ethyl acetate). The major slower moving spot eluted by ethyl acetate (290 mg), recrystallized from ether (100 mg) of **22**: mp 200–202°; uv λ_{max} (MeOH), 270 (10,610), 327 (25,050), 342 mμ (21,210); ir (Nujol), 1660 cm^{-1}; nmr [$(CD_3)_2SO$], δ 14.3 (s, 1, exchangeable sharp NH), 12.8 (s, 1, exchangeable broad NH), 7.58 (4, A_2B_2, approx), 3.62 (s, 8), 1.66 (s, 12); ms [70 eV] *m/e* 382 (1), 298 (1), 159 (100).

Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.80; H, 6.85. Found: C, 62.81; H, 7.27.

The faster moving material (52 mg) was crystallized from ethanol to give crystals, mp 266–268°.

Quantitative conversion of the slower moving isomer to the faster could be effected by heating at the melting point (200°) for 10 min under N_2. The residue was recrystallized from ethanol to mp 266–268°, identical by melting point, mixture melting point, tlc, and spectra with the minor product of the reaction (**25**): uv λ_{max} (MeOH), 230 (20,600), 246 (16,500), 320 mμ (11,100); ir (Nujol), 1735 ,1635 cm^{-1}; nmr [$(CD_3)_2SO$], δ 13.8 (s, 1, exchangeable), 8.5–7.2 (m, 4), 3.64 (s, 4), 1.66 (s, 6); ms (70 eV) M^+ 297.123 ($C_{15}H_{15}N_5O_2$ requires 297.31).

Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.77; H, 5.42. Found: C, 60.59; H, 5.09.

Reaction of 14 with Pyrrolidine to 23.—**14** (6 g) was refluxed in pyrrolidine (20 ml) overnight; excess amine was removed. The residue was crystallized and recrystallized from ethanol (**23**) (3.5 g, 50%, mp 226–228°): uv λ_{max} (MeOH), 266 (11,400), 328 (24,060), 342 mμ (21,140); ir (Nujol), 1667, 1636, 1615 cm^{-1}; nmr [$(CD_3)_2SO$], 13.8 δ (s, 1, exchangeable NH), 12.1(s, 1, broad exchangeable NH), 7.50 (4, A_2B_2, approx), 3.58 (m, 8, $-CH_2-N$), 1.92 (m, 8).

Anal. Calcd for $C_{18}H_{22}N_6O_2$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.77; H, 6.51; N, 23.40.

Reaction of 14 and Aniline.—Compound **14** (500 mg) was refluxed in aniline for 1 hr. The aniline was removed, the oil triturated with ethanol, and the resultant solid recrystallized from ethanol to give crystals (183 mg, 53%, mp 240–241°) identified by melting point, mixture melting point, and ir spectra as diphenylurea. No other crystalline material could be isolated from the mother liquors.

2-Benzimidazoleacetic Piperamide.—Ethyl 2-benzimidazole acetic ester (**17** g) was refluxed in piperidine (50 ml) for 1 hr. The mixture was poured into water and the solid (12.04 g, 60% mp 161–165°) collected. Recrystallization from water gave **26**: mp 162–163°; uv λ_{max} (MeOH), 243 (6740), 274 (7980), 281 mμ (8930); ir (Nujol), 3200, 1634, 1620 cm^{-1}; nmr ($CDCl_3$), δ 7.70, 7.00 (m, 4), 4.1 (s, 2), 3.56 (m, 4), 1.54 (s, 6).

Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.40; H, 6.77; N, 17.61.

Formation of 27 from 26.—To a solution of **26**, (2.433 g) in methylene chloride (40 ml) was added diethyl azodicarboxylate (1.916 g). The mixture was refluxed for 1 hr. Progress of the reaction could be followed by tlc (silica gel–ethyl acetate). The reaction mixture was poured onto a silica gel column made up in methylene chloride. Elution by methylene chloride gave a gum (0.5 g). The main band was eluted by 40–80% ethyl acetate in methylene chloride. This material crystallized (2.76 g, 66%). Recrystallization from ether–petroleum ether gave an analytical sample (**27**): mp 88°; uv λ_{max} [MeOH], 247 [6500], 269 [3690], 274 [8420], 283 mμ [8280].

Anal. Calcd for $C_{20}H_{27}N_5O_6$: C, 57.54; H, 6.52. Found: C, 57.49; H, 6.41.

Attempted Oxidative Cyclization of 27.—Bromine (933 mg) was added in one portion to a well stirred solution of **27** (2.116 g) in methylene chloride (50 ml) containing Hünig base ([1.658 g). The mixture was stirred at room temperature for 15 min [*i.e.*, until a negative starch–iodide test], washed with water, dried, and concentrated. The resultant brown foam was chromatographed (silica gel–methylene chloride–ethyl acetate) but no crystalline material could be isolated.

Formation of 31 from 2-Benzimidazoleacetonitrile (1).—2-Benzimidazoleacetonitrile[7] (1.57 g) was dissolved in DMF (3 ml). Dimethyl acetylenedicarboxylic ester (1.6 g) was added; an exothermic reaction ensued. The mixture was heated on a steam bath for 30 min. On cooling a solid separated which was collected and washed with methanol (870 mg, 32%, mp 284–288°). Recrystallization from DMF gave **31**: mp 290–292°; uv λ_{max} [MeOH], 228 [19,160], 255 [23,380], 284 [21,570], 387 mμ [10,100]; ir (Nujol), 2214, 1724, 1660 cm^{-1}; nmr [$(CD_3)_2SO$], 8.5 δ [d, 1, J = 7 Hz], 6.40 [s, 1], 3.90 [s, 3].

Anal. Calcd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.73. Found: C, 62.80; H, 3.52; N, 15.71.

Formation of 32 from Ethyl 2-Benzimidazoleacetic Ester (2).—Ethyl 2-benzimidazoleacetic ester (2.04 g) was dissolved in DMF (5 ml). Dimethyl acetylenedicarboxylic ester (1.56 g) was added. The exothermic reaction was heated for an hour on a steam bath, then stood in the ice box overnight. The crystals (505 mg, 16%, mp 221–223°] were crystallized from DMF to give **32**: mp 223–224°; uv λ_{max} (MeOH), 228 (18,000), 241 (19,980), 273 (9910), 298 [28,430], 357 mμ [16,100]; ir (Nujol), 3300, 1744, 1732, 1696, 1652 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.32; H, 4.40; N, 9.13.

Acetylation of 31 to 34.—Compound **31** (1.331 g) was slurried in methylene chloride (10 ml); Hünig base (714 mg) and acetyl chloride (440 mg) were added with stirring until dissolved. After 1 hr the methylene chloride was washed with water, dried ($MgSO_4$), and removed. The crystalline residue was recrystallized from methylene chloride/ethanol to give crystals (**34**): 1.13 g, 73%; mp 296–298°; uv λ_{max} (MeOH), 223 (19,140), 247 (17,500), 264 (17,890), 377 mμ (10,630); ir (Nujol), 2224, 1730, 1678 cm^{-1}.

Anal. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.59; N, 13.59. Found: C, 62.20; H, 3.41; N, 13.33.

Acetylation of 32 to 35.—Compound **32** (6.28 g) was acetylated by the above procedure to give a crude crystalline product (6.50 g), which was recrystallized from ethanol to give **35** (4.239 g, 60%, mp 144–146°): uv λ_{max} (MeOH), 236 (20,360), 299 (15,720), 359 mμ (15,200); ir (Nujol), 1746, 1725, 1692, 1662 cm^{-1}; nmr ($(CD_3)_2SO$), 6.37 δ (s, 1), 4.22 (q, 2), 3.86 (s, 3), 2.56 (s, 3).

Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.74; H, 4.61; N, 8.01.

Formation of 33 from 1-Methyl-2-benzimidazoleacetonitrile (3).—1-Methyl-2-benzimidazoleacetonitrile (**3**) (2.18 g) was dissolved in DMF (10 ml). Dimethyl acetylenedicarboxylic ester (1.42 g) was added and heated on a steam bath for 1 hr. On cooling crystals (0.86 g, 30%, mp 235–237°) were deposited. They were collected and recrystallized from DMF to **33**: mp 239°; uv λ_{max} (MeOH), 229 (22,340), 253 (24,910), 295 (21,450), 385 mμ (10,960); ir (Nujol), 2220, 1734, 1668 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_3O_4$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.96; H, 3.92; N, 14.76.

Methylation of 31 to 33.—Compound **31** (665 mg) was dissolved in DMF (25 ml) at 100°, NaH 50% in mineral oil (125 mg) added. The sodio derivative precipitated. Methyl iodide (0.6 ml) was added. A clear solution developed within a few minutes.

Heating was continued for 90 min. On cooling a solid separated 33 [402 mg, 56%, mp 236–238°]. The melting point of this material was not depressed on admixture with a sample of material from the above experiment. The uv and ir spectra were identical.

Registry No.—1, 4414-88-4; 2, 14741-71-0; 4, 22712-49-8; 8, 22712-50-1; 9, 22712-43-2; 11, 22712-44-3; 12, 22712-45-4; 14, 22712-47-6; 15, 25183-97-5; 16, 22712-48-7; 17, 22776-80-3; 22, 25184-00-3; 23, 25184-01-4; 25, 25184-02-5; 26, 25184-03-6; 27, 25184-04-7; 31, 25184-05-8; 32, 25184-06-9; 33, 25184-07-0; 34, 25184-08-1; 35, 25150-05-4; N-ethyl-2-benzimidozoleacetonitrile, 25184-09-2; ethyl- 1-methyl-2-benzimidozoleacetic ester, 2735-61-7.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens and helpful discussions with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Dihydro-Reissert Compounds

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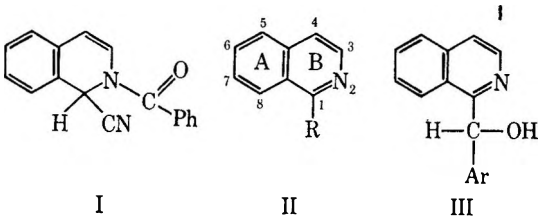
The dihydro-Reissert compound IV has been alkylated at C-1 to give VIIa, b, or c. Acid hydrolysis of VIIc afforded the acid amide VIII, from which the corresponding methyl ester amide IX could be derived. Hydrolysis of either VIIc or VIII in phosphoric acid furnished the amino acid X. Esterification to XII followed by N-benzoylation resulted in regeneration of the methyl ester amide IX. N-Methylation of the methyl ester XII could be achieved through reductive alkylation. But attempts at internal Friedel–Crafts acylation to obtain an ochotensimine analog did not yield any of the desired tetracyclic product.

Three practical procedures are presently available for the preparation of Reissert compounds,[1-3] and these methods allow for the synthesis of a wide variety of compounds related to structure I.

Two reactions of Reissert compounds have proven particularly useful in the synthesis of benzylisoquinolines. These are alkylation by alkyl halides followed by hydrolysis to yield C-1 alkylated isoquinolines (II),[4] and base-catalyzed condensation with aromatic aldehydes succeeded by hydrolysis to afford isoquinolines of type III.[5,6]



I II III

The literature is virtually devoid, however, of attempts aimed at expanding the Reissert approach to the direct synthesis of 1,2,3,4-tetrahydroisoquinolines. In fact, in only two cases have Reissert compounds lacking the C(3)–C(4) double bond been reported. These two cases are the preparation[6] of a compound tentatively identified as IV, a structure which we confirm in this report, and the synthesis of the amino alcohols V.[7] In neither instance were further reactions attempted on these species for which we now suggest the name "dihydro-Reissert compounds."

(1) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 11 (1955); F. D. Popp, *Advan. Heterocycl. Chem.*, 9 (1968).
(2) J. M. Groscheintz and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **63**, 2021 (1941).
(3) F. D. Popp and W. Blount, *Chem. Ind. (London)*, 550 (1961).
(4) F. D. Popp and J. W. Wefer, *Chem. Commun.*, 207 (1966).
(5) L. Walters, N. Iyer, and W. E. McEwen, *J. Amer. Chem. Soc.*, **80**, 1177 (1958).
(6) H. W. Gibson and F. D. Popp, *J. Chem. Soc. C*, 1860 (1966).
(7) W. Schneider and E. Kaemmerer, *Arch. Pharm.* (Weinheim), **299**, 817 (1966).

Our interest in dihydro-Reissert compounds arose from efforts to synthesize the spirobenzylisoquinoline alkaloid ochotensimine (VI) which incorporates a 1,1-disubstituted 1,2,3,4-tetrahydroisoquinoline skeleton. In the preparation of isoquinolines II and III, the elimination of cyanide ion under hydrolytic conditions is greatly facilitated by the concurrent aromatization of ring B. In dihydro-Reissert compounds, however, such complete aromatization is impossible, and it was surmised that hydrolysis of the cyano group and the amide could proceed without elimination.

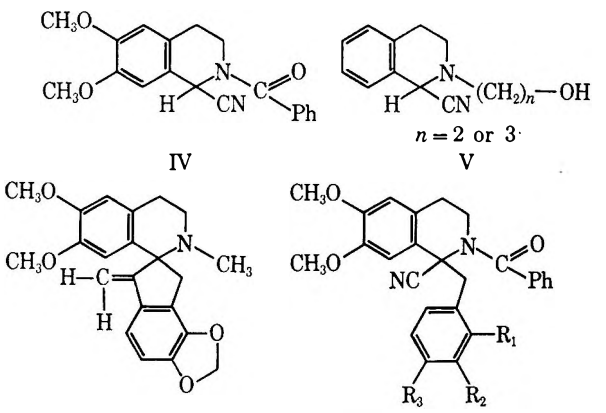
As described in the literature,[3,6] it was found that 3,4-dihydro-6,7-dimethoxyisoquinoline, prepared from N-formylhomoveratrylamine by the Bischler–Napieralski cyclization, could be condensed in the presence of potassium cyanide and benzoyl chloride to afford IV. Treatment of IV with 1 equiv of sodium hydride in dimethylformamide, followed by addition of deuterium oxide, gave starting material in which the hydrogen at C-1 had been completely exchanged for deuterium. It was then found that the anion of IV when treated with benzyl chloride gave a high yield of the tricyclic cyanoamide VIIa. This product was fully characterized spectroscopically. Its formation serves to demonstrate that alkylation of a dihydro-Reissert species proceeds for all practical purposes as readily as that of a Reissert compound.

Similarly prepared were the tricyclic cyanoamides VIIb and VIIc. The oxygenation pattern in the latter product is closely related to that for ochotensimine (VI), so that solely this material was employed in the subsequent investigations.

It was found possible to convert the nitrile function in VIIc to a carbonyl group by first complexing VIIc with zinc chloride in ether, and then hydrolyzing the complex in water. The resulting crystalline acid amide VIII (92% yield) was then esterified.

It will be recalled that loss of cyanide ion occurs readily upon hydrolysis of an alkylated Reissert compound to generate a C-1 substituted isoquinoline sys-

tem. With the alkylated dihydro-Reissert compound VIIc, on the other hand, hydrolysis with phosphoric acid, followed by dilution with water and neutralization, gave rise to a high yield of the desired amino acid X, also obtained by acid hydrolysis of VIII.



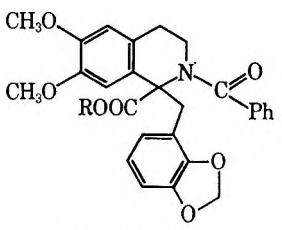
IV

$n = 2$ or 3

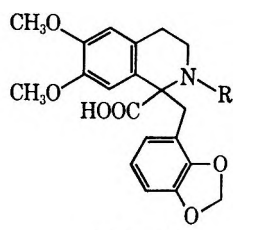
V

VI

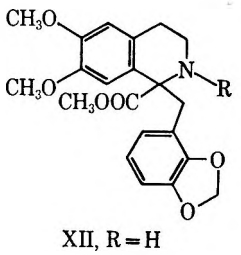
VIIa, $R_1 = R_2 = R_3 = H$
b, $R_1 = H$; $R_2 = R_3$ = methylenedioxy
c, $R_1 = R_2$ = methylenedioxy; $R_3 = H$



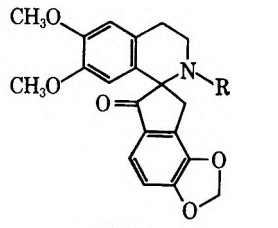
VIII, R = H
IX, R = CH_3



X, R = H
XI, R = CH_3



XII, R = H
XIII, R = CH_3



XIV

Although the insolubility of the amino acid X precluded full characterization, a number of derivatives were prepared. The methyl ester XII was formed by refluxing X in methanolic hydrogen chloride followed by column chromatography over silica gel. N-Benzoylation of this ester provided the methyl ester amide IX, which had earlier been prepared from the acid amide VIII.

N-Methylation of the methyl ester XII was achieved through reductive alkylation employing formalin over a palladium on carbon catalyst. The crystalline tertiary amine XIII was somewhat unstable to air. It could be hydrolyzed to the amino acid XI, and this material could in turn be reesterified to XIII.

A number of attempts to cyclize the tricyclic 1,1-disubstituted benzylisoquinolines VIIc and VIII–XIII by internal Friedel–Crafts type acylation to obtain a species such as XIV were unsuccessful. The same difficulty has been noted by Uyeo in closely related systems.[8] However, Kametani has succeeded in carrying out a cyclization of this type,[9] although in poor yield. Our own efforts at Friedel–Crafts acylation were abandoned when it was found that a biogenetic approach to the spirobenzylisoquinolines of type XIV was more promising.[10]

In conclusion then, it can be stated that dihydro-Reissert compounds can be readily prepared from 3,4-dihydroisoquinolines. The C-1 alkylation of these derivatives proceeds in high yield, thus providing an alternate route to 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines. Finally, removal of the benzoyl group and modification of the cyano function of C-1 alkylated dihydro-Reissert compounds can be carried out without destroying the C-1,1 disubstitution pattern or altering the oxidation state of ring B.

Experimental Section

Standard Experimental Procedures.—All infrared spectra were obtained using a Perkin-Elmer 257 grating infrared spectrometer. The ultraviolet spectra were taken in 95% ethanol and were measured on a Coleman Hitachi 124 double beam spectrophotometer. The nmr data were recorded on a Varian A-60A spectrometer. Except where specified otherwise, deuteriochloroform was the solvent and tetramethylsilane was employed as an internal reference. All mass spectra were obtained on a AEI-MS-902 spectrometer at 70 eV.

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

Preparation of 2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (IV).—To 22.6 g (0.118 mol) of 3,4-dihydro-6,7-dimethoxyisoquinoline in 200 cc of methylene chloride was added 35 g (0.54 mol) of KCN in 80 ml of water. Then 48 g (0.34 mol) of benzoyl chloride was added dropwise over 3 hr. After stirring an additional hour, the methylene chloride layer was separated, washed with 10% HCl, 5% NaOH, and dried over magnesium sulfate. Filtration followed by removal of solvent gave a brown oil which after vacuum drying, scratching, and washing with cold methanol yielded white prisms, 25.4 g (67%), mp 215–216°, lit.[6] mp 212–213°; ir ($CHCl_3$) 6.08 μ (amide C=O) and 4.48 (C≡N).

Alkylation of IV.—In a 25-ml flask was placed a suspension of 644 mg (2 mmol) of IV in 4 ml of distilled dry DMF. To the mixture was added 380 mg (2.7 mmol) of benzyl chloride and no visible change was noted on this addition. The suspension was stirred and chilled in an ice bath and then treated with 48 mg (2.0 mmol) of sodium hydride. The ice bath was removed and stirring was continued for 3 hr during which some yellow color appeared in the mixture. The contents were poured into a large volume of water and extracted with chloroform. The chloroform was dried over magnesium sulfate and evaporated to give a white solid which after recrystallization from methanol provided 691 mg (84%) of 1-benzyl-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIa). Mp 185–186°; ir ($CHCl_3$) 6.07 μ (amide C=O) and 4.48 (C≡N); nmr δ 3.88 (s, 6, $ArOCH_3$), 3.94 (AB, 2, ics = 53 Hz and J = 13 Hz, $PhCH_2$), 6.5 to 7.5 (m, 12, Ar-H).

Anal. Calcd for $C_{26}H_{24}O_3N_2$: C, 75.70; H, 5.87; N, 6.79. Found: C, 75.45; H, 5.98; N, 6.60.

Using the appropriately substituted benzyl chlorides, 1-(3′,4′-methylenedioxylbenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIb) and 1-(2′,3′-methylenedioxybenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIc) were prepared in the same manner as VIIa. The following data were obtained for these compounds. VIIb: ir ($CHCl_3$) 6.07 μ (amide C=O), 4.48 (C≡N); mp 191–192°; uv max (95% C_2H_5OH), 285 mμ (log ϵ 3.68); nmr δ 3.92, 2.94 (s, 6, $ArOCH_3$), 5.90 (s, 2, $O\text{-}CH_2\text{-}O$), 6.1 to 7.5 (m, 10, ArH). VIIc: ir ($CHCl_3$) 6.07 μ (amide C=O), 4.48 (C≡N); mp 187–188°; uv max (95% C_2H_5OH), 284 mμ (log ϵ 3.70); nmr δ 3.82 (s, 6, $ArOCH_3$), 3,89 (AB, 2, ics = 48 Hz, J = 13.5 Hz, Ar-CH_2-C(CN)-), 5.53 (AB, 2, ics = 5 Hz, J = 1.3 Hz, $O\text{-}CH_2\text{-}O$),

(8) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc. C*, 3051 (1968).

(9) T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Jap.*, **88**, 1123 (1968).

(10) M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, **91**, 4009 (1969).

6.2 to 7.5 (m, 10, Ar-H); mass spectrum M^+ at m/e 456 for $C_{27}H_{24}O_5N_2$.

1-(2′,3′-Methylenedioxybenzyl)-2-benzoyl-6,7-dimethoxy-1,2,-3,4-tetrahydroisoquinaldic Acid (VIII).—In a 500-ml flask was placed a mixture of the above VIIc (10 g, 0.022 mol), 200 cc of dry ether, and 10 g (0.074 mol) of anhydrous zinc chloride. The mixture was chilled to 0° and dry HCl was bubbled in for 8 hr during which time the formation of a yellow complex was noted. The mixture was then allowed to stand for an additional 10 hr and the ether evaporated to a yellow hygroscopic mass which was dissolved in water and chloroform. The chloroform layer was separated, washed with water, dried over magnesium sulfate, filtered, and evaporated. White crystals were obtained which recrystallized well from methanol. The yield of VIII by this procedure was 9.5 g (92%). Mp 216–218°; ir ($CHCl_3$) 5.79 to 5.85 μ (acid C=O), 6.13 (amide C=O); uv max (95% C_2H_5OH), 285 mμ (log ϵ 4.06); nmr δ 3.73, 3.78 (s, 6, $ArOCH_3$), 3.85 (AB, 2, ics = 40 Hz, J = 14 Hz, $Ar-CH_2-\underset{|}{C}-COOH$), 5.75 (AB, 2, ics = 7 Hz, J = 0, $O-CH_2-O$), 6.1 to 7.6 (m, 10, ArH); mass spectrum M^+ at m/e 475 for $C_{27}H_{25}O_7N$.

Anal. Calcd for $C_{27}H_{25}O_7N$: C, 68.20; H, 5.30; N, 2.98; O, 23.56. Found: C, 68.05; H, 5.35; N, 3.05; O, 23.90.

Preparation of 1-(2′,3′-Methylenedioxybenzyl)-2-benzoyl-1,2,-3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (IX). Method 1. Direct Esterification.—A mixture consisting of 500 mg of VIII, 10 cc of water, 10 cc of concentrated HCl, and 10 cc of methanol was refluxed together vigorously for 12 hr. During the reflux, the product (IX) separated from the reaction mixture as white crystals. It was collected by filtration and after drying the crude methyl ester was recrystallized from methanol–water, 413 mg (80%).

Method 2. Formation of Acid Chloride and Reaction with Methanol.—A sample of VIII which had been vacuum dried over P_2O_5 was stirred for 3 hr with 1 cc of purified thionyl chloride. The excess reagent was evaporated and 10 ml of methanol added. After standing for 1 hr, the methanol was evaporated to yield a white residue which was recrystallized as above to give 490 mg (95%) of IX.

The products produced by the above methods were identical in all respects and gave the following analytical data. Mp 215–216°; ir ($CHCl_3$) 5.79 μ (ester C=O), 6.13 (amide C=O); uv max (95% C_2H_5OH), 283 mμ (log ϵ 4.10); nmr δ 3.70 (s, 3, $COOCH_3$), 3.86, 3.92 (s, 6, $ArOCH_3$), 3.98 (AB, 2, ics = 46 Hz, $O-CH_2-O$), 6.1 to 7.5 (m, 10, Ar-H); mass spectrum M^+ at m/e 489 for $C_{28}H_{27}O_7N$.

Anal. Calcd for $C_{28}H_{27}O_7N$: C, 68.75; H, 5.58; N, 2.86; O, 22.91. Found: C, 68.52; H, 5.76; N, 2.80; O, 23.20.

1-(2′,3′-Methylenedioxobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid (X).—This amino acid can be prepared by the phosphoric acid catalyzed hydrolysis of either VIIc or VIII.

In a 100-cc flask, 40 cc of 85% phosphoric acid was heated under N_2 in an oil bath to 100°. There was then added 5.0 g of powdered starting material (VIIc or VIII) and the mixture was heated for 10 min while stirring vigorously. Benzoic acid appeared on the inner walls of the flask. At the end of the heating period 40 ml of water was added, the mixture cooled, and the benzoic acid removed by filtration. The light yellow filtrate was carefully basified to pH 7 with concentrated ammonium hydroxide while cooling in an ice bath. This caused precipitation of a creamy mass which after collection, washing with water, and vacuum drying gave light tan crystals, mp 275° dec, which left no residue on ignition. Regardless of which starting material was used, the yield was 90%. Due to its extreme insolubility in all common solvents, little direct spectral data were obtained for the amino acid; ir ($CHCl_3$) 6.15 μ (amino acid C=O). Instead, the characterization of X rested on further chemical transformations.

1-(2′,3′-Methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (XII).—The above amino acid, X, 12 g (0.034 mol), was suspended in 300 ml of methanol and saturated for 4 hr with dry HCl. The resulting solution was refluxed for 60 hr under N_2, during which some darkening occurred. The brown reaction mixture was evaporated to dryness, water added, and the mixture basified with ammonium hydroxide and extracted with ether. After drying over magnesium sulfate, filtration, and removal of solvent, the crude ester was obtained as a brown oil. Purification by chromatography over a $1^1/_4$ in. × 4 ft silica gel column with ether eluent gave 8.2 g (66%) of XII as a light tan oil. Ir ($CHCl_3$) 5.80 μ (ester C=O); nmr δ 3.62 (s, 3, $COOCH_3$), 3.77, 3.83 (s, 6, $ArOCH_3$), 5.79 (s, 2, $O-CH_2-O$), 6.4 to 7.2 (m, 5, ArH); mass spectrum M^+ at m/e 385 correct for $C_{21}H_{23}O_6N$.

A sample of the tan oil was benzoylated with benzoyl chloride in the presence of triethylamine to give IX.

Anal. Calcd for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.15; H, 6.02.

1-(2′,3′-Methylenedioxybenzyl)-2-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (XIII).—The ester XII, 1.5 g (3.9 mmol), was dissolved in 70 ml of methanol, treated with 10 cc of formalin, and hydrogenated over 0.5 g of 5% Pd on carbon at room temperature for 12 hr. Crystallization of the product by trituration with ether gave 800 mg (51%) of white crystals which slowly turned yellow when exposed to air. Mp 112–114°; ir ($CHCl_3$) 5.82 μ (ester C=O); uv max (95% C_2H_5OH) 284 mμ (log ϵ 3.76); nmr δ 2.52 (s, 3, $N-CH_3$), 3.72 (s, 3, $COOCH_3$), 3.80, 3.82 (s, 6, $ArOCH_3$), 5.68 (AB, 2, ics = 12 Hz, J = 1.5 Hz, $O-CH_2-O$), 6.1 to 6.6 (m, 5, ArH); mass spectrum M^+ at m/e 399 for $C_{22}H_{25}O_6N$.

Anal. Calcd for $C_{22}H_{25}O_6N$: C, 66.15; H, 6.31. Found: C, 65.99; H, 6.25.

1-(2′,3′-Methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,-4-tetrahydroisoquinaldic Acid (XI).—A solution of 700 mg (1.75 mmol) of XIII in 20 ml of methanol was mixed with 1.0 g of KOH in 20 ml of water and refluxed for 12 hr to give a pale yellow solution. The mixture was cooled and the methanol evaporated. The residual aqueous phase was washed several times with ether. The aqueous solution was then adjusted to pH 6 with phosphoric acid whereupon white crystals appeared. After collection on a filter and drying, the slightly tan crystals weighed 532 mg (79%). Mp 200–205° dec; ir ($CHCl_3$) 6.09 μ (acid C=O); nmr δ 2.90 (s, 3, $N-CH_3$), 3.84 (s, 6, $ArOCH_3$), 5.81 (s, 2, $O-CH_2-O$), 5.7 to 7.3 (m, 5, Ar–H), 7.8 (s, 1, COOH).

Reesterification of XI with methanol–HCl gave a 70% yield of XIII.

Registry No.—VIIa, 25186-58-7; VIIb, 25186-59-8; VIIc, 25186-60-1; VIII, 25186-61-2; IX, 25186-62-3; X, 25186-63-4; XI, 25186-64-5; XII, 25150-09-8; XIII, 25186-65-6.

Acknowledgments.—The authors are grateful to the National Institutes of Health for Research Fellowship 2 FO1 GM-33,013-03 to C. D. J., and for Research Grant 9 RO1 HE 12971-08 from the National Institutes of Health.

Cycloalkapyrrolones *via* Decarboxylative Ring Closure of Pyrrole-3-alkanoic Acids and Derivatives

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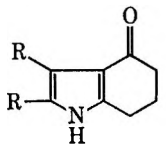
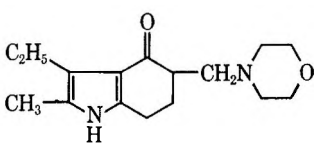
Received February 10, 1970

Acylation of pyrroles 1–2 with ω-(methoxycarbonyl)acyl chlorides followed by catalytic reduction produces 3-pyrrolealkanoic acid esters (4a–d) with chains bearing 3 and 4 methylene groups. Alkylation of malonic ester with quaternary salts of Mannich bases 10a–c followed by hydrolysis and decarboxylation yields derivatives 4e–i and 14a–b with chains bearing 2 methylene groups. Treatment of these intermediates with polyphosphoric acid affords cycloalkapyrrolones of classes III and IV. One of these compounds, a 7-ketotetrahydroindole (5), was aromatized to produce the corresponding indol-7-ol 9. The infrared and ultraviolet spectra and their relationship to structure are discussed.

Our interest in cycloalkapyrrolones stems from the finding that Mannich bases derived from 6,7-dihydroindol-4(5H)-ones (I) exhibit central nervous system depressant effects.[1] The morpholino Mannich base II (molindone) has been found to be a potent antipsychotic agent in man.[2]

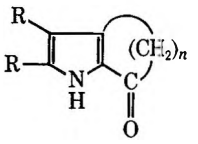


I

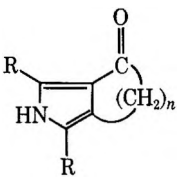


II

In order to study related systems we required appropriate cycloalkapyrrolones of classes III and IV.



III



IV

Although compounds of type I have been described,[3] little work has been done on systems included in III and IV.[4] In this paper we shall describe general synthetic routes to these latter systems.

It has been reported[5] that compounds **1a–b** undergo Friedel–Crafts acetylation. Accordingly, we found that acylations of **1a** and **2** with the acid chloride esters of succinic and glutaric acids give the keto diesters **3a–d** easily and in good yield (Scheme I).

The conversion of the esters **3a–d** to the subsequent intermediates **4a–d** requires selective reducing conditions. Ketopyrroles, which bear some chemical resemblance to vinylogous amides, are not reduced by sodium borohydrides. More drastic hydride reduction, as with diborane, can result in ester reduction as well as ketone reduction.[6,7]

Wolff–Kishner reduction, when applied to compounds of type **3** ($n = 2$), has been found to result in pyridazine formation.[8]

Catalytic hydrogenation under conditions of high temperature and pressure has been used to reduce ketopyrroles, some bearing ethoxycarbonyl groups on the pyrrole nucleus.[9] It seemed probable that the presence of electron-attracting ethoxycarbonyl groups would enhance the ketonic character of compounds **3a–d**, making such drastic conditions unnecessary.

Indeed, it was found that ketoalkanoic esters **3a–d** underwent very rapid reduction and hydrogenolysis to yield esters **4a–d** when subjected to the action of hydrogen at 50 psi at ambient temperatures in the presence of palladium on charcoal. In all cases the theoretical uptake of hydrogen was complete within 2 hr, whereupon the reaction ceased. Reduced products were obtained in high yield.

Regarding the cyclization of systems related to **4a–d**, it was found that polyphosphoric acid (PPA) was a superior agent for the conversion of indole-3-alkanoic acids into cycloalka[*b*]indolones.[10] Although indole-alkanoic acids are stable materials, pyrrolealkanoic acids which lack electron-withdrawing substituents on the ring are relatively unstable compounds.[11] The preparation and isolation of these compounds was avoided by generating them from **4a–d** *in situ* in PPA at 130–140°. Ester cleavage, decarboxylation, and ring closure occurred in one step to yield the six- and seven-membered cycloalkapyrrolones **5–8**.

Previous workers[12] found that treatment of compounds of type I with Pd–C in high-boiling hydrocarbon

(1) K. Schoen, I. J. Pachter, and A. A. Rubin, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, No. M46.

(2) A. A. Sugerman and J. Herrmann, *Clin. Pharmacol. Ther.*, **8**, 261 (1967); G. M. Simpson and L. Krakov, *Curr. Ther. Res. Clin. Exp.*, **10**, 41 (1968).

(3) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 20 (1962); K. E. Schulte, J. Reisch, and H. Lang, *Chem. Ber.*, **96**, 1470 (1963); S. Hauptmann and M. Martin, *Z. Chem.*, **8**, 333 (1968); J. M. Bobbitt and C. P. Dutta, *Chem. Commun.*, 1429 (1968).

(4) (a) M. E. Flaugh and H. Rappaport, *J. Amer. Chem. Soc.*, **90**, 6877 (1968), have reported preparation of a 4,5-dihydrocyclopenta[*b*]pyrrol-6(1H)-one. (b) A. J. Castro, *et al.*, Abstracts, 158th Meeting of the American Chemical Society, New York, N. Y., Sept. 1969, No. ORGN 85, reported the isolation of 4,5-dihydroindol-7(6H)-one in very low yield from the reaction of pyrrolyl magnesium bromide with 4-chlorobutyronitrile. (c) The isolation of both 6,7-dihydroindol-4 (5H)-one and 4,5-dihydroindole-7(6H)-one from the cyclization of the mixed carbonic anhydride of 4-(2-pyrrolyl)butyric acid has been recently reported. The conversion of these compounds to the corresponding hydroxy indoles is also described: M. Julia, French Patent 1540484 (1968); *Chem. Abstr.*, **71**, 81163w (1969).

(5) H. Fischer and E. Fink, *Hoppe-Seyler's Z. Physiol. Chem.*, **283**, 152 (1948); H. Fischer and W. Kutscher, *Justus Liebigs Ann. Chem.*, **481**, 201 (1930).

(6) R. L. Hinman and S. Thodoropoulous, *J. Org. Chem.*, **28**, 3052 (1963), and references therein.

(7) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1967).

(8) H. Fischer, H. Bayer, and E. Zaucker, *Justus Liebigs Ann. Chem.*, **486**, 55 (1931); H. Fischer and W. Kutscher, *ibid.*, **481**, 193 (1930).

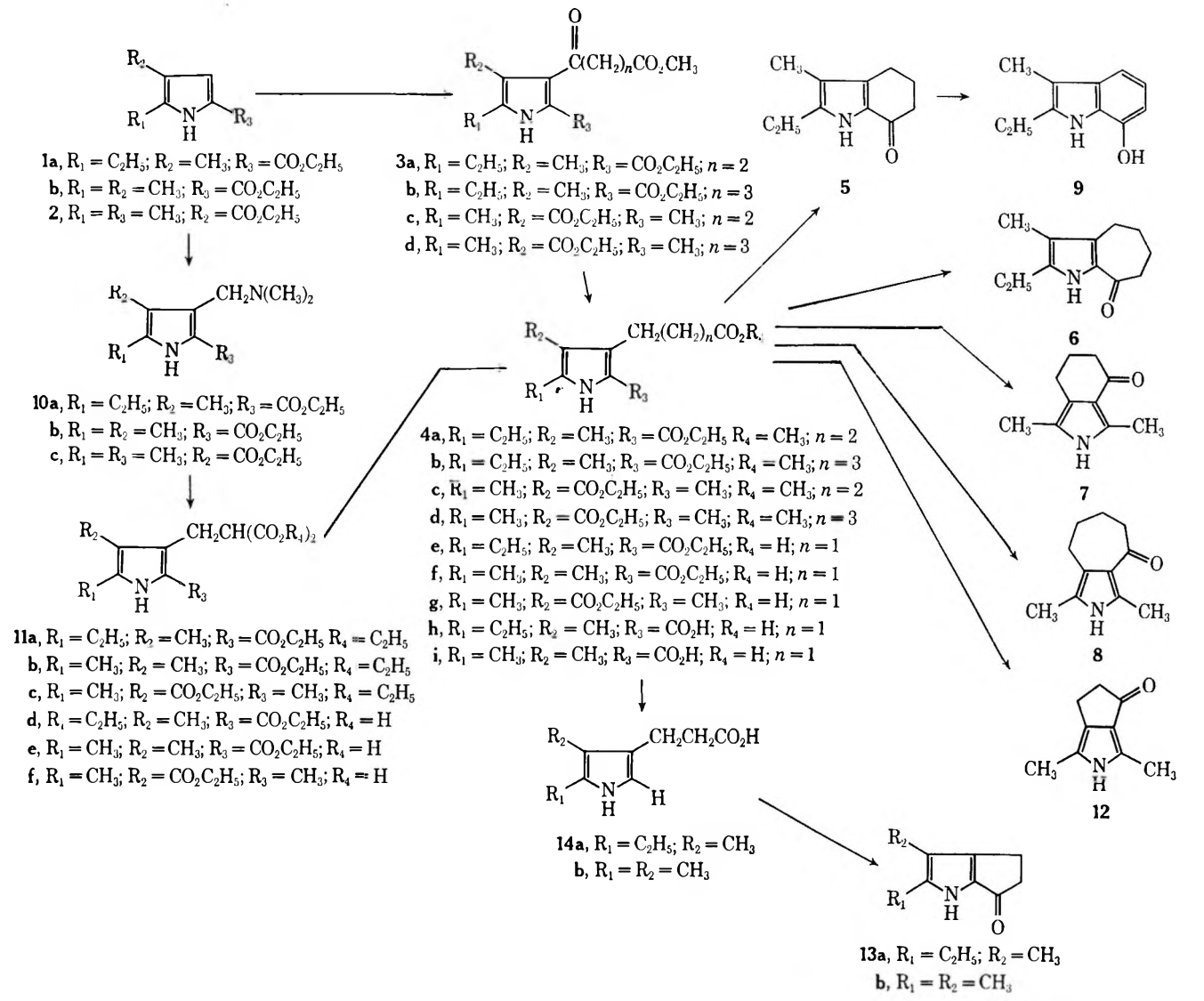
(9) F. K. Signaigo and H. Adkins, *J. Amer. Chem. Soc.*, **58**, 709 (1936); R. A. Nicolaus, G. Narni, M. Piatelli, and A. Vitale, *Rend. Accad. Sci. Fis. Mat., Naples*, **26** [4], 135 (1959); *Chem. Abstr.*, **55**, 14426*f* (1961).

(10) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 863 (1967).

(11) These compounds darken rapidly on exposure to air and/or light: *cf.* H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, pp 271–272.

(12) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 5262 (1965); H. Pleininger and K. Klinga, *Chem. Ber.*, **101**, 2605 (1968).

SCHEME I



solvents afforded 4-hydroxyindoles. Similar treatment of **5** has been found to result in formation of the indol-7-ol **9**, suggesting a useful synthetic route to these compounds.[4c] Attempts to aromatize **7** were unsuccessful.

Next we undertook the synthesis of the cyclopentapyrrolones. In reactions related to those which gave **3a–d**, we found that **1a** with ethylmalonyl chloride resulted only in recovery of starting material. Consequently another method of elaborating the propionic acid side chain was sought.

The observation has been made[13a] that the ethoxycarbonyl group in compounds of the type **1a** and **1b** exhibits a profound deactivating effect on the free β position toward electrophilic attack. While a later report[13b] indicated that 2-methyl-5-carbethoxypyrrole-3-propionic acid underwent the Mannich reaction with piperidine (but not with diethylamine or dimethylamine), this reactivity was attributed to stabilization of the product by inner salt formation, since the ethyl ester failed to react. We have found that both **1a** and **1b** readily undergo the Mannich reaction to give **10a** and **10b** in good yield. Compound **2** has been reported to undergo the Mannich reaction with diethylamine and piperidine,[14] although the products were described only as their perchlorate salts. Attempts to free the bases from these salts were reported to be unsuccessful. In our hands no difficulty was experienced in preparing **10c** from **2**.

Quaternization of **10a–c** with methyl sulfate, followed by treatment with sodiomalonic ester gave the corresponding substituted malonic esters **11a–c**.[15] These esters could be selectively hydrolyzed to the free malonic acids **11d–f** by refluxing briefly with methanolic KOH. Decarboxylation to give **4e–g** was effected by heating above the melting point until cessation of gas evolution. Acid ester **4g** was converted directly to **12** by heating with PPA.

Hydrolysis of **4e** and **4f** to the dicarboxylic acids **4h** and **4i** was effected by heating with aqueous alkali. The diacids, which were isolated but not characterized, were decarboxylated by heating briefly in water on the steam bath to give the pyrrolepropionic acids **14a** and **14b**. This sequence of reactions for preparing these important pyrrole derivatives may be considered as an

(13) (a) S. F. MacDonald, *J. Chem. Soc.*, 4176 (1952); (b) A. Triebs and W. Ott, *Justus Liebigs Ann. Chem.*, **615**, 137 (1958).

(14) H. Fischer and C. Nenitzescu, *ibid.*, **443**, 113 (1925).

(15) W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959).

TABLE I

CARBONYL STRETCHING FREQUENCIES OF CYCLOALKAPYRROLONES[a]

	Ring size	Compd	$\nu_{C=O}$, cm^{-1}
Cycloalka[*b*] series	5	**13a**	1657
	5	**13b**	1658
	6	**5**	1643, 1630
	7	**6**	1612
		2-Acetyl-3,4,5-trimethylpyrrole	1624[b]
		2-Acetyl-3,4-dimethyl-5-*n*-propylpyrrole	1630
Cycloalka[c] series	5	**12**	1690[c]
	6	**7**	1663
	7	**8**	1650
		3-Acetyl-2,4,5-trimethylpyrrole	1657[b]

[a] 5×10^{-3} *M* in CCl_4. [b] Reference 17. [c] 1.8×10^{-3} *M*.

TABLE II

ULTRAVIOLET SPECTRA OF CYCLOALKAPYRROLONES[a]

	Ring size	Compd	λ_{max}, mμ	$10^3\epsilon$	θ
Cycloalka[*b*] series	5	**13b**	292	20.2	0
			257.5	7.68	
	6	**5**	305.5	19.6	10
			268[b]	5.82	
	7	**6**	314	16.7	24
			270[b]	5.37	
		2-Acetyl-3,5-dimethyl-4-ethylpyrrole	308	19.6	10
			266[b]	4.70	
Cycloalka[c] series	5	**12**	305	3.81	0
			250	13.4	
	6	**7**	306	3.98	22
			254	11.5	
	7	**8**	302	3.73	35
			253.5	8.85	
		3-Acetyl-2,5-dimethyl-4-*n*-propylpyrrole	296	4.56	27
			253.5	10.7	

[a] Solvent ethanol. [b] Shoulder.

alternate to several described in the literature[13,16] which are very laborious and/or require difficultly accessible starting materials. The 2,3-dialkyl-5-ethoxycarbonylpyrroles required for our scheme are easily available.[5,9] PPA proved useful for the cyclization of **14a–b** and the five-membered cycloalkapyrrolones **13a–b** were synthesized.

It has been shown that[17] the carbonyl stretching frequency of 2-acylpyrroles in dilute carbon tetrachloride solution is appreciably lower than that of the 3-acyl derivatives. This effect is presumably due to intramolecular hydrogen bonding, and is shown by the cycloalkapyrrolones (Table I). In addition, a lowering of the carbonyl stretching frequency is noted in going from the five- to the seven-membered cycloalkapyrrolones. This behavior is parallel to that observed for a series of closely related cycloalka[*b*]indolones,[18a] as well as the benzocyclanones,[18b] and was attributed to changes in the C–O bond character with increasing bond angle.[18b] A splitting of the carbonyl band of the six-membered ketone **5** is observed. This behavior was also noted with the six-membered ketones in the indolone series.[18a]

The ultraviolet spectra of the cycloalkapyrrolones (Table II) show behavior which conforms to a general pattern previously established[19] for pyrroles substituted with –M substituents. In both series, the intensity of the major band is decreased with increasing ring size. This effect may be attributed to the inhibition of coplanarity of the carbonyl group with the pyrrole ring by nonbonded interactions in the saturated ring, which increase with increasing ring size. This effect has already been noticed in the previously mentioned cycloalka[*b*]indolones,[18a] which provides an interesting parallel to the present work.

By use of the $\cos^2\theta$ rule,[20] the angle θ by which the carbonyl group is twisted out of the plane of the aromatic ring may be approximated. For the cycloalka[*b*]pyrrolones these angles are considerably smaller than in the corresponding cycloalka[*b*]indolones.[18a] This may be rationalized by postulating that canonical forms of the cycloalka[*b*]pyrrolones such as V are important contributors to the total structure of III, whereas forms such as VI are not as important to the total

(16) (a) H. Plieninger, P. Hesa, and J. Rupert, *Chem. Ber.*, **101**, 240 (1968); (b) F. Morsingh and S. F. MacDonald, *J. Amer. Chem. Soc.*, **82**, 4377 (1960).

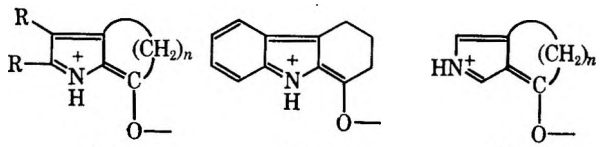
(17) R. W. Guy and R. A. Jones, *Aust. J. Chem.*, **19**, 107 (1966).

(18) (a) T. Shioiri, K. Ishizumi, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1010 (1967); (b) W. M. Schubert and W. A. Sweeney, *J. Amer. Chem. Soc.*, **77**, 4172 (1955).

(19) U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

(20) $\cos^2\theta = \epsilon/\epsilon^\circ$, where ϵ° is the extinction coefficient for the planar homolog ($\theta = 0°$): E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

picture of the cycloalkaindolones since this structure requires disturbance of benzenoid resonance. This concept has already been employed to explain differences in chemical reactivity between pyrroles and indoles.[6] Application of the $\cos^2\theta$ rule to the cycloalka[*c*] series yields angles which are in the same range as those of the cycloalka[*b*]indolones, indicating that form VII is a less significant contributor to IV.



V VI VII

The absorption bands of the type III ketones exhibit concomitant bathochromic and hypochromic effects with increasing ring size, behavior typical of nonalternant aromatic systems.[21] However, the type IV ketones show spectral behavior which is more typical of alternant systems such as the benzocyclanones.[22] It is of interest to note that open-chain trisubstituted pyrrole ketones are also apparently twisted out of plane.

The nmr spectrum of compound **5** (see Experimental Section) was determined and appears consistent with the proposed structure.

Experimental Section[23]

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methyl-γ-oxopyrrole-3-butyrate (3a).—Aluminum chloride (200 g, 1.5 mol) was added in large portions to a solution of ethyl 2-ethyl-3-methylpyrrole-5-carboxylate (136 g, 0.75 mol) and methyl 3-(chloroformyl)-propionate (Aldrich, 450 g, 3.0 mol) in 2.2 l. of carbon disulfide contained in a 5-l. 3-necked flask equipped with a mechanical stirrer and a reflux condenser topped with a $CaCl_2$ drying tube. The stirred mixture was gently heated at reflux for 4 hr during which time a gummy brown reaction complex separated. After cooling the mixture to room temperature, the CS_2 was decanted and the remaining complex decomposed with ice. The solid product which separated was filtered off, dissolved in benzene, and washed with Na_2CO_3 solution, then with saturated NaCl. The solution was then dried over $MgSO_4$, the solvent removed *in vacuo*, and the residue recrystallized from methanol–water to give 175 g (78%) of material: mp 70–72°; ir (Nujol) 5.75 (aliphatic ester), 5.89 (pyrrole ketone), 6.01 μ (pyrrole ester). *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.06; H, 7.08; N, 4.54.

Methyl 2-ethoxycarbonyl-5-ethyl-4-methyl-δ-oxopyrrole-3-valerate (3b) was prepared from **1a** and methyl 4-(chloroformyl)-butyrate as above in 84% yield. Colorless needles from hexane, mp 38–39.5°. *Anal.* Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53: Found: C, 62.17; H, 7.51; N, 4.53.

Methyl 4-Ethoxycarbonyl-2,5-dimethyl-γ-oxopyrrole-3-butyrate (3c).—From **2** as described for **3a** in 75% yield. The compound was obtained as an oil which solidified to a crystalline material mp 53–56° upon standing in moist air. Attempts to dry the solid *in vacuo* at 25° resulted in reconversion to an oil. A satisfactory analysis could not be obtained.

Methyl 4-Ethoxycarbonyl-2,5-dimethyl-δ-oxopyrrole-3-valerate (3d).—From **2** in 95% yield as a yellow oil which failed to crystallize.

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-butyrate (4a).—A solution of **3a** (59 g, 0.2 mol) in 250 ml of abs ethanol was hydrogenated over 10 g of 10% Pd–C at 50 psi in a Parr apparatus at room temperature. Uptake of hydrogen (98% of theory) was complete after 2 hr. Catalyst was filtered off and the filtrate evaporated to give a colorless oil which soon solidified. Recrystallization from ether–petroleum ether (30–60°) gave white needles (35.5 g, 63%): mp 65–67°; ir (Nujol) 5.73 (aliphatic ester), 6.01 μ (pyrrole ester). *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.75; H, 8.30; N, 4.87.

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-valerate (4b).—From **3b** in 85% yield as white crystals from pentane, mp 34–36°. *Anal.* Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.89; H, 8.71; N, 4.67.

Methyl 4-Ethoxycarbonyl-2,5-dimethylpyrrole-4-butyrate (4c).—From **3c** in 78% yield as white crystals from ether, mp 85.5–86.5°. *Anal.* Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.91; H, 7.80; N, 5.18.

Methyl 4-Ethoxycarbonyl-2,5-dimethylpyrrole-3-valerate (4d). From **3d** in 71% yield as white crystals from benzene–hexane, mp 45.5–47.5°. *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.15; H, 8.22; N, 4.91.

Ethyl 3-(Dimethylamino)methyl-5-ethyl-4-methylpyrrole-2-carboxylate (10a).—A mixture of ethyl 5-ethyl-4-methylpyrrole-2-carboxylate (270 g, 1.5 mol), 36% aqueous formaldehyde (125 ml, 1.5 mol), and anhydrous dimethylamine (67.5 g, 1.5 mol) in 2 l. of ethanol was heated at 80–95° under a nitrogen atmosphere in a 3 l. steel bomb for 16 hr. The contents of the bomb were then evaporated *in vacuo*, the residue was taken up in ether and extracted with several portions of 2 *N* HCl. Work-up of the ether layer gave 81 g of recovered starting material.

The acid extracts were basified with NaOH, and the precipitated oil was extracted into ether. The extracts were washed with water, dried over anhydrous K_2CO_3, and evaporated to yield a dark oil which quickly crystallized. Recrystallization from pentane gave white needles (169.2 g), mp 76–78°. The recovered starting material was recycled to give another 67.3 g of product, total yield 66%. *Anal.* Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.57; H, 9.38; N, 11.86.

Ethyl 3-(Dimethylamino)methyl-4,5-dimethylpyrrole-2-carboxylate (10b).—From **1b** as above in 45% yield. Thick staffs from pentane, mp 87–89°. *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.19; H, 9.00; N, 12.35.

Ethyl 4-(Dimethylamino)methyl-2,5-dimethylpyrrole-3-carboxylate (10c).—From **2** as above in 68% yield. Pale yellow crystals from benzene–hexane, mp 111–113°. *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.43; H, 9.02; N, 12.59.

Diethyl [(2-Ethoxycarbonyl-5-ethyl-4-methylpyrrol-3-yl)methyl]-malonate (11a).—Dimethyl sulfate (126 g, 1.0 mol) was slowly added to a solution of **10a** (238 g, 1.0 mol) in 550 ml of ethanol. The solution warmed and was allowed to stand for 2 hr before adding a freshly prepared solution of sodio diethyl malonate (from sodium (28.6 g, 1.25 g-atom) and diethyl malonate (190 ml, 1.25 mol) in 500 ml of ethanol. The resulting mixture was then allowed to stand at room temperature for 3.5 days.

Alcohol was then removed *in vacuo*, and the residue treated with benzene and water. The benzene layer was separated, extracted with 1 *N* HCl, washed with water, and dried ($MgSO_4$). Removal of solvent left a pale yellow oil which soon solidified, and was recrystallized from pentane. Thusly was obtained 227 g (64%) of white needles, mp 46–48°. *Anal.* Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.94; H, 7.63; N, 3.87.

Treatment of this material (70.6 g) with 500 ml of 20% methanolic potassium hydroxide gave an initially clear solution, which began to deposit a voluminous white solid within 5 min at room temperature. This mixture was warmed at reflux for 15 min and the potassium salt filtered off, washed with some cold methanol and dissolved in 600 ml of water. A stream of SO_2 gas was passed into the solution until pH 3 was reached. The precipitated acid (**11d**) was filtered off and dried to give 48 g (81%) of white crystals, mp 170–171° dec; 80.5 mg required 5.72 ml of 0.1 *N* NaOH (neutral equiv 140.5, theory 148.5).

Diethyl [(2-Ethoxycarbonyl)-4,5-dimethylpyrrol-3-yl)methyl]-malonate (11b).—From **10b** in 69% yield. Needles from pentane, mp 55–56.5°. *Anal.* Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.18; H, 7.40; N, 4.16.

(21) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 434–437.

(22) G. D. Hedden and W. G. Brown, *J. Amer. Chem. Soc.*, **75**, 3744 (1953).

(23) Melting points are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra as Nujol mulls were determined on a Perkin-Elmer Model 137 Infracord. Solution spectra were determined in 1.0-mm matched NaCl cells on a Perkin-Elmer Model 221 spectrophotometer. Ultraviolet spectra were determined on a Cary 14 recording spectrophotometer. Nmr spectra were determined; courtesy of Dr. J. Swinehart of the Perkin-Elmer Laboratories, Norwalk, Conn. on a Model R-12 spectrometer.

This material was hydrolyzed to the corresponding malonic acid (**11e**), mp 169–170° dec, which was not further characterized.

Diethyl [(4-Ethoxycarbonyl-2,5-dimethylpyrrol-3-yl)methyl]-malonate (11c).—From **10c** in 51% yield. White crystals from 80% ethanol, mp 75–76°. *Anal.* Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.22; H, 7.41; N, 4.17.

Hydrolysis gave **11f**, mp 155–157° dec.

2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-propionic Acid (4e).—Decarboxylation of **11d** was effected by heating the compound (48 g) in an Erlenmeyer flask immersed in an oil bath at 190–200° until evolution of CO_2 was complete (10–15 min). The liquid product was allowed to solidify and was then scraped out of the flask, giving 40.2 g (98%) of crude **4e**.

An analytical sample was recrystallized from ethanol–water as long needles, mp 145.5–147.5°; ir (Nujol) 5.84 (COOH), 6.01 (pyrrole ester). *Anal.* Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.57; N, 5.53.

2-Ethoxycarbonyl-4,5-dimethylpyrrole-3-propionic Acid (4f).—From **11e**. Needles from ethanol–water, mp 155–157°. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.14; H, 7.09; N, 5.83.

4-Ethoxycarbonyl-2,5-dimethylpyrrole-3-propionic Acid (4g).—From **11f**. Needles from ethanol–water, mp 172–175°. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.27; H, 7.23; N, 5.83.

2-Ethyl-3-methylpyrrole-4-propionic Acid (14a).—The above described crude **4e** was heated for 1 hr at reflux with 250 ml of 20% aqueous potassium hydroxide. The mixture was then cooled and diluted with 250 ml of water; a stream of SO_2 gas was passed into the solution until pH 3 was obtained. Precipitated solid (**4h**) was filtered off and the filtrate extracted with ether. The ether extracts were evaporated, leaving a yellow oil which was combined with the filtered solids, moistened with some water, and heated on the steam bath until gas evolution was complete. Water was removed from the resulting product on the rotary evaporator and the residue extracted with several portions of boiling hexane totalling 2.5 l. On cooling, long colorless needles of **14a** formed, which were filtered off and dried. There was obtained 24.4 g (85%) of product, mp 83–84.5° [lit.[24] mp 85–88°].

2,3-Dimethylpyrrole-4-propionic Acid (Haemopyrrolecarboxylic Acid, (14b).—Prepared as above from **4f**, mp 126.5–127.5 [lit.[16b] mp 127–129°].

2-Ethyl-4,5-dihydro-3-methylindol-7(6H)-one (5).—The diester **4a** (31 g) and 458 g of polyphosphoric acid were heated slowly to 125–130°. Frothing commenced at about 80° and the mixture was stirred vigorously with a glass rod to prevent overflow. The dark mixture was heated for 30 min after the frothing had ended, cooled to 60°, and poured into a large volume of cold water. After stirring to dissolve the polyphosphoric acid, the mixture was chilled in ice for 30 min; the solid product was filtered off and thoroughly washed with water. After drying, the highly colored crude product was sublimed at 125° (0.1 mm) to give white crystals (8.8 g, 45% yield). An analytical sample was recrystallized from ether–hexane, mp 135–136°; nmr ($CDCl_3$) δ 1.18 (t, 3, J = 7 Hz, CH_3–CH_2), 1.89 (s, 3, CH_3–), 1.96–2.82 (m, 8, combined $-CH_2-$). *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.44; C, 8.41; N, 7.93.

The following ketopyrroles were prepared as above using a 15 fold excess of PPA: **2-ethyl-4,5,6,7-tetrahydro-3-methylcyclohepta[b]pyrrol-8(1H)-one (6).** From **4b** in 17% yield. Needles from hexane, mp 120–121°. *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.30; H, 9.05; N, 7.35.

6,7-Dihydro-1,3-dimethylisoindol-4(5H)-one (7).—From **4c** in 65% yield. Crystals from methanol, mp 151–152° (lit.[25] mp 151–152°). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.75; H, 7.97; N, 8.64.

5,6,7,8-Tetrahydro-1,3-dimethylcyclohepta[c]pyrrol-4(2H)-one (8).—From **4d** in 28% yield. Needles from hexane–benzene, mp 136–138°. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.01°. Found: C, 74.56; H, 8.52; N, 6.90.

2-Ethyl-4,5-dihydro-3-methylcyclopenta[b]pyrrol-6(1H)-one (13a).—From **14a** in 62% yield. Rhombs from hexane, mp 179.5–181.5°. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.55; H, 8.01; N, 8.64.

4,5-Dihydro-2,3-dimethylcyclopenta[b]pyrrol-6(1H)-one (13b).—From **14b** in 67% yield. Microcrystals from hexane, mp 223–223.5°. *Anal.* Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.53; H, 7.33; N, 9.40.

5,6-Dihydro-1,3-dimethylcyclopenta[c]pyrrol-4(2H)-one (12).—From **4g** in 38% yield. Feathers from toluene, mp 244–246° (lit.[25] mp 245–248° dec). *Anal.* Calcd for $C_9H_{11}NO$: C, 72.45; 7.43; N, 9.39. Found: C, 72.30; H, 7.62; N, 9.42.

2-Ethyl-3-methylindol-7-ol (9).—A mixture of **5** (3.8 g), 10% Pd–C (4.0 g), and 125 ml of cumene was heated with stirring at reflux under nitrogen for 20 hr. The hot reaction mixture was then filtered, and the solvent evaporated *in vacuo* to give a light orange residue (2.7 g) which solidified on trituration under pentane. Recrystallization from hexane gave white needles, mp 86–88°, soluble in 1 *N* NaOH and giving a violet color with $FeCl_3$ solution. Ultraviolet spectrum (MeOH): 293 (5075), 271 mμ (7884). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.13; H, 7.55; N, 8.02.

Registry No.—**3a**, 25109-99-3; **3b**, 25110-00-3; **3c**, 25110-01-4; **4a**, 25110-02-5; **4b**, 25110-03-6; **4c**, 25110-04-7; **4d**, 25110-05-8; **4e**, 25110-06-9; **4f**, 25110-07-0; **4g**, 6315-16-8; **5**, 25110-09-2; **6**, 25158-24-1; **7**, 21770-35-4; **8**, 25110-11-6; **9**, 25158-25-2; **10a**, 25110-12-7; **10b**, 25110-13-8; **10c**, 25110-14-9; **11a**, 25110-15-0; **11b**, 25158-26-3; **11c**, 25158-27-4; **11d**, 25110-16-1; **12**, 21770-33-2; **13a**, 25110-18-3; **13b**, 25110-19-4; 2-acetyl-3,4,5-trimethylpyrrole, 22186-84-1; 2-acetyl-3,4-dimethyl-5-*n*-propylpyrrole, 25110-21-8; 3-acetyl-2,4,5-trimethylpyrrole, 19005-95-9; 2-acetyl-3,5-dimethyl-4-ethylpyrrole, 1500-91-0; 3-acetyl-2,5-dimethyl-4-*n*-propylpyrrole, 10594-44-2.

(24) V. L. Archibald, D. M. Walker, K. B. Shaw, A. Markovac, and S. F. MacDonald, *Can. J. Chem.*, **44**, 345 (1966).

(25) I. J. Pachter and W. Herz, U. S. Patent 3, 415, 843 (1968).

6H,12H-6,12-Methanodibenzo[b,f][1,5]dioxocins from the Reactions of o-Alkenylphenols and Salicylaldehydes

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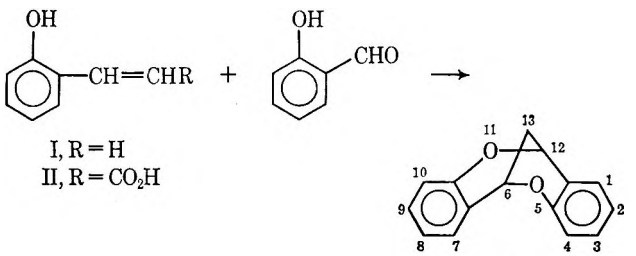
The condensation of o-vinylphenols with alkyl substituents on the α and/or β positions of the vinyl side chain with salicylaldehydes yields 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocins with alkyl substituents on the methylene carbon and/or a bridgehead carbon in the heterocyclic ring system, respectively. The use of an acetic acid–hydrobromic acid or a benzene–concentrated sulfuric acid reaction medium gives improved product yields over the previously reported aqueous reaction medium. Intermolecular dimerization and intramolecular cyclization of the o-alkylphenols can be serious competing reactions. The hydrogenolysis of these compounds to bisphenols is of limited synthetic value.

It was recently reported that the 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin system (III) could be conveniently synthesized, albeit in low yield, by the condensation of either o-vinylphenol (I) or o-coumaric acid (II) and salicylaldehyde.[1]



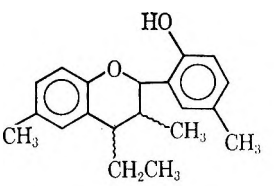
III

The more readily available o-coumaric acid was the starting material of choice. The previous work[1] was extended to include a few samples with substituents on the aromatic rings. It appeared likely that alkyl substituents could be incorporated into the heterocyclic ring system by the utilization of o-vinylphenols with side chain alkyl substituents. This article describes the synthesis of these types of compounds and a study to increase the yields of this new reaction. Some competing reactions which lower the yield of desired products were briefly examined.

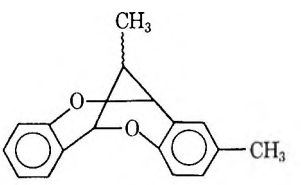
It was previously reported that a heterogeneous reaction medium of either o-vinylphenol or o-coumaric acid and salicylaldehyde in dilute aqueous hydrobromic acid at reflux temperature yielded 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocins. This study utilized two alternative methods which are superior when an o-vinylphenol is employed. Method A consisted of a homogeneous acetic acid–concentrated hydrobromic acid reaction medium at room temperature for 10 min. This provides a simple quick access to this complicated structure. Longer reaction times and higher temperatures resulted in poorer yields. Method B utilized a benzene solvent with catalytic quantities of concentrated sulfuric acid at room temperature for 1 hr. Method B was generally superior. For example, Method A was totally ineffective in producing compounds **7–9**. o-Coumaric acid failed to react by either method. The reaction temperatures were too low to cause decarboxylation of o-coumaric acid to yield the o-vinylphenol, the reactive intermediate.

Two product types representing reactions competing with the 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin synthesis were isolated. This does not represent an exhaustive search of side reactions. These products were found incidentally to the preparations of the subject compounds.

The o-alkenylphenol is capable of intermolecular dimerization under the conditions of these syntheses. For example, approximately equal yields of 2-(4-ethyl-3,6-dimethyl-2-chromanyl)-p-cresol (**18**) and 2,13-dimethyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin (**2**) were isolated from the reaction of 4-methyl-2-propenylphenol and salicylaldehyde. The dimerization reaction of o-propenylphenol has been reported.[2]

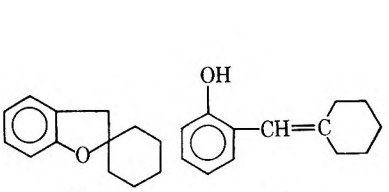


18

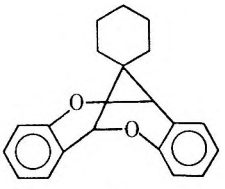


2

Intramolecular cyclization of the o-alkenylphenol was also detected. For example, only spiro(benzofuran-2(3H),1′-cyclohexane) (**19**) was isolated from the reaction of α-cyclohexylidene-o-cresol (**20**) and salicylaldehyde. None of the anticipated product **21** was isolable. Spiro(benzofuran-2(3H),1′-cyclohexane (**19**) is a known chemical and was previously prepared[3] by the cyclization of α-(1-cyclohexenyl)-o-cresol. Thus both reactions are well documented. No efforts were made to characterize polymeric materials and tars which also detract from the synthesis.



19 20



21

The previously reported hydrogenolysis of 6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin to 2,2′-trimethylenedipheno. proceeded in only a modest 30% yield.[1] This reaction was applied to two more systems with

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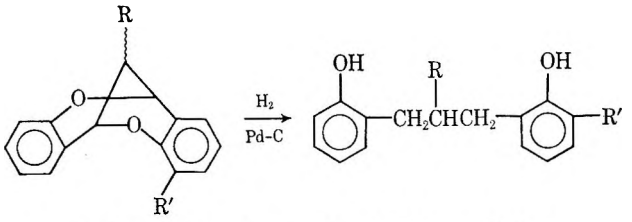
(3) G. Práter and H. Schmid, *Helv. Chim. Acta*, **50**, 255 (1967).

similar results. Thus this method of synthesizing 2,2′-trimethylenediphenols is of questionable value.



Starting compd	R	R′	Product	Yield, %
1	CH_3	H	22	25
5	CH_3	CH_3	23	3.9

Experimental Section[4]

Starting Materials.—2-Propenylphenol,[5] 4-methyl-2-propenylphenol,[6] 6-methyl-2-propenylphenol,[7] 4,6-dichloro-2-propenylphenol,[8] 2-isopropenylphenol,[9] 4-methyl-2-isopropenylphenol,[10] 2-(1-ethylpropenyl)-phenol,[11] 5-methylsalicylaldehyde,[12] and 5-bromosalicylaldehyde[13] were prepared by published procedures. 3,5-Dichlorosalicylaldehyde (K and K Laboratories, Inc.) and 2-hydroxy-1-naphthaldehyde (Aldrich Chemical Co., Inc.) were purchased.

4-Chloro-2-isopropenylphenol.—The chemical was previously prepared by the reaction of methyl 5-chlorosalicylate with sodium to yield the sodium salt and reaction of the salt with methylmagnesium iodide to give the carbinol which was thermally dehydrated to the product.[14] The chemical was prepared in this study by the reaction of methyl 5-chlorosalicylate with methylmagnesium iodide.

To a mixture of 36.5 g (1.5 g-atom) of magnesium turnings and 400 ml of absolute ether was added dropwise with stirring 213 g (1.5 mol) of methyl iodide at a rate to maintain a gentle reflux. Stirring and heating were continued after methyl iodide addition until all the magnesium had reacted. Then 93 g (0.50 mol) of methyl 5-chlorosalicylate was added dropwise with stirring. Stirring and heating at the reflux temperature were continued for 2 hr after the ester addition. Saturated aqueous ammonium chloride solution (600 ml) was added slowly to decompose the Grignard complex. The aqueous and organic layers were separated. The ethereal solution was extracted with 100-ml portions of 10% sodium hydroxide solution three times. The combined extracts were acidified to pH 7 with dilute acetic acid. The carbinol, which precipitated as a white solid, was collected, dried, and then dehydrated by heating at 180° (500 mm) for 30 min. The crude 4-chloro-2-isopropenylphenol was purified by distillation to yield 11 g (26%) of a colorless oil, bp 76–79° (1 mm) (lit.[14] bp 75–80° (1 mm)).

4-Bromo-2-isopropenylphenol.—The compound was prepared as described for 4-chloro-2-isopropenylphenol. There was obtained a 25% yield of a colorless viscous oil, bp 89–93° (2 mm) (lit.[14] bp 89–93° (2 mm)).

4-Phenyl-2-propenylphenol.—A solution of 115 g (1.05 mol) of 4-phenyl-2-allylphenol[15] and 90 g of potassium hydroxide dissolved in 225 ml of methanol was distilled until a pot temperature of 135° was attained. Removal of distillate was discontinued and the reaction mixture was heated at the reflux temperature for 2 hr. Water (200 ml) was added to the cooled mixture to dissolve the precipitated solid, followed by 135 ml of concentrated hydrochloric acid. The product which solidified was separated and purified by recrystallization from 170 ml of Skellysolvent (bp 60–100°) to yield 79 g (72%) of product as long white needles, mp 78–80°. An analytical sample, mp 82.5–83.5°, was prepared by a second recrystallization.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.9; H, 6.90.

2-(1-Methylpropenyl)phenol.—Ethyl bromide (121 g, 1.1 mol) was added dropwise at a rate to maintain a gentle reflux to a stirred mixture of 24 g (1.0 g-atom) of magnesium turnings and 300 ml of absolute ether. Additional heating and stirring were required for complete reaction. Then 65 g (0.45 mol) of *o*-hydroxyacetophenone dissolved in 300 ml of absolute ether was added. The reaction mixture was stirred and heated at the reflux temperature for 1 hr to complete the reaction. The Grignard addition complex was decomposed by the addition of an ice-cold solution of 100 g of ammonium chloride dissolved in 500 ml of water. The layers were separated. The organic layer was extracted with 300 ml of a 10% sodium hydroxide solution. The alkaline extract was carbonated with Dry Ice giving an oily layer which was extracted with toluene. The toluene was removed by distillation under slightly reduced pressure (~20 mm) and the crude product distilled to yield 37 g (55%) of a colorless oil, bp 51–53° (0.5 mm).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.16. Found: C, 80.8; H, 8.09.

Preparation of 6H,12H-6,12-Methanodibenzo[*b*,*f*][1,5]dioxocins. Method A.—A solution containing 0.025 mol of the *o*-alkenylphenol, 0.100 mol of the salicylaldehyde, 10.5 ml of glacial acetic acid, and 7.5 ml of 48% hydrobromic acid was prepared. There was a slight exothermic effect and an oil layer separated. The mixture was allowed to stand at room temperature for 10 min. Then an excess of 10% sodium hydroxide solution (450 ml) was added with stirring. The crude solid product which remained undissolved was collected and recrystallized from an appropriate solvent to yield the purified product.

Method B.—The *o*-alkenylphenol (0.050 mol) and the salicylaldehyde (0.078 mol) were dissolved in 250 ml of benzene. Concentrated sulfuric acid (0.5 ml) was added and the solution was stirred at room temperature for an hour. The benzene solution was extracted four times with 100-ml portions of a 10% sodium hydroxide solution and then evaporated to dryness in a rotary flash evaporator. The residue was recrystallized from an appropriate solvent to produce a purified product.

2-(4-Ethyl-3,6-dimethyl-2-chromanyl)-*p*-cresol (4-Methyl-2-propenylphenol Dimer) (18).—A solution of 26 g (0.175 mol) of 4-methyl-2-propenylphenol, 42.7 g (0.35 mol) of salicylaldehyde, 75 ml of glacial acetic acid, and 52.5 ml of concentrated hydrobromic acid was allowed to stand at room temperature for 10 min. Then 1 l. of 10% sodium hydroxide solution was slowly added with stirring. A gummy undissolved solid was collected and recrystallized from Skellysolvent (bp 60–100°) to yield 4.45 g (17%) of **18**, a light tan crystalline solid, mp 123–124.5°. An analytical sample was recrystallized from the same solvent to yield a white crystalline solid, mp 124–126°.

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16: mol wt, 296. Found: C, 81.2; H, 8.10; mol wt, 296 (mass spectrum).

The filtrate from the recrystallization was reduced in volume by evaporation, yielding a second crop of crystals. This product was also purified by recrystallization from Skellysolvent (bp 60–100°) to yield 7.7 g (18%) of 2,13-dimethyl-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**2**) (Table I).

Spiro(benzofuran-2(3H),1′-cyclohexane) (19).—A mixture of 14.0 g (0.075 mol) of α-cyclohexylidene-*o*-cresol (**20**), 30.0 g (0.30 mol) of salicylaldehyde, 50 ml of glacial acetic acid, and 30 g of 48% hydrobromic acid was stirred at room temperature for 10 min. The reaction mixture was poured into an excess of 10% sodium hydroxide solution. The expected undissolved solid did not appear. The alkaline solution was extracted with toluene. Evaporation of the toluene solvent gave 9 g of a colorless oily product which was recrystallized from ethanol to yield 8.8 g (63%) of spiro(benzofuran-2(3H),1′-cyclohexane) (**19**) as white needles, mp 30–31° (lit.[3] "an oil"). This compound is also referred to as "grisan."[16]

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.6; H, 8.33.

2-Methyl-1,3-di-(*o*-hydroxyphenyl)propane (22).—A mixture

(4) 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.

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(6) L. Claisen and O. Eisleb, *ibid.*, **401**, 45 (1913).

(7) K. von Auwers and G. Wittig, *Ber.*, **57**, 1270 (1924).

(8) L. Claisen and E. Tietze, *Justus Liebigs Ann. Chem.*, **449**, 100 (1926).

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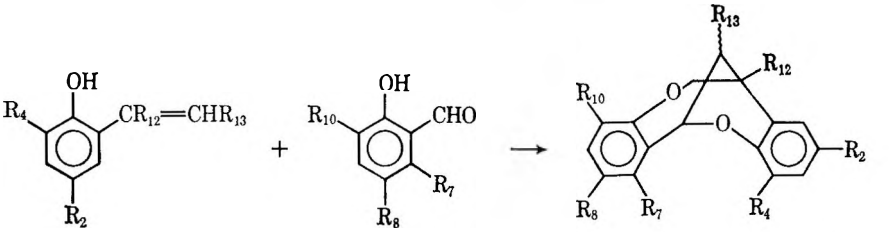
TABLE I

6H,12H-6,12-METHANODIBENZO[b,f][1,5]DIOXOCINS



Compd[a]	R_2	R_4	R_7	R_8	R_{10}	R_{12}	R_{13}	Prep method[b]	Recrystallization solvent[c]	Yield, %	Mp, °C
1	H	H	H	H	H	H	CH_3	A	1	18	137.5–138.5
								B	1	29	136–138
2	CH_3	H	H	H	H	H	CH_3	A	2	18	140–141
3	H	H	H	Br	H	H	CH_3	A	1	2.4	144–145
4	C_6H_5	H	H	H	H	H	CH_3	A	3	6.6	165–166.5
5	H	CH_3	H	H	H	H	CH_3	A	3	7.0	156–157
6	CH_3	H	H	CH_3	H	H	CH_3	A	3	11	141.5–142.5
7	Cl	Cl	H	H	H	H	CH_3	A		0.0	
								B	4	16	197–198
8	H	H	H	Cl	Cl	H	CH_3	A		0.0	
								B	4	20	197–198
9	Cl	Cl	H	Cl	Cl	H	CH_3	A		0.0	
								B	4	22	184–186
10	H	H	H	H	H	CH_3	H	A	3	56	122–122.5
11	CH_3	H	H	H	H	CH_3	H	A	1	58	160–161
12	Br	H	H	H	H	CH_3	H	A	4	49	145–146
13	Cl	H	H	H	H	CH_3	H	A	4	41	143–145
14	H	H	H	H	H	CH_3	CH_3	A	3	56	154.5–155
15	H	H	H	H	H	CH_3CH_2	CH_3	A	4	39	154–155
								B	3	38	154–155
16	H	H	*o*-C_6H_4[d]		H	CH_3	CH_3	A	1	42	192–193
17	H	H	*o*-C_6H_4[d]		H	CH_3CH_2	CH_3	A	1	11	185–189

[a] Satisfactory analyses (±0.3%) in carbon, hydrogen, and halogen were reported for all compounds with the exception of chlorine in compound 9 (Calcd: Cl, 37.77. Found: Cl, 37.3), Ed. [b] Preparation conditions: (A) acetic acid–hydrobromic acid reaction medium at room temperature for 10 min; (b) benzene solvent, sulfuric acid catalyst, at room temperature for 1 hr. [c] Recrystallization solvent: (1) ethanol–water, (2) Skellysolvent, bp 60–100°, (3) ethanol, (4) acetone–water. [d] *o*-Phenylene radical thus representing a naphthalene nucleus.

of 6.0 g (0.025 mol) of 13-methyl-6H,12H-6,12-methanodibenzo-[*b*,*f*][1,5]dioxocin (**1**), 1.0 g of 5% palladium-on-charcoal catalyst, and 300 ml of 2B absolute ethanol was placed in a Parr series 4500 medium-pressure reactor. The heterocyclic compound was hydrogenolyzed for 4 hr at 90° at 200 lb/in.^{2} of hydrogen pressure. The catalyst was collected on a filter and the ethanol solvent was removed by distillation under reduced pressure. The residue was dissolved in toluene and the toluene solution was extracted with a 10% sodium hydroxide solution. The alkaline solution was acidified with concentrated hydrochloric acid. The solid which precipitated upon acidification was collected and recrystallized from Skellysolvent (bp 60–100°) to yield 1.5 g (25%) of **22** as white needles, mp 118.5–119°.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.6; H, 7.55.

2-Methyl-1-(2-hydroxyphenyl)-3-(2-hydroxy-3-methylphenyl)-propane (23).—In a manner similar to that described for the preparation of **22**, **23** was prepared by the hydrogenolysis of 4,13-dimethyl-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**5**) in 3.9% yield as white needles, mp 111–111.5°.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.6; H, 7.89.

Registry No.—**1**, 25356-06-3; **2**, 25356-07-4; **3**, 25356-08-5; **4**, 25356-09-6; **5**, 25356-10-9; **6**, 25356-11-0; **7**, 25356-12-1; **9**, 25356-14-3; **10**, 25297-04-5; **11**, 25297-05-6; **12**, 25297-06-7; **13**, 25297-07-8; **14**, 25297-08-9; **15**, 25297-09-0; **16**, 25297-10-3; **17**, 25297-11-4; 4-phenyl-2-propenylphenol, 25297-12-5; 2-(1-methylpropenyl)phenol, 25356-15-4; **18**, 25297-13-6; **22**, 25297-14-7; **23**, 25297-15-18.

Reaction of 1,4,5,6-Tetrahydronicotinamide with Hydroxylamine[1]

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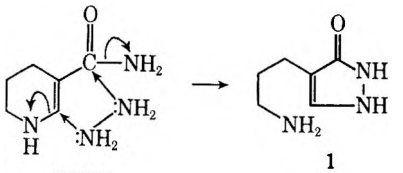
The ring of 1,4,5,6-tetrahydronicotinamide (THNA) is opened on reaction with an equivalent of hydroxylamine at room temperature, and a new heterocyclic compound, 4-(3-aminopropyl)-2-isoxazolin-5-one, is formed. This compound is also susceptible to ring opening and readily forms 5-amino-2-cyanopentanoic acid. The acid also is the major product when the THNA–hydroxylamine reaction is conducted at elevated temperatures. With a large excess of hydroxylamine, still another compound, 2-hydroximinopiperidine, can be formed from these reactants. The precursor of this compound is the 5-amino-2-cyanopentanoic acid formed from the isoxazolone. Any of the three products may be obtained in good yield.

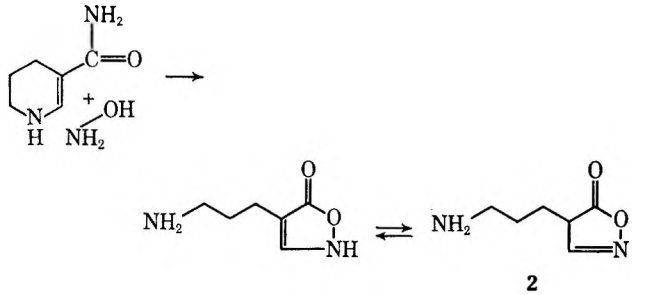
THNA was shown earlier[2] to be easily obtained by atmospheric pressure hydrogenation of nicotinamide over palladium. In exploring the properties of this new structure, it was found that hydrazine reacted at both the enamine and the amide sites, cleaving the original pyridine ring and forming 4-(3-aminopropyl)-2-pyrazolin-5-one (1) in high yield. It would appear that



THNA 1

other binucleophiles should react similarly with THNA or related 3-acyltetrahydropyridines, thereby forming various heterocycles with the aminopropyl substituent. In the present paper, results of a study of the reaction of hydroxylamine with THNA are given. It will be seen that the expected reaction occurs, and an isoxazolone (2) can be obtained. Depending on the reaction conditions, however, two other compounds could also result. Any of the three could be made the major product, and since all are novel structures, the reaction has proved to be of some synthetic value.

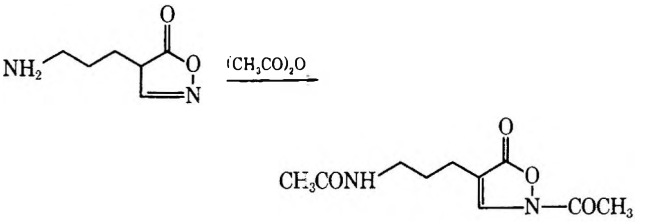
Isoxazolone Formation.—When the reaction of THNA with one equivalent of free hydroxylamine was conducted at room temperature in aqueous alcohol solution, the product was 4-(3-aminopropyl)-2-isoxazolin-5-one (2). The use of aqueous or ethanolic hydroxylamine hydrochloride caused formation of 2 at a



2

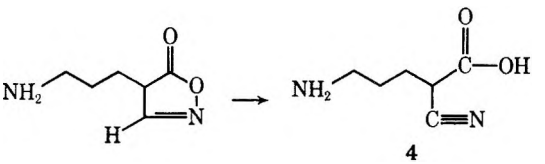
faster rate, suggesting the possibility of acid catalysis of the reaction. The mechanism of the reaction has not been studied; it is possible that the first step is addition of the nucleophile to the double bond, followed by ring-opening, rather than a direct displacement at the 2 position as implied in the equation above. The course of the reaction was easily followed by uv spectroscopy. THNA has a strong maximum at 285 mμ; this diminished as the reaction proceeded, while a maximum at 255 mμ for 2 developed. Reactions were stopped when the 285 mμ maximum had vanished. Ethyl tetrahydronicotinate also reacted with hydroxylamine (but not its hydrochloride) to form 2.

The isoxazolone proved difficult to isolate and purify; it was a hydroscopic solid easily undergoing ring-opening. While some spectroscopic measurements were made directly on 2, analysis was performed on the diacetyl derivative (3). Although the ring acetyl was particularly sensitive to hydrolysis, this derivative was suitable for characterization of 2.



3

That hydroxylamine had attacked as indicated and not in the reverse sense (*i.e.*, $-NH_2$ attacking at carbonyl) is clear from the structure of the ring-opened product, 5-amino-2-cyanopentanoic acid (4). This reaction is described more fully in the next section.



4

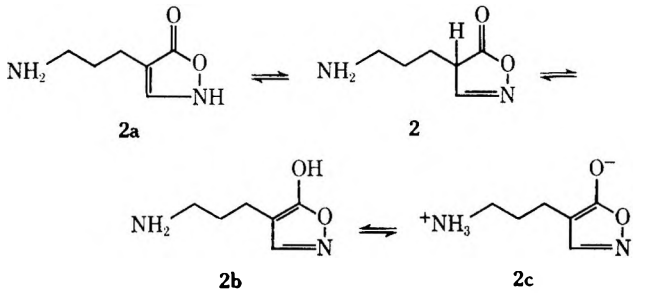
Isoxazolones may be involved in tautomeric changes; 2-unsubstituted 5-isoxazolones are generally expressed with the double bond in the 2 position. However, an added complication existed for 2, as revealed especially by its infrared spectrum (KBr). There was no signal for the carbonyl group, and strong broad absorption over the range 3600–2600 cm^{-1} suggested[3] the presence

(1) From the Ph.D. Dissertation of D. O. Pinion, Duke University, 1969. Presented at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968.

(2) F. M. Quan and L. D. Quin, *J. Org. Chem.*, **31**, 2487 (1966).

(3) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 96–97.

of $-NH_3^+$ rather than NH_2. Similar spectral features were found[2] for pyrazolone 1. Insolubility in ether and other nonpolar solvents also indicated a dipolar structure. Structure 2c is proposed for the solid isoxazolone, although in solution equilibria involving several forms may prevail.

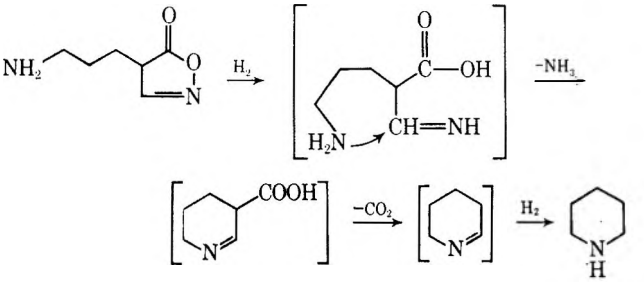


The mobility of the C-4 proton, as seen in 2 ⇄ 2b, is a well known property of 2-isoxazolin-5-ones, which are acidic substances (*e.g.*, 4-methyl-2-isoxazolin-5-one, $pK_a = 4.5$[4]). Zwitterion formation would be a natural consequence of the presence of a group of this acidity with a primary amino group. The nmr spectrum (D_2O) reveals the absence of a proton at C-4; signals were obtained only for the three methylene groups and the C-3 proton. The latter was markedly deshielded (δ 8.0 ppm), as noted also for pyrazolone 1.[2]

Amphoteric properties as required by formulation 2c were demonstrated by paper electrophoresis studies. The primary amino group gave the usual color reaction with ninhydrin, making possible easy detection of migration. In acetic acid solution, the compound migrated toward the cathode. In a pH 10.6 buffer, movement occurred toward the anode. 5-Aminopentanoic acid, used for comparative purposes, had similar mobility in the two systems. It was established that the basic buffer did not cause ring-opening of the isoxazolone by eluting the compound from the paper prior to ninhydrin treatment. The uv maximum (258 mμ) was the same as that found for a solution of the isoxazolone in the same buffer; the ring-opened product 4 has a maximum near 210 mμ.

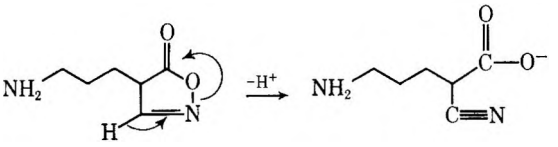
Spectral features of the diacetyl derivative (3) were also helpful in defining the structure of the parent isoxazolone. This derivative cannot participate in the tautomeric changes, and in addition to carbonyl stretching at 1641 (primary amide) and 1717 cm^{-1} (acetyl on ring[5]), there was a strong signal at 1749 cm^{-1} readily attributed to the ring carbonyl.[5] As noted, the isoxazolone showed no carbonyl band, consistent with form 2c. N–H stretching in 3 was also quite different, and consisted of a sharp amide signal at 3294 cm^{-1}. The electron-withdrawing ring acetyl of 3 caused a downfield shift of the nmr signal for the C-3 proton to δ 8.40 ppm.

Hydrogenation at atmospheric pressure over Adams' catalyst opened the isozazolone ring. The only product isolated proved to be piperidine, whose formation can be accounted for by the series below (the exact sequence of the steps is not known).



5-Amino-2-cyanopentanoic Acid Formation.—When 1:1 or 2:1 mixtures of hydroxylamine and THNA were refluxed in methanol for 24 hr, an entirely different product resulted. It was established as 4 from (1) its amphoteric behavior, seen by paper electrophoresis and titrations, which with both acid and base gave values in accord with 4, (2) the presence in its infrared spectrum of a C≡N stretching band (2247 cm^{-1}) and typical amino acid signals[3] ($-NH_3^+$ at 3100–2600 and 2123, $-COO^-$ at 1639 and 1376), and (3) facile acid hydrolysis, accompanied by decarboxylation, to a known compound, 5-aminopentanoic acid (5). Acid 4 had no uv maximum above 210 mμ. It readily lost carbon dioxide on melting.

Acid 4 originated from isoxazolone 2, the initial product. An aqueous solution of the isoxazolone heated on the steam bath lost the characteristic uv maximum at 255 mμ after 3 hr. A 64% yield of 4 was then isolated. A similar yield of 4 resulted from refluxing the isoxazolone in ethanol for 2 hr. The ring-opening process can be accounted for in the following manner. At the time



4

this reaction was observed in this laboratory, the ring-opening reaction of 3-unsubstituted isoxazolones[6] was novel. However, very recently[4] two 4-alkyl-2-isoxazolin-5-ones have been reported to undergo the same ring-opening process under mild conditions.

Acid 4 is a new compound and may be practically synthesized with the reaction described herein. For this, we prefer to preform the isoxazolone and then reflux it in ethanol, from which 4 precipitates. The overall yield from THNA is 67%.

2-(Hydroximino)piperidine Formation.—Refluxing an aqueous ethanol solution of THNA with a large excess (5:1) of hydroxylamine gave still another product, in moderate yield (32.2%) but good purity. A deposit of white solid developed in the condenser; it was identified as ammonium carbonate (and/or bicarbonate). A decarboxylation reaction was indicated, and indeed the formula of the compound ($C_5H_{10}N_2O$) required this. The compound was quite soluble in water, giving a basic solution. An attempt at acid hydrolysis was not successful when conducted in 6 *N* hydrochloric acid at 110° for 19 hr; only the hydrochloride of the base resulted. However, in 3 *N* acid for a longer period (3 days reflux), enough hydrolysis did occur to permit the detection of some 5-aminopentanoic acid (5) in the mixture.

(4) F. DeSarlo and G. Dini, *J. Heterocycl. Chem.*, **4**, 533 (1967).

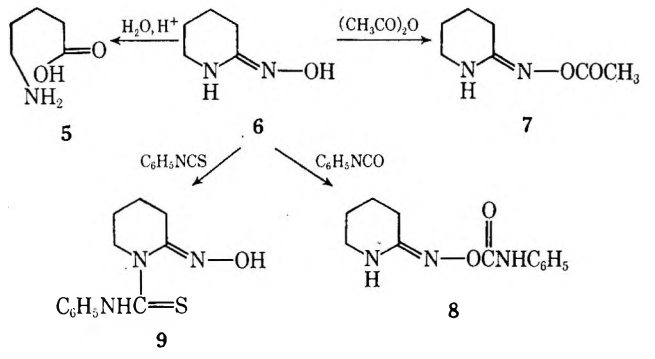
(5) C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **26**, 4923 (1961).

(6) Indeed, only one such compound (4-carboethoxy-2-isoxazolin-5-one) had been reported: L. Claisen, *Chem. Ber.*, **30**, 1481 (1897); S. Ruhemann, *ibid.*, **30**, 1083, 2031 (1897).

The infrared spectrum showed no bands for nitrile or carbonyl. A complex series of peaks (sharp but weak at 3413, broad and weak at 3096 and several broad bands over the range 2830–2400 cm^{-1}) suggested the presence of NH and OH groups, and the pattern resembled that of an amidoxime.[7] Pointing to the same possible structure was a sharp band at 1644 cm^{-1} suggesting C=N stretching. Confirming the amidoxime possibility, ferric chloride gave the magenta color characteristic of these compounds,[8] a precipitation test[9] with ferric nitrate–potassium isothiocyanate was positive, and a specific test[10] for the N–O bond (decomposition to release nitric oxide, detected with Griess' reagent) was also positive.

These data permit the assignment of cyclic amidoxime structure **6** to the product. Some reactions of value in characterizing it are shown in Chart I. Amid-

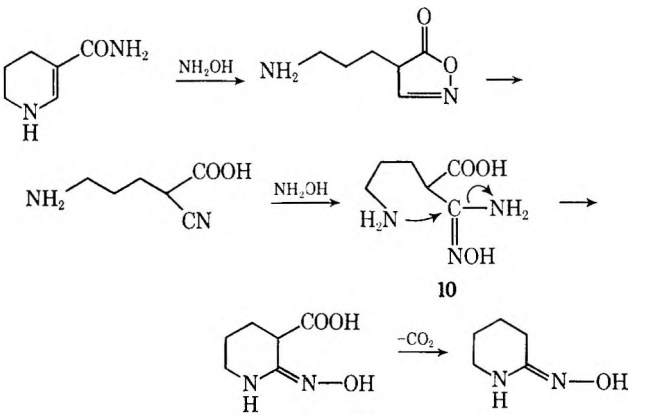
CHART I



oximes give O-acyl[11] and O-carbamoyl[12] derivatives with acid anhydrides and isocyanates, respectively, and **6** readily formed such derivatives (**7** and **8**). That O-attack had occurred was evident from the solubility of these derivatives in acid but not base, suggesting the absence of the –OH function. The nmr spectrum ($CDCl_3$) of **7** showed the ring NH signal at δ 5.58 but no signal characteristic of oxime OH (δ 8–9 ppm). Compound **8** also had an NH signal at δ 5.84 ppm, comparable to that of **7**, with a second one possibly due to the carbamate NH at δ 8.67. Amidoximes react at nitrogen with phenyl isothiocyanate to form thiourea derivatives[13] and such a product (**9**) was presumably obtained from **6**. However, its instability prevented adequate characterization.

The precursor of **6** in reactions of THNA with hydroxylamine may be 5-amino-2-cyanopentanoic acid (**4**), since this acid on reaction with hydroxylamine gave a good yield of **6**. The reaction of a nitrile with hydroxylamine is a standard synthetic method for amidoximes; the cyclic structure **6** may result from cyclization of a linear amidoxime (**10**) initially formed from **5**. Formation of **6** is therefore the end result of a complex sequence, which may be summarized as in Chart II. It

CHART II



is not known, however, if decarboxylation follows ring closure, as shown, or if the reverse sequence occurs.

Experimental Section[14]

4-(3-Aminopropyl)-2-isoxazolin-5-one (2).—A mixture of hydroxylamine hydrochloride (1.00 g, 14.4 mmol) and sodium carbonate (1.00 g, 9.4 mmol) in 20 ml of methanol was boiled for 5 min. After cooling, insoluble salts were removed by filtration and THNA (1.00 g, 7.94 mmol) was dissolved in the filtrate. After 18 hr at room temperature, the uv spectrum contained no absorption for starting material (285 mμ), but there was strong absorption at 255 mμ. Remaining inorganic materials were further precipitated by diluting with 4 ml of absolute ether, chilling for 30 min, and then filtering. This process was repeated three more times with 4-, 10-, and 15-ml portions of absolute ether. Dilution with 30 ml more of absolute ether caused precipitation of a gum. The ether–methanol layer was decanted; on further dilution with 40 ml of absolute ether, more precipitation occurred. No additional material could be obtained on additional dilution. The gum was dried under vacuum at room temperature for 4 hr, giving a dry foam (hygroscopic). The yield of **2** was 0.537 g (47.7%). In melting point determination, it became gummy at 40–50°, solidified at 95–100°, and decomposed at 170°; ir (KBr) 3600–2300 (nearly continuous, for NH_3^+), 2100, 1600 and 1500; nmr (D_2O) δ 8.00 (s, 1, H at C-3 of ring), 2.91 (t, 2, NCH_2), 1.91 (m, 4, other methylenes).

2-Acetyl-4-(3-acetamidopropyl)-3-isoxazolin-5-one (3). A synthesis of **2** in ethanol was performed. THNA (5.00 g, 39.7 mmol) and hydroxylamine hydrochloride (2.78 g, 40 mmol) were reacted directly in 95% ethanol (30 ml). After stirring for 24 hr, precipitated ammonium chloride was removed by filtration and the filtrate was stirred with sodium carbonate (2.12 g, 20 mmol) for 2 hr and then filtered. The filtrate was diluted to 50 ml with ethanol; uv measurements proved the presence of **2**. A 10-ml portion of the above isoxazolone solution was concentrated under vacuum nearly to dryness in the cold. An excess of acetic anhydride (4 ml, 42 mmol) was added to the gummy residue; a slightly exothermic reaction occurred as the gum dissolved. The flask was shaken vigorously until the mixture had cooled to room temperature. Rapid dilution with 100 ml of absolute ether caused a gum to precipitate, which was removed by filtration. Evaporation of ether from the filtrate caused precipitation of a white solid. The precipitate was recrystallized from benzene to give 0.553 g (30.5%) of **3**, sintering at 111–112° before melting at 112–113°; uv max (95% EtOH) 283 mμ (ϵ 16,700); ir (KBr) 3294 (amide NH), 1749 (ring C=O), 1717 (C=O of ring acetyl), 1641 (C=O of chain acetyl); nmr ($CDCl_3$) δ 8.40 (s, 1, H at C-3 of ring), 6.70 (broad s, 1, NH), 3.29 (apparent q, appearing as t when NH exchanged with D_2O, 2, $N-CH_2$), 2.41 (s, 3, CH_3CO

(7) C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **29**, 2873 (1964).

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 127.

(9) K. R. Manolov, *Z. Anal. Chem.*, **234**, 37 (1968).

(10) F. Feigl and J. R. Amaral, *Mikrochim. Acta*, 337 (1958).

(11) F. Eloy, R. Lenaers, and R. Buyle, *Bull. Soc. Chim. Belges*, **73**, 518 (1964).

(12) R. Buyle, F. Eloy, and R. Lenaers, *Helv. Chim. Acta*, **46**, 1073 (1963).

(13) H. Koch, *Chem. Ber.*, **24**, 394 (1891); P. Kruger, *ibid.*, **18**, 1053. (1885).

(14) THNA was prepared as described earlier.[2] Melting points are corrected. Infrared spectra were obtained with Perkin-Elmer Model 137 or 237 spectrophotometers, uv spectra with a Beckman Model DB-G spectrophotometer, and nmr spectra with a Varian A-60 spectrometer. Gas chromatography was performed with a Varian Model 202-B instrument, using a 1/4 in. × 5 ft stainless steel column packed with SE-30 on Chromosorb W, 60–80 mesh (1:4). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich.

on ring), 1.98 (s, 3, terminal CH_3CO), 1.70–2.50 (m, other side-chain methylenes).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38. Found: C, 53.35; H, 5.93; N, 12.24.

Hydrogenation of 4-(3-Aminopropyl)-2-isoxazolin-5-one (2).—A solution of 1.00 g (7.94 mmol) of THNA and 0.609 g (8.6 mmol) of hydroxylamine hydrochloride in 10 ml of absolute methanol was stirred with 0.465 g (4.3 mmol) of powdered sodium carbonate for 21 hr. The mixture was filtered and the filtrate (having the expected uv spectrum for **2**) was diluted to 15 ml with more methanol. Prereduced platinum oxide (0.1 g) in 15 ml of methanol was added and hydrogenation performed at atmospheric pressure and room temperature. Uptake was 305 ml (12.4 mmol) of hydrogen. That carbon dioxide was released during this process was shown by nitrogen-flushing of the gases from the hydrogenation apparatus through a saturated barium hydroxide solution; precipitation of barium carbonate occurred. The catalyst was filtered from the reaction mixture. Gas chromatography (100°) showed, in addition to solvent, only one peak (retention 2.6 min at 80 ml of He per min), which was enhanced by addition of piperidine to a small portion of the solution. The methanol filtrate was acidified with 1.5 ml of concentrated hydrochloric acid and then vacuum-evaporated, leaving a gummy solid. Redissolving in 25 ml of methanol and again vacuum-evaporating left crude piperidine hydrochloride as a solid. A portion was added to 1 ml of 6 *N* sodium hydroxide, forming an oil on the surface. Benzenesulfonyl chloride (0.5 ml) was added and the mixture stirred 2 hr. A white precipitate was removed by filtration. Its ir was identical with that of an authentic sample of N-benzenesulfonylpiperidine.

5-Amino-2-cyanopentanoic acid (4).—A solution of 2.22 g (32 mmol) of hydroxylamine hydrochloride in 20 ml of methanol was boiled for 10 min with 1.70 g (16 mmol) of powdered sodium carbonate. The mixture was cooled to room temperature and filtered and 2.00 g (15.9 mmol) of THNA was dissolved in the filtrate. The solution was refluxed for 23 hr, and then precipitated product was removed. The filtrate had uv max 212 mμ and no absorptions at 250–260 mμ for **2** or 280–290 mμ for THNA. The filtrate was evaporated to yield a second crop of product. The combined precipitates (1.94 g, 85.2%) of mp 173–175° dec were recrystallized from ethanol–water (20:3) to yield 1.23 g (54.1%) of **4**, mp 183–185° dec; ir (KBr) 3100–2600 and 2123 ($-NH_3^+$), 2247 ($C\equiv N$), 1639 and 1376 cm^{-1} ($-CO_2^-$); nmr (D_2O) δ 3.05 (t, 2, NCH_2), 1.88 (m, 4, $NCH_2CH_2CH_2$). The equiv. weight (calcd 142.1) was determined by potentiometric titrations: 142.9 with 0.0989 *N* aqueous NaOH in 85% ethanol; 142.3 with 0.0984 *N* $HClO_4$ in glacial acetic acid.

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.68; H, 7.09; N, 19.17. Found: C, 50.95; H, 7.18; N, 19.63.

Hydrolysis of 5-Amino-2-cyanopentanoic Acid (4).—A 500-mg sample of **4** was hydrolyzed by refluxing for 17 hr in 25 ml of 6 *N* hydrochloric acid. The solution was stripped of solvent *in vacuo*, and the residue was redissolved in water and evaporated again to removed residual hydrochloric acid. The residue was applied in water to an ion exchange column (Dowex 50W, X-8, H^+). After a water wash, the column was eluted with aqueous ammonia (4:1, v/v). Recrystallization from benzene–methanol gave a tacky solid, which after trituration with a small amount of methanol gave a low yield of an off-white powder, mp 150–151.5°; authentic (Aldrich Chem. Co.) 5-aminopentanoic acid (**5**) had mp 155–156° and an identical ir (KBr) spectrum. Comparative descending paper chromatography of the hydrochlorides in butanol–acetic acid–water (4:1:2) gave authentic **5**, R_f 0.51; the hydrolysis product, R_f 0.49; **4**, R_f 0.32.

Isomerization of Isoxazolone (2).—Compound **2** was first prepared from THNA (5.00 g, 39.7 mmol) and hydroxylamine hydrochloride (2.78 g, 40 mmol) in 50 ml of absolute ethanol on heating at 57° for 2 hr, and standing at room temperature for 24 hr. Precipitated ammonium chloride was filtered off and the filtrate shown to contain **2** from its uv max at 255 mμ. The solution was refluxed 15 min, then left at room temperature for 12 hr. A precipitate (1.63 g) was removed by filtration. The filtrate was refluxed again (2.5 hr), giving an additional 2.17 g of precipitate. The combined precipitates (3.80 g, 66.6%) had mp 179–180° dec and the expected ir spectrum for **4**.

Isomerization also occurred on certain manipulations of **2**. Thus, a solution of **2** prepared as above was evaporated *in vacuo* at room temperature to leave a white foamy semisolid. The solid was twice redissolved in methanol and reevaporated. It had the uv max of 255 mμ for **2**. After standing overnight at room temperature, the material became oily and only partially soluble in methanol. The methanolic mixture was filtered, the filtrate evaporated to dryness, and the residue extracted with methanol. Again insolubles were present. The combined methanol-insoluble material (0.726 g, 69.5%) had mp 175–178° dec, and was therefore shown to be **4**.

Paper Electrophoresis.—Compound **2** was prepared in methanol as in preceding experiments; after solvent-stripping, a water solution of the residue was made. A sample was applied to Whatman's No. 1 paper, along with aqueous solutions of **4** and 5-aminopentanoic acid (**5**). Electrophoresis was performed with a Beckman Model R Durrum-type instrument at 10 mA constant current for 5.5 hr in a pH 10.6 buffer (100 ml of 0.05 *M* sodium bicarbonate and 22.7 ml of 0.1 *N* sodium hydroxide). After drying at 100° for 30 min, the strips were sprayed with 30% acetic acid, redried, and then sprayed with ninhydrin. The isoxazolone (**2**) had migrated 2.6 cm (a light band at 6.8 cm was attributed to some **4**), **5** had migrated 2.9 cm, and **4**, 7.1 cm. Another strip containing **2**, without spraying, was cut at the proper location and eluted with ethanol. The solution (basic) had uv max 258 mμ; authentic **2** in dilute NaOH also had uv max 258 mμ.

2-Hydroximinopiperidine (6). Starting with THNA.—A solution of 3.0 g (43.2 mmol) of hydroxylamine hydrochloride in 5 ml of water was adjusted to pH 9 with 6 *N* NaOH, diluted with 10 ml of ethanol, and filtered. THNA (1.0 g, 7.9 mmol) was added and the solution refluxed 15 hr. A white solid deposited in the condenser, and from its ir spectrum and chemical properties was found to be ammonium carbonate (and/or bicarbonate). The solution was stripped to dryness, and the residue was extracted twice with 50-ml portions of boiling benzene. After charcoal decolorization and evaporating to 15 ml, hexane (100 ml) was added, and a solid precipitated. After chilling for 1 hr, the mixture was filtered. The residue of **6** weighed 0.29 g (32.2%), mp 120–121.5°; uv max (95% EtOH) 218 mμ (ε 6,723); ir (KBr) 3322 (NH), 3030 (broad, OH), 2891–2400 (complex, NH and OH), 1642 cm^{-1} (C=N); nmr ($CDCl_3$) δ 9.7–5.0 (very broad and shallow, 2, NH and OH), 3.20 (irregular t, 2, NCH_2), 2.27 (irregular t, 2, $N{=}CCH_2$), 1.5–2.0 (m, 4, other CH_2 groups); equiv wt (calcd 114) 115.8 from titration with $HClO_4$ in glacial acetic acid.

Anal. Calcd for $C_5H_{10}N_2O$: C, 52.63; H, 8.77; N, 24.56. Found: C, 52.74; H, 8.86; N, 24.32.

2-Hydroxyiminopiperidine (6). Starting with 5-Amino-2-cyanopentanoic Acid (4).—A solution of 1.47 g (21.1 mmol) of hydroxylamine hydrochloride in 30 ml of absolute ethanol was neutralized with a solution of 0.485 g (21.1 mmol) of sodium in 20 ml of absolute ethanol. The mixture was filtered; the filtrate was heated to reflux and treated over a 30-min period with a solution of 0.60 g (4.22 mmol) of **4** in 2 ml of water. After an additional 2 hr of reflux, the solution was evaporated to dryness and the residue was extracted with 50 ml of boiling benzene. After filtration, the volume of solution was reduced to 5 ml, and then 100 ml of petroleum ether (bp 30–60°) was added to precipitate **6**, 0.45 g (93.7%), mp 119–120°.

Qualitative Tests for Amidoxime Function in 6. N–O Bond.—A small sample of **6** in a micro test tube was thermally decomposed; the vapors impinging on a filter paper moistened with Greiss' reagent (equal portions of 1% sulfanilic acid in 30% acetic acid and 1% α-naphthylamine in 30% acetic acid) caused a pink circle, a positive test. **Amidoxime Group.**—A small amount of amidoxime in 2 ml of water was treated with 0.5 ml of 5 *M* potassium isothiocyanate and 1–2 drops of 0.1 *N* ferric nitrate. A red-brown precipitate presumed to be $Fe(amidoxime)_2SCN$ indicated a positive test. A blank solution was dark red without any precipitate.

Acid Hydrolysis of 2-Hydroximinopiperidine (6).—A solution of 200 mg of **6** in 6 ml of 3 *N* hydrochloric acid was refluxed for 3 days. Vacuum-evaporation left an oily noncrystallizing residue which was redissolved in 10 ml of absolute ethanol, diluted to 125 ml with ether, and stored overnight in a freezer. Precipitated solid was recovered and dissolved in 1 ml of water. This solution was placed on a Dowex 50W, X-8 (H^+) ion-exchange column. After a water wash, the column was eluted with aqueous ammonia (4:1, v/v). Ninhydrin-positive fractions were combined and evaporated to dryness. The solid residue was taken up in 5 ml of methanol, filtered, and evaporated to dryness. The residue was redissolved in 3 ml of water and freeze-dried. The off-white crystalline material had an ir spectrum similar to that of 5-aminopentanoic acid (**5**) but melted over a wide range (70–120°).

Extraction with 5 ml of boiling benzene left a white powdery solid having an ir spectrum now identical with that of **5** but having a low melting point (141–145°); authentic **5**, mp 155–156°. The benzene extract was evaporated to ~2 ml and then diluted to 15 ml with petroleum ether (bp 30–60°) to give a small amount of crude **6**.

2-Acetoxyiminopiperidine (7).—2-Hydroximinopiperidine (**6**) (100 mg, 0.87 mmol) dissolved exothermically in 1.0 ml of acetic anhydride. The solution was heated at 50° for 15 min, then cooled, and diluted with 20 ml of ether. A precipitate was removed and discarded. Vacuum-evaporation of the filtrate left a white granular solid which was recrystallized by dissolving it in 20 ml of ether and then diluting the solution to 100 ml with petroleum ether. Crystallization occurred on standing overnight in a freezer. The product (**7**) (51 mg, 38%) sintered at 94° and melted at 97–100°; ir (KBr) 3700–3100 (broad, NH), 1742 (C=O), 1623 cm^{-1} (C=N); nmr ($CDCl_3$), δ 5.58 (s, broad, 1, NH), 3.30 (m, 2, NCH_2), 2.38 (m, 2, $N{=}CCH_2$), 2.12 (s, 3, CH_3CO), and 1.77 ppm (m, 4, other CH_2 groups).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.85; H, 7.55; N, 17.88.

Phenylcarbamoyl Derivative of 2-Hydroximinopiperidine (6).—To a solution of **6** (200 mg, 1.75 mmol) in 2 ml of chloroform was added phenyl isocyanate (209 mg, 1.75 mmol) dissolved in 2 ml of chloroform. A mild exothermic reaction set in; the mixture was shaken and then allowed to stand for 1 hr. It was diluted with 10 ml of chloroform, heated nearly to boiling on a steam bath, and then diluted with petroleum ether (bp 30–60°) to a volume of 125 ml. Placing the solution in a freezer overnight caused precipitation of a white solid (309 mg, 75.7%), sintering at 134° and melting at 136–138°; uv max (95% EtOH) 237 mμ (ε 22,000); ir (KBr) 3344 and 3184 (NH), 1700 (C=O) and 1621 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.67 (broad, 1, CONH), 7.3 (m, 5, phenyl), 5.8 (broad, 1, ring NH), 3.25 (m, 2, NCH_2), 2.37 (m, 2, $N{=}CCH_2$), and 1.67 ppm (m, 4, other CH_2 groups). An analytical sample was recrystallized from ethanol–water; it sintered at 141–142° and melted at 142–143°.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.44; N, 18.03. Found: C, 61.66; H, 6.46; N, 17.87.

Registry No.—THNA, 7032-11-3; hydroxylamine, 7803-49-8; **2**, 25055-43-0; **3**, 25055-44-1; **4**, 25055-45-2; **5**, 660-88-8; **6**, 4515-19-9; **7**, 25055-48-5; **8**, 25055-49-6.

Acknowledgment.—Generous support from the American Tobacco Co., Richmond, Va., is gratefully acknowledged.

Notes

Pyrazoles from Reaction of 3-Acetyl-1,4,5,6-tetrahydropyridine with Hydrazine and Phenylhydrazine[1]

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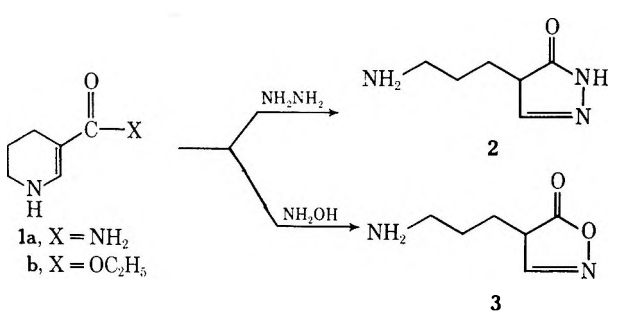
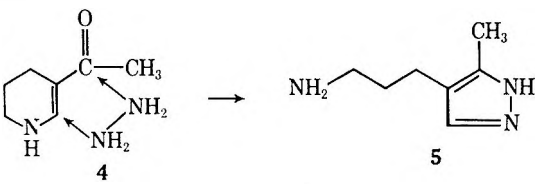
We have previously shown that 1,4,5,6-tetrahydronicotinamide (**1a**) and ethyl 1,4,5,6-tetrahydronicotinate (**1b**), which are readily available from hydrogenation of the corresponding pyridine compounds, react with binucleophiles such as hydrazine[2] and hydroxylamine[3] at both the enamino and carbonyl functions. The original ring is opened and new heterocyclic rings (pyrazolone **2** and isoxazolone **3**, respectively) are formed. In addition to nicotinic acid derivatives, 3-acylpyridines are cleanly reduced to the tetrahydro stage.[2,4] The reaction of hydrazine with such a keto compound should yield a pyrazole, and in this paper the formation of 3(5)-methyl-4-(3-aminopropyl)pyrazole (**5**) from 3-acetyl-1,4,5,6-tetrahydropyridine (**4**) is described.



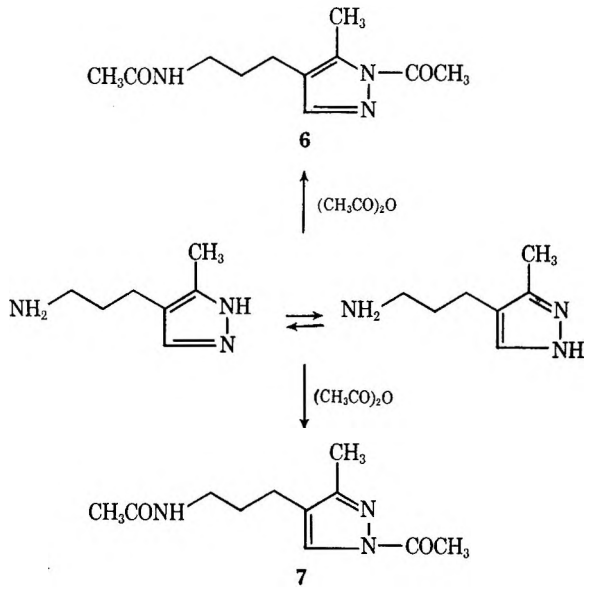


The reaction was brought about by refluxing the reactants in aqueous alcohol. The course of the reaction was easily followed by uv spectroscopy; **4** has a strong maximum at 300 mμ, which gradually diminished as the maximum for **5** (220 mμ) developed. The product was a distillable liquid, obtained in 68% yield.

The ir spectrum of **5** contained the expected pyrazole features.[5] The terminal amino group was suggested to be strongly associated from its broad band at 3600–2400 cm^{-1}. The nmr spectrum ($CDCl_3$) had C–H signals in agreement with structure **5**. Pyrazoles generally have NH signals around 11 ppm;[5] compound **5** had only one signal (δ 5.59) other than those for C–H. The integration was not conclusive, giving a value of 2.5 H. Nevertheless, it appears that the signal is derived from protons of the amino group as well as the ring NH, presumably undergoing rapid exchange. The signal disappeared on deuteration; no other changes occurred in the spectrum.

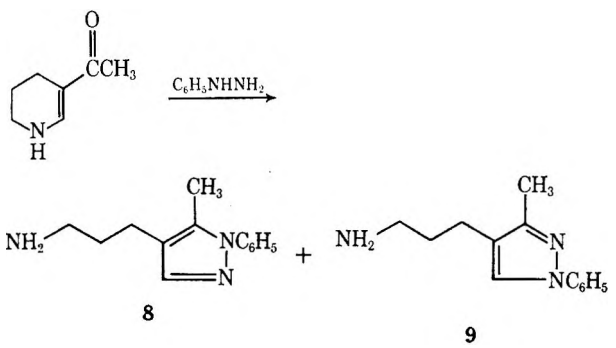
(1) From the Ph.D. Dissertation of D. O. Pinion, Duke University, 1969.
(2) P. M. Quan and L. D. Quin, *J. Org. Chem.*, **31**, 2487 (1966).
(3) L. D. Quin and D. O. Pinion, *ibid.*, **35**, 3130 (1970).
(4) M. Freifelder, *ibid.*, **29**, 2895 (1964).
(5) G. Zerbi and C. Alberti, *Spectrochim. Acta*, **18**, 407 (1962); **19**, 1261 (1963).

Pyrazole **5** was acetylated readily. Two isomers (**6** and **7**) are possible from this reaction, but the product appeared to be homogeneous since the nmr spectrum contained only one ring-CH_3 signal (δ 2.25 ppm). It seems likely that the compound has structure **7**



since steric hindrance with the methyl group can be expected to direct acylation to the remote nitrogen. Thus, acetylation of 3(5)-methylpyrazole occurs at this nitrogen.[6] The chemical shift of the ring CH_3 is in accord with this assignment; it compares with the value (δ 2.22) reported for the 3-methyl of 1-acetyl-3,5-dimethylpyrazole rather than for the 5-methyl (δ 2.52).[7] Uv spectroscopy provides further support. The maximum is at rather long wavelength (252 mμ), compared to 1-acetyl-3,5-dimethylpyrazole (241 mμ[8]). This may be taken to mean that the acetyl can better stabilize the excited state in **7**, suggesting its location where maximum resonance interaction (coplanarity of ring and carbonyl) can occur. In the dimethylpyrazole, steric interaction of acetyl with methyl on the adjacent carbon could hinder this resonance effect.

Phenylhydrazine on refluxing with **4** in a slightly acidic aqueous medium gave a 1:1 mixture of isomeric pyrazoles **8** and **9**. The isomer ratio was evident from



the nmr spectrum, which contained two ring-CH_3 singlets of equal area at δ 2.19 and 2.31 ppm. The isomer mixture has not yet been separated. The isomer with CH_3 singlet at 2.19 ppm was made to predominate (7:3 by nmr analysis) by conducting the reaction at 145–150° in ethylene glycol. It is likely, but not conclusively established, that the major isomer is the 5-methyl derivative **8**; this is suggested by the upfield position of the ring-CH_3 signal, an effect attributable to shielding by an adjacent phenyl group. Also the uv spectrum of the 7:3 mixture had a maximum at 252 mμ; a fraction enriched in the other isomer by ether–water partitioning of the 1:1 mixture had a maximum at 260 mμ. Adjacent phenyl can again account for this difference; in **8**, steric hindrance prevents maximum resonance stabilization of the excited state, accounting for absorption at lower wave length. This effect has been observed for a simpler isomer pair: 1-phenyl-5-methylpyrazole, λ_{max} 240 mμ; 1-phenyl-3-methylpyrazole, λ_{max} 256 mμ.[9]

Experimental Section[10]

3-Acetyl-1,4,5,6-tetrahydropyridine (**4**).—The procedure of Freifelder[4] was used. 3-Acetylpyridine (45 g) in 250 ml of ethanol was hydrogenated at 3 atm over 2.5 g of 10% palladium on charcoal. The product (27.1 g, 58.2%) was recovered by distillation at 130–135° (0.2 mm), lit.[4] bp 175° (10 mm); uv max (95% EtOH) 300 mμ (ϵ 21,000), lit.[4] 301 mμ (ϵ 21,150).

3(5)-Methyl-4-(3-aminopropyl)pyrazole (**5**).—A mixture of 5.0 g (0.04 mol) of **4** and 10 ml of 64% aqueous hydrazine in 10 ml of 95% ethanol was refluxed for 4.5 hr. The uv maximum of **4** had disappeared, and a peak at 220 mμ for **5** developed. Solvent was stripped from the solution and the residue distilled; **5** was received at 123–124° (0.08 mm). The yield was 3.8 g (68%): uv max (95% EtOH) 220 mμ (ϵ 2800); ir (neat) 3135 (broad, NH), 1572, 1481, and 1308 cm^{-1}; nmr ($CDCl_3$) δ 7.41 (s, 1, ring proton), 5.59 (s, 2.5, NH_2 and NH), 2.70 (t, 2, NCH_2), 2.43 (t, 2, $NCH_2CH_2CH_2$), 2.21 (s, 3, CH_3), and 1.63 (m, 2, $CH_2CH_2CH_2$) ppm. By titration with perchloric acid in acetic acid, the equivalent weight was found to be 69.7 (calcd 69.5).

Anal. Calcd for $C_7H_{13}N_3$: C, 60.43; H, 9.35; N, 30.22. Found: C, 60.82; H, 9.51; N, 29.78.

Acetylation of 5. A solution of 250 mg (1.8 mmol) of **5** in 1 ml of chloroform was treated with 1 ml of acetic anhydride. After the exothermic reaction subsided, the mixture was allowed to stand for 4 hr and then stripped of solvent. The oily residue was dissolved in 100 ml of ether; on chilling, the product crystallized. After recrystallization from ether, the yield of **7** was 328 mg (82%): mp 92–94°; uv max (95% EtOH) 252 mμ (ϵ 8680); ir (KBr) 3322 (NH), 1724 (C=O of ring acetyl), 1634 cm^{-1} (C=O of terminal acetyl); nmr ($CDCl_3$) δ 8.05 (s, 1, ring proton), 6.96 (broad s, 1, NH), 3.38 (apparent q, becoming t on adding D_2O, 2, NCH_2), 2.62 (s, 3, ring CH_3CO), 2.49 (m, 2, $NCH_2CH_2CH_2$), 2.25 (s, 3, 3-CH_3), 2.00 (s, 3, CH_3CONH), and 1.86 (m, 2, $NCH_2CH_2CH_2$) ppm.

Anal. Calcd for $C_{11}H_{12}N_3O_2$: C, 59.19; H, 7.62; N, 18.83. Found: C, 59.51; H, 7.78; N, 19.12.

Reaction of 4 with Phenylhydrazine.—A solution of **4** (3.00 g, 0.024 mol) and phenylhydrazine (2.59 g, 0.024 mol) in 12 ml of ethylene glycol containing 0.25 ml of concentrated hydrochloric acid was heated in an oil bath at 145–150° for 4 hr. Gas chromatography showed negligible amounts of starting materials. After adding 0.5 ml of 6 *N* sodium hydroxide, ethylene glycol was removed by distillation under reduced pressure; the product, an oil, had bp 134–144° (0.07–0.14 mm), 3.15 g (61.0%). Redistillation gave bp 137–138° (0.14 mm): uv max (95% EtOH) 252 mμ (ϵ 10,000); ir (neat) 3311 (NH), 1602, 1567, 1499 cm^{-1}; nmr ($CDCl_3$) δ 8.05–7.22 (m, 6, phenyl and C-3(5) ring protons), 2.73 (t, 2, NCH_2CH_2), 2.50 (t, 2, $NCH_2CH_2CH_2$), 2.31 and 2.19 [both s, 3 H total for 3-CH_3 (28.1%) and 5-CH_3 (71.9%)], 1.72

(6) K. V. Auwers and W. Daniel, *J. Prakt. Chem.*, **110**, 153 (1925).
(7) L. G. Tensmeyer and C. Ainsworth, *ibid.*, **31**, 1878 (1966).
(8) W. Otling and H. A. Staab, *Justus Liebigs Ann. Chem.*, **622**, 23 (1959).
(9) S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Tetrahedron*, **22**, 2703 (1966).
(10) Melting points are corrected. Infrared spectra were obtained with Perkin-Elmer Model 137 or 237 spectrophotometers, uv spectra with a Beckman Model DB-G spectrophotometer, and nmr spectra with a Varian A-60 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(m, 2, $CH_2CH_2CH_2$) and 1.35 (s, 2, NH; disappears with D_2O) ppm.

Titration with perchloric acid in glacial acetic acid gave equiv wt 107.7 (calcd 107.5).

Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.51; H, 7.96; N, 19.53. Found: C, 72.05; H, 8.11; N, 19.67.

Registry No.—**4**, 7032-12-4; hydrazine, 302-01-2; phenylhydrazine, 100-63-0; **5**, 24978-50-5; **7**, 24978-51-6; **8**, 24978-52-7; **9**, 25080-59-5.

Acknowledgment.—Generous support from the American Tobacco Co., Richmond, Va., is gratefully acknowledged.

Reduction of 2-(2-Imidazolin-2-yl)benzophenone

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In the course of the structural investigation of compounds obtained by the condensation of *o*-benzoylbenzaldehyde with aliphatic diamines,[2] we decided to study the reduction of these products. The equilibrium between the two tautomeric forms of the imidazoline derivatives **1a** and **1b** has been previously discussed.[2] Reduction with borohydride gave a nearly quantitative yield of the tautomeric dihydro compound **3a–b**.

The uv absorption of **3** is similar to that of **4** and different from that of **6** (Table I). This is probably due to steric hindrance in compounds **3** and **4**. These results indicate the presence of $C_6H_5C{=}N$ moiety in **3**, but do not allow a quantitative estimate of the equilibrium **3a** ⇌ **3b**. The near ir spectrum of **3** was recorded in $CHCl_3$ at three different concentrations. All spectra exhibit a band at 1.494 μ (ϵ 0.8) (NH of **3a**), a broad small band at 153 μ (NH of **3b**), and a very broad band at 1.4 μ area (strongly bonded OH of **3a**). This gives an approximate ratio for **3a**:**3b** of 9:1. For comparison, the near ir spectrum of salicylideneaniline (Frinton Laboratories) was recorded. With this compound the OH also forms a very strong intramolecular bonding and no absorption for nonbonded OH was detected. Compounds **4** and **6** exhibit only one kind of NH and no OH. Polarograms of **3** and **6** were recorded in 0.1 *N* KOH. The half-wave potential $E^{1/2}$ (reduction of –C=N–) of both compounds is similar (−1.755 and −1.730 V, respectively, *vs.* Ag|AgCl electrode) but the intensity of the molar diffusion currents (I_d) is different ($I_d \times 10^{-3}$ for **3** = 9.38 μA; and $I_d \times 10^{-3}$ for **6** = 12.72 μA), indicating the presence of some **3b** in 0.1 *N* KOH. On the assumption that reduction at the mercury dropping electrode is faster than the tautomeric equilibrium rate and that the diffusion coefficients are essentially the same for compounds **3** and **6**, these data also suggest a predominance of **3a**.

As expected, the results of chemical reactions were compatible with either structural possibility. Thus, hydrolysis gave 3-phenylphthalide and treatment of **3** with an acidic catalyst gave the imidazoisoindoline **2**.

Reduction of compound **2** with lithium aluminum hydride in boiling tetrahydrofuran yielded the 2-benzylphenylimidazoline **4** as the major product. The same product was obtained by heating the amide **8**, a compound which in turn was obtained either from the reaction of *o*-benzyl benzoate and ethylenediamine or by the reduction of compound **3** with zinc in acetic acid (Scheme I).

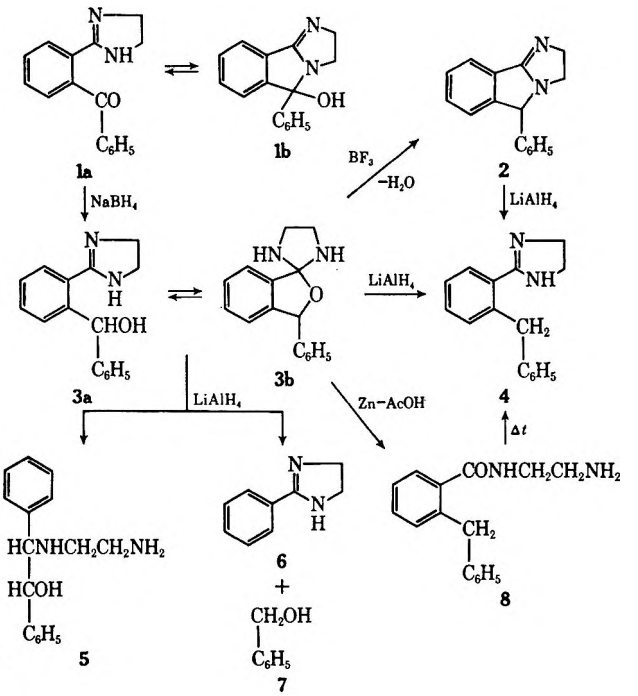
TABLE I

ULTRAVIOLET ABSORPTION DATA

Compd	Solvent	λ_{max}, mμ[a]	$\epsilon \times 10^{-3}$
3	2-Propanol	260 (s), 275 (i), 284 (i)	2.52, 2.20, 1.65
	$CHCl_3$	260 (i), 275 (i), 283 (s)	3.00, 2.28, 1.68
	0.1 *N* HCl	235 (i), 273 (i)	7.60, 1.40
	0.1 *N* KOH	265 (i), 283 (i)	2.10, 0.95
6	2-Propanol	230, 270 (i)	12.50, 3.80
	0.1 *N* HCl	236, 270 (i)	16.65, 3.30
	0.1 *N* KOH	266, 265	13.25, 3.90
4	0.1 *N* HCl	235 (i), 262 (i), 269 (i)	7.30, 2.0, 1.60
	0.1 *N* KOH	263 (i), 269 (i)	2.20, 1.72

[a] s, shoulder; i, inflection.

SCHEME I



On prolonged treatment (>60 hr) of compound **3** with lithium aluminum hydride in boiling tetrahydrofuran a mixture of products was obtained which consisted of compounds **4**, **5**, **6**, and **7** in a molar ratio of 1:9:13:12. Compound **5** could be isolated directly from the reaction mixture in 24% yield as the least ether soluble product. Compound **6** was obtained

(1) To whom inquiries should be addressed.

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

from the mother liquor as a maleate and identified with an authentic specimen. Compound **4** was isolated after chromatographic separation on an alumina column. Benzyl alcohol (**7**) was identified by mass spectroscopy after chromatographic separation.

Compounds **5**, **6**, and **7** are products of a carbon–carbon cleavage.[3] The formation of the 1,2-diphenylethanolamine derivative **5** requires a carbon–carbon cleavage, a carbon–nitrogen cleavage, and the migration of a benzyl group. Although no mechanism is proposed for this reaction, the result is perhaps best explained by assuming an initial carbon–nitrogen cleavage in structure **3b**. Such a hydrogenolysis is unlikely for structure **3a** since the imidazoline derivatives **4** and **6** were found to be stable under the reduction conditions used.

From nmr data (J = 6 cps) the *erythro* configuration was proposed for compound **5**.[4] For comparison this compound was prepared by the reaction of *trans*-stilbene oxide and ethylene diamine. This established both the structure and the configuration of **5** since it is known that the reaction of stilbeneoxides with amines generally proceeds by a *trans* addition.[5] The formation of **5** appears to be stereospecific since treatment of the corresponding *threo* isomer **9** (prepared by the reaction of *cis*-stilbene oxide with ethylenediamine) under the same $LiAlH_4$ conditions gave no trace of compound **5**. In order to see whether **5** could be prepared from the imidazoline **6** with benzyl alcohol or with benzaldehyde, various combinations of the reactants were mixed and heated under reflux in tetrahydrofuran either alone or together with lithium aluminum hydride or sodium carbonate or sodium hydride. Under the conditions used, we were unable to detect the presence of compound **5** in the reaction mixture by tlc examination.

Experimental Section[6]

2,3-Dihydro-5-phenyl-5H-imidazo[2,1-*a*]isoindole Sulfate (2·H_2SO_4).—A solution of 0.4 g (0.0016 mol) of **3** in 40 ml of chloroform was treated with 0.25 ml of boron fluoride etherate. The solution was heated at reflux under nitrogen for 6 hr and then kept at 25° for 18 hr. After the addition of another 0.25 ml of boron fluoride etherate and heating at reflux for 3 hr, the solution was washed with aqueous sodium carbonate solution. Concentration of the dried chloroform solution gave a yellow oil which was dissolved in tetrahydrofuran.

Acidification with ethanolic sulfuric acid and addition of ethyl acetate gave a crystalline product which after recrystallization from a mixture of methanol and ethyl acetate gave 0.15 g (28%) of 2·H_2SO_4 as white prisms, mp 216–223° dec, mmp 219–224° dec with an authentic sample.[2]

3′-Phenylspiro[imidazolidine-2,1′-phthalan] and/or 2-[2′-(α-Hydroxybenzyl)phenyl]-2-imidazoline (3). A. From 1 with Sodium Borohydride.—A solution of 5 g (0.135 mol) of sodium borohydride in 100 ml of ethanol was treated with 25 g (0.1 mol) of 1[2] added in small portions. The suspension was stirred at 25° for 18 hr and poured into 600 ml of ice water. Filtration gave 24.5 g (97%) of a crystalline product, mp 117–119°. A sample was recrystallized from a mixture of methylene chloride, ether, and petroleum ether (bp 30–60°) to give **3** as white prisms: mp 119–121°; nmr peaks ($CDCl_3$) at δ 3.47 (4 H singlet, CH_2-CH_2), 5.80 (1 H singlet, CH), 6.23 (2 H singlet, OH, NH); near-ir ($CHCl_3$) max 1.49 μ (ε 0.9) (NH).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.24; H, 6.43; N, 11.29.

B. From 1 by Catalytic Hydrogenation.—A suspension of 2.5 g (0.01 mol) of **1** and approximately 0.5 g of Raney nickel in 50 ml of ethanol was shaken in an atmosphere of hydrogen at 25° and 1 atm. After 22 hr, the uptake was 240 ml (*ca.* 0.01 mol). The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether to give 1.5 g (60%) of **3** as white prisms, mp 117–121°.

Hydrolysis of 3 to 3-Phenylphthalide.—A solution of 0.2 g of **3** in 2 ml of 2 *N* hydrochloric acid was heated on a steam bath for 1.5 hr and then kept at 25° for 18 hr. The crystals which had separated were collected, mp 115–117°, and were identified by comparison with an authentic sample of 3-phenylphthalide.[7]

2-(2-Benzylphenyl)-2-imidazoline (4). A. From Compound 8.—A melt of 1.3 g of **8** was kept at 230–240° for 25 min. Distillation at 0.5 mm and 200° (bath temperature) gave an oil which was dissolved in ethyl acetate. Cooling gave **4** as white prisms, mp 111–113°.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83. Found: C, 81.09; H, 7.02.

B. By Reduction of 2.—A solution of 1.25 g of lithium aluminum hydride in 25 ml of tetrahydrofuran was treated with 0.5 g of 2·H_2SO_4, and the mixture was refluxed for 70 hr. After cooling, 6 ml of water was added slowly and the mixture was filtered. The filtrate was concentrated *in vacuo* and the residual oil was placed on a column of 5 g of neutral alumina No. III (Woelm) and was eluted with methylene chloride. Evaporation of the solvent gave white prisms which after distillation in a bulb tube at 0.2 mm and 150° (bath temperature) gave **4**, mp and mmp 107–110° with a sample prepared as described in part A.

C. From Compound 3.—See description in preparation of **5** by reduction of **3**.

***erythro*-2-(2-Aminoethylamino)-1,2-diphenylethanol (5). A. By Reduction of 3.**—A suspension of 5 g (0.13 mol) of lithium aluminum hydride in 100 ml of tetrahydrofuran was treated with 10 g (0.04 mol) of **3** in small portions. The mixture was refluxed for 65 hr, cooled, and poured into 500 ml of ether. After the dropwise addition of 15 ml of water and filtration, the filtrate was concentrated to give 9.5 g of a partly crystalline residue. The crystals were collected on a filter and washed with ether. (For work-up of mother liquor, see below.) Recrystallization of the residue from methylene chloride and petroleum ether gave 2.5 g (24%) of **5** as white prisms: mp 123–125°; uv max (2-propanol) 259 mμ (ε 500); nmr peaks ($CDCl_3$) at δ 1.90 (4 H singlet, NH, NH_2OH), 2.52 (4-proton multiplet, CH_2CH_2), 3.83, 4.95 (2-proton AB quartet, J = 6 cps, CHCH).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86. Found: C, 74.69; H, 7.75.

The mother liquor of product **5** initially obtained was concentrated and the residue was dissolved in 35 ml of ethanol and 3.5 g of maleic acid was added. After 1 hr, 1 g of a crystalline precipitate was collected on a filter (maleate of **6**). The mother liquor of this crop was diluted with 75 ml of ether and after standing for 18 hr gave an additional 4.9 g of the salt. This fraction was treated with aqueous sodium hydroxide and ether. The ether extract gave a material which after recrystallization from a mixture of benzene and petroleum ether yielded **6** as white prisms, mp 99–102° (lit.[8] mp 101°).

The mother liquor obtained after removal of compound **5** and the maleate of compound **6** was concentrated and partitioned between aqueous sodium hydroxide and methylene chloride. The organic extract was placed on a column of 60 g of neutral

(3) The cleavage of compound of type $C_6H_5CHOHC\lessdot$ on reduction with lithium–aluminum hydride has been described in the literature: see P. Reynaud and J. Matti, *Bull. Soc. Chim. Fr.*, **612**, (1951); P. Rona and U. Feldman, *J. Chem. Soc.*, 1737 (1958); P. T. Lansbury, *J. Amer. Chem. Soc.*, **83**, 429 (1961).

(4) Similar ethanolamine derivatives have been described in the literature and their stereochemistry was known and correlated with nmr data. See J. W. Huffmann and R. P. Eliott, *J. Org. Chem.*, **30**, 365 (1965), and G. G. Lyle and M. L. Durand, *ibid.*, **32**, 3295 (1967).

(5) R. E. Lutz, J. A. Freek, and R. S. Murphey, *J. Amer. Chem. Soc.*, **70**, 2015 (1948).

(6) Melting points were determined using a Mettler FP-1 instrument and are corrected. Uv and near-infrared spectra were determined using a Cary 14 spectrophotometer; ir spectra, using a Beckman IR-9 spectrophotometer and nmr spectra, using a Varian A-60 spectrometer at 60 Mc/sec. Polarographic reductions were carried out on a Metrohm Polarecord Model E 216. The identity of compounds was established by a comparison of spectral properties and by mixture melting point. The purity of compounds was checked by thin layer chromatography.

(7) F. Ullmann, *Justus Liebigs Ann. Chem.*, **291**, 23 (1896).

(8) G. Forssel, *Ber.*, **25**, 2132 (1892).

alumina No. III (Woelm) and eluted with methylene chloride. In the first fractions benzyl alcohol was identified by vapor phase chromatography and mass spectroscopy. The subsequent fractions containing crystalline material were combined and recrystallized from a mixture of ethanol and petroleum ether to give **4** as white prisms, mp 111–113°.

The ratio of the products in the crude reaction mixture, obtained after reduction and (a) after removal of the inorganic material and (b) after concentration of the solution, was determined with a 0.25 in. o.d. × 6 ft column containing 4% polyethylene glycol, mol wt 20,000, and 2% KOH on Chromosorb W support in a F & M Model 810 gas chromatograph with a dual flame detector. The column temperature was programmed for 150 to 250°, 6°/min). Nitrogen was used as carrier gas at 100 ml/min. The molar ratio of **4**:**5**:**6**:**7** was found to be approximately 1:9:13:12.[9]

B. Preparation of 5 from *trans*-Stilbene Oxide.—A solution of 5 g of *trans*-stilbene oxide in 15 ml of ethylenediamine was refluxed for 18 hr. The mixture was cooled, poured into water, and extracted with methylene chloride. The dried extract was concentrated to give **5** as white prisms which on recrystallization from a mixture of methylene chloride and petroleum ether gave 4.5 g (69%) of the pure product, mp 121–123°.

***threo*-2-(2-Aminoethylamino)-1,2-diphenylethanol (9).**—In an exactly analogous manner as that used for the preparation of compound **5**, 5 g of *cis*-stilene oxide[10] gave 4.7 g (72%) of **9** as white prisms: mp 82–86°; nmr peaks ($CDCl_3$) at δ 2.50 (4 H singlet, $NH_1OH_1NH_2$), 2.62 (4 H multiplet, CH_2CH_2), 3.62, 4.60 (2-proton AB quartet, J = 8.5 cps, CHCH).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.10; H, 8.00; N, 10.95.

N-(2-Aminoethyl)-2-benzylbenzamide (8). A. By Reduction of 3.—A solution of 5 g (0.02 mol) of **3** in 50 ml of acetic acid was treated with 10 g of zinc dust. The temperature of the mixture rose during the addition to 35° and after that was kept at 25° for 16 hr. Filtration gave a solution which was poured on ice, basified with sodium hydroxide, and extracted with methylene chloride. The dried extract was concentrated and the residue on distillation at 0.2 mm (bath temperature *ca.* 150°) gave 3 g (59%) of **8** as white, waxy prisms: mp 84–86°; ir ($CHCl_3$) 1660, 1520 cm^{-1} (NHCO).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13. Found: C, 75.64; H, 7.23.

A solution of 10 g of **8** in 50 ml of methanol was treated with 20 ml of a 6 *N* methanolic hydrogen chloride solution. The precipitate was collected after 30 min and recrystallized from methanol to give 8.7 g (76%) of the hydrochloride of **8** as white needles: mp 200–201°; ir (KBr) 1645, 1540 cm^{-1}.

B. By the Condensation of Methyl o-Benzylbenzoate with Ethylenediamine.—A mixture of 35 g (0.16 mol) of methyl *o*-benzylbenzoate[11] and 350 ml of ethylenediamine was heated under reflux for 6 hr. The mixture was concentrated *in vacuo* and the residual oil was dissolved in aqueous sodium hydroxide to give a clear solution which was extracted with methylene chloride. The dried extract was concentrated and gave 14.5 g (38%) of **8** as a tan solid, mp 79–83°.

Registry No.—**1a**, 16780-90-8; **3a**, 25293-56-5; **3b**, 24811-71-0; **4**, 25293-58-7; **5**, 25286-80-0; **6**, 936-49-2; **8**, 25286-81-1; **9**, 25286-83-3.

Acknowledgment.—We are indebted to the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. F. Scheidl for microanalytical data; Mr. H. Jenny, Mr. S. Traiman, and Dr. F. Vane for spectroscopic data and interpretations. We also thank Mr. F. Jenkins for able assistance in the preparations.

(9) Average of vapor phase chromatographic determinations in three independent reduction experiments. The fact that a slight excess of **6** over **7** was consistently found is best explained by assuming that some of the more volatile benzyl alcohol is lost in the work-up procedure.

(10) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **80**, 2844 (1958).

(11) E. Barnett, J. Cook, and I. Nixon, *J. Chem. Soc.*, 508 (1927).

Maleimide Syntheses by Amine Reaction with Acetylenedicarboxylate Esters

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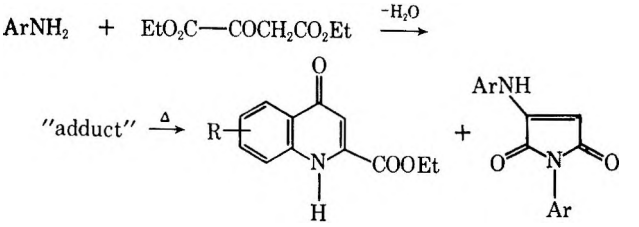
Received February 18, 1970

In the course of our study of amine–acetylene ester reactions we reported that certain aniline–acetylenedicarboxylate adducts could undergo facile ammonolysis to α-anilinomaleimides.[1] Related N-aryl-α-anilinomaleimides were observed as by-products in the pyrolytic quinoline cyclization of the condensation adducts



from anilines and ethyl ethoxalylacetate (**1**).[2] Landquist[3] has demonstrated that if residual aryl amine were removed prior to thermolysis of these adducts, the maleimide normally formed could be minimized.

In contrast to the addition of arylhydrazines to dimethyl acetylenedicarboxylate, a reaction which produces both imine and enamine tautomers,[4] the addition of aryl amines yields exclusively anilinofumarate enamines.[5,6] It would be reasonable to expect the same anilinofumarates as principal products of anilines and ethoxalylacetate. Adducts prepared in this fashion have been variously described as either iminosuccinates[3,7] or anilinomaleates[2] but without any firm experimental evidence for either structure.

We have repeated Surrey and Cutler's synthesis[2] of the adducts of aniline and *m*-chloroaniline with ethyl ethoxalylacetate, (**1**), and have found their products to be identical in all respects with the corresponding aniline plus diethyl acetylenedicarboxylate adducts (*i.e.*, *trans* enamines). These products were distinguished by a fumarate vinyl singlet at δ 5.31 ppm in the aniline adduct and at δ 5.41 ppm in the *m*-chloroaniline product. Huisgen has shown that the normal position of such fumarate vinyl resonances is δ 5.4 ppm and for maleate vinyls approximately δ 4.8 ppm.[5] These differences have been explained on the basis of relative vinyl deshieldings by the ester carbonyls.[8] Although Surrey and Cutler's "maleates" were distilled *in vacuo* to obtain analytical material, we have shown that the composition of the product is not changed by distillation.

(1) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

(2) A. R. Surrey and R. A. Cutler, *J. Amer. Chem. Soc.*, **68**, 514 (1946).

(3) J. K. Landquist, *J. Chem. Soc.*, 1038 (1951).

(4) N. D. Heindel, P. D. Kennewell, and M. A. Pfau, *Chem. Commun.*, 757 (1969), and *J. Org. Chem.*, **35**, 80 (1970).

(5) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(6) N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *J. Org. Chem.*, **32**, 4155 (1967).

(7) A. C. Mueller and C. S. Hamilton, *J. Amer. Chem. Soc.*, **65**, 1017 (1943).

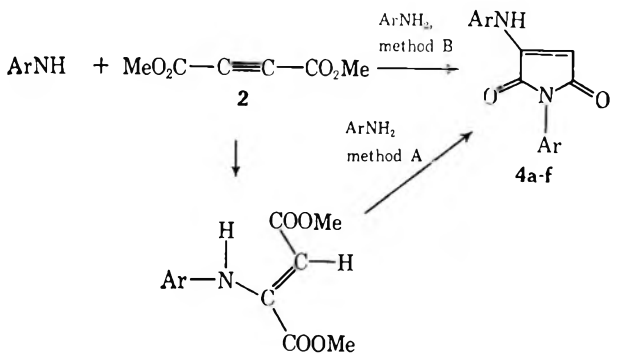
(8) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

TABLE I
MALEIMIDE SYNTHESES

Compd no.	RNH_2 (R =)	+ Coreactant	Method	% yield[a]	Mp, °C
4a	3-Cl-4-$MeOC_6H_3$-	2	B	66	269-270
4b	4-$MeOC_6H_4$-	2	B	62	221-223[b]
4b	4-$MeOC_6H_4$-	3b[c]	A	73	221-223
4c	4-FC_6H_4-	2	B	69	274-276
4c	4-FC_6H_4-	3c[d]	A	58	274-276
4d	4-BrC_6H_4-	2	B	61	260-262[e]
4e	3-ClC_6H_4-	DEADC[f]	B	54	221-223[g]
4f	C_6H_5-	2	B	50	230-232[h]
5a	H	3 (Ar = 4-ClC_6H_4)[c]	C	44	249-251
5b	H	3b[c]	C	40	204-206
5c	H	3f[c]	C	51	210-212[i]

[a] Satisfactory analytical values (±0.35) for C, H, N were reported for compounds 4a-c and 5a-c. Ed. [b] Lit.[3] mp 225-226°. [c] Prepared as in ref 5. [d] See ref 9. [e] Lit. mp 260°: F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, **123**, 663 (1923). [f] Diethyl acetylenedicarboxylate. [g] Lit.[2] mp 220-221°. [h] Lit. mp 232-233°: L. Clarke and E. K. Bolten, *J. Amer. Chem. Soc.*, **36**, 1906 (1914). [i] Lit. mp 206.5-207°: M. T. Bogert and R. A. Gortner, *ibid.*, **32**, 119 (1910).

Excellent yields of six N-aryl-α-anilinomaleimides have been obtained by pyrolysis of these anilinofumarates in the presence of a fourfold molar excess of the corresponding aniline (see Table I, Method A). Isolation of the intermediate adducts, **3**, however, appeared to offer little advantage over the direct combination of acetylenedicarboxylate with a fivefold excess of the aniline (Method B). In the latter technique, the initially vigorous reaction of the amine was allowed to subside before the mixture was heated at reflux (220–245°) for 5 min.



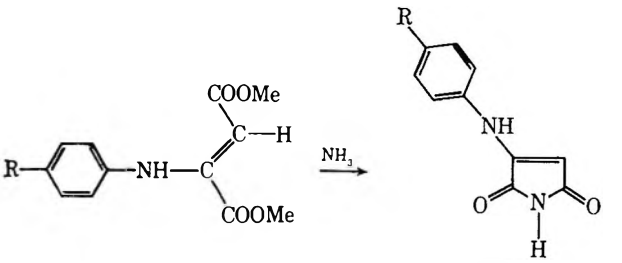
a, Ar = 3-Cl-4-$MeOC_6H_3$
b, Ar = 4-$MeOC_6H_4$
c, Ar = 4-FC_6H_4
d, Ar = 4-BrC_6H_4
e, Ar = 3-ClC_6H_4
f, Ar = C_6H_5

It has not been possible to prepare pure "mixed" maleimides in which the aryl moiety at the α carbon is different from that on the imino nitrogen. Thus, the reaction of *p*-anisidine with dimethyl 3,5-dichloroanilinofumarate[9] gave a maleimide mixture and with dimethyl 4-chlorophenoxyfumarate gave 57% of **4b**. Further evidence for a disproportionation–recombination was obtained when **3b** and *o*-chloroaniline produced a 34% yield of **4b** as the only isolable product.

It was possible to subject aniline–acetylenedicarboxylate adducts to ammonolysis in methanol solutions and to obtain α-anilinomaleimides (Method C).

This ammonolysis and the aniline thermolysis (Methods A and B) must naturally involve geometric isomerization of the enamine linkage prior to maleimide formation. Such conversions are not without precedent, since it has been recently shown that the rotational barrier about an enamine bond is less than one-third that of a normal C=C.[10] Presumably the ammonia–methanol medium used to generate the maleimides could effect a base catalyzed *trans*-to-*cis* isomerism of the enamine.

All the maleimide products displayed a characteristic imide carbonyl absorption. A weak C=O band at 1770 ± 5 and an intense band at 1705 ± 5 cm^{-1} could be observed in all the products. This strong–weak carbonyl set is a well known feature of five-membered imides.[11] Solubility difficulties precluded a comprehensive nmr analysis of all the maleimide products, but **4b**, **4d**, **4f**, **5b**, and **5c** were sufficiently soluble in Sulfolane-W[12] to give suitable spectra. All were distinguished by a unit proton resonance at δ 5.60 ± 0.2 ppm for the maleimide vinyl-H therefore eliminating the possibility of imino tautomers in this series.



5a, R = Cl
b, R = MeO
c, R = H

Experimental Section[13]

General Technique for Maleimide Synthesis. Method A.—Anilinofumarates (0.01 mol), prepared by published methods

(9) N. D. Heindel, I. S. Bechara, P. D. Kennewell, J. Molnar, C. J. Ohnmacht, S. M. Lemke, and T. F. Lemke, *J. Med. Chem.*, **11**, 1218 (1968).

(10) Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Lett.*, 3259 (1967).

(11) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 47.

(12) Gift of Shell Development Company.

(13) Nmr spectra were obtained on a Perkin-Elmer Hitachi R20A nmr spectrometer and are reported in δ ppm units from tetramethylsilane. Infrared spectra were obtained as paraffin oil mulls on a Perkin-Elmer 257 infrared spectrometer. We gratefully acknowledge the financial assistance of the National Science Foundation which made possible the purchase of these instruments. Combustion analyses were provided by the late Dr. Velmer B. Fish of these laboratories and by Dr. George I. Robertson, Florham Park, N. J.

from aryl amines and dimethyl acetylenedicarboxylate (2)[5,9] or aryl amines and ethyl ethoxalylacetate (1), were intimately mixed with 0.04 mol of the same aryl amine and heated to reflux for 10 min. The hot melt was cooled to room temperature and the resulting crystals thoroughly triturated with cold methanol. The maleimides were virtually insoluble in methanol but could be purified by sublimation [200° (0.1 mm)] or by recrystallization from acetic acid.

Method B.—The dimethyl acetylenedicarboxylate (0.01 mol) was added to 0.05 mol of the aryl amine and the initially vigorous reaction allowed to subside. The medium was then heated at reflux for 10 min and the maleimide product isolated as above.

Method C.—A solution of 0.01 mol of the appropriate anilinofumarate, synthesized as described by Huisgen,[5] was prepared in 100 ml of anhydrous methanol. The solution was saturated with anhydrous ammonia gas at 0° and sealed. After standing at room temperature for 1 week it was opened, resaturated with ammonia, and sealed for an additional week. The methanol was then chilled and the precipitated maleimide filtered off, dried, and sublimed *in vacuo*.

Dimethyl 4-Chlorophenoxyfumarate.—Following the procedure outlined for phenol,[14] 4-chlorophenol (30 mmol) was dissolved in 25 ml of ether containing 30 mmol of N-methylmorpholine. To this solution was added 30 mmol of 2 dissolved in 25 ml of ether. The mixture was allowed to stand at room temperature for 3 days, the ether removed by distillation, and the oily residue dissolved in benzene. The benzene phase was washed well with water, dried ($MgSO_4$), and concentrated to an oil which on cooling deposited 3.08 g (38%) of pale yellow crystals. An analytical sample was prepared by recrystallization from 1:1 benzene:hexane: mp 57–59°; ir (Nujol mull) 1740 and 1725 (C=O) and 1660 cm^{-1} (C=C); nmr ($CDCl_3$) δ 3.67 (s, 3, OCH_3), 3.72 (s, 3, OCH_3), 6.60[15] (s, 1, =CHCOOCH$_3$), and 6.8 to 7.4 ppm (m, 4, ArH).

Anal. Calcd for $C_{12}H_{11}ClO_6$: C, 53.33; H, 4.07. Found: C, 53.42; H, 4.10.

Reaction of this 4-chlorophenoxy adduct with *p*-anisidine according to Method A gave a 57% yield of **4b**.

Registry No.—**4a**, 25024-00-4; **4b**, 24978-24-3; **4c**, 24978-25-4; **4d**, 24978-26-5; **4e**, 24978-27-6; **4f**, 13797-26-7; **5a**, 24978-29-8; **5b**, 24978-30-1; **5c**, 17244-42-7; dimethyl 4-chlorophenoxyfumarate, 24355-81-5.

(14) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

(15) The observation that fumarate vinyls in phenoxy adducts fall at δ 6.45–6.68 ppm while maleate vinyls appear at 5.00–5.05 ppm permits assignment of fumarate geometry to this material. See ref 14 and N. D. Heindel and L. A. Schaeffer, *J. Org. Chem.*, in press, for similar examples.

Glyoxal Derivatives. II. Reaction of Glyoxal with Aromatic Primary Amines

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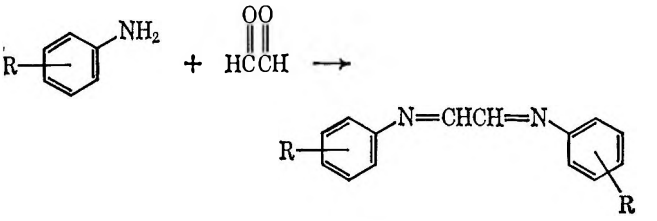
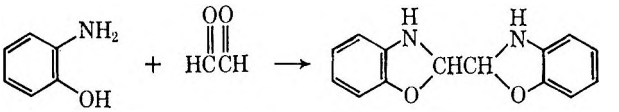
We have recently reported on the reaction of glyoxal with aromatic and aliphatic primary amines.[1] In that case, the products were N-substituted 1,2-diimines. In this paper we continue with our observations on the reaction of aromatic primary amines with glyoxal.

In earlier work it has been found that *p*-(N,N-dimethylamino)aniline,[2] *p*-aminophenol,[3] 2-hydroxy-5-chloroaniline, and 2-hydroxy-5-nitroaniline[4] react with glyoxal to give N-substituted aromatic 1,2-diimines.



Chwala and Bartek[5] report that *p*-anisidine and glyoxal sulfate react in the presence of sodium acetate to give the diimine corresponding to the above 1,2-diimines. Bayer has reported that *o*-aminophenol gave a 1,2-diimine;[6] however, Murase demonstrated that it was actually a cyclization product.[3]



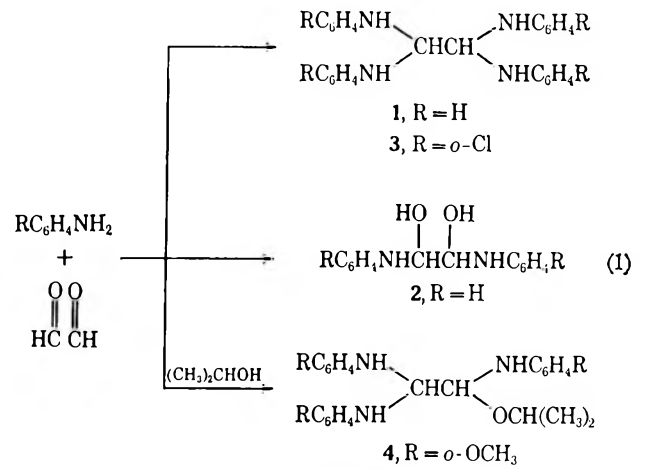
Other reports[7,8] state that aniline and glyoxal give only tars.

Somewhat related is the report by Malik, *et al.*,[9] that phenylglyoxal hydrate reacts with various aromatic primary amines to give imines; however, Proctor and Rehman offer evidence that the products are actually α-diamines or products incorporating alcohol solvent.[10]

Results and Discussion

We have found that aromatic primary amines react with 40% aqueous glyoxal to give either 1,2-diimines, 1,2-dihydroxy-1,2-diamino compounds, or tri- and tetraaminoethane derivatives. Thus, glyoxal reacts with excess aniline in isopropyl alcohol to give a 47% yield of 1,1′,2,2′-tetrakis(phenylamino)ethane, **1**, or with two molar equivalents of aniline to give 1,2-bis(phenylamino)-1,2-dihydroxyethane, **2**, in 54% yield.

Similarly, *o*-chloroaniline reacts with glyoxal giving a 47% yield of 1,1′,2,2′-tetrakis(*o*-chlorophenylamino)ethane, **3**, and *o*-anisidine gives 1,1′,2-tris(*o*-methoxyphenylamino)-2-isopropoxyethane, **4**, in 41% yield when the reaction is carried out in isopropyl alcohol solvent. These reactions are summarized in eq 1.



(1)

(4) O. Leminger and M. Farsky, *Collect. Czech. Chem. Commun.*, **30**, 607 (1965).

(5) A. Chwala and W. Bartek, *Monatsh. Chem.*, **82**, 652 (1951).

(6) E. Bayer, *Chem. Ber.*, **90**, 2325 (1957).

(7) I. S. Bengelsdorf, *J. Amer. Chem. Soc.*, **75**, 3138 (1953).

(8) S. B. Needleman and M. C. C. Kuo, *Chem. Rev.*, **62**, 422 (1962).

(9) W. U. Malik, D. R. Gupta, and C. L. Taploo, *J. Chem. Eng. Data*, **11** (2), 211 (1966).

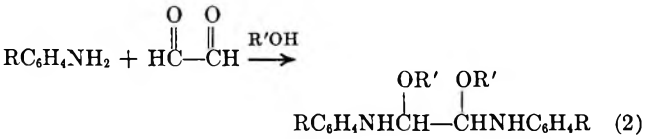
(10) G. R. Proctor and M. A. Rehman, *J. Chem. Soc. C*, **1967** (2696).

(1) (a) Preliminary communication: J. M. Kliegman and R. K. Barnes, *Tetrahedron Lett.*, 1953 (1969); (b) J. M. Kliegman and R. K. Barnes, *Tetrahedron*, in press.

(2) Y. Tominatsu, *Yakugaku. Zasshi*, **77**, 292 (1957).

(3) I. Murase, *Bull. Chem. Soc. Jap.*, **32**, 827 (1959).

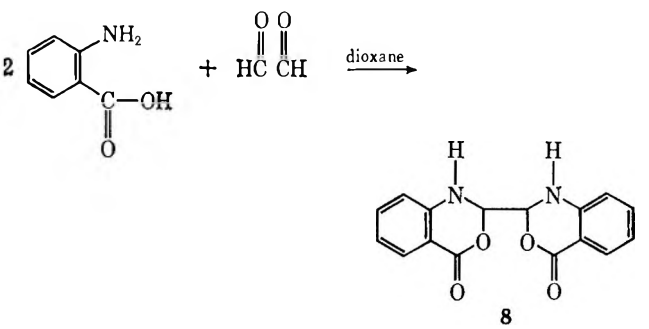
Ethylene glycol derivatives similar to compound **2** were also obtained from nitroanilines. *p*-Nitroaniline reacts with glyoxal in methyl alcohol to give a 32% yield of 1,2-bis(*p*-nitrophenylamino)-1,2-dimethoxyethane, **5**, while in acetic acid solvent the product is 1,2-bis(*p*-nitrophenylamino)-1,2-diacetoxyethane, **6**, in 77% yield. Glyoxal reacts with *m*-nitroaniline in methyl alcohol to give a 45% yield of 1,2-bis(*m*-nitrophenylamino)-1,2-dimethoxyethane, **7**. No diimines were isolated from these reaction mixtures. Equation 2 summarizes the above.



(2)

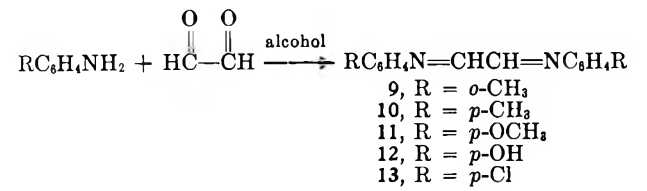
5, R = *p*-NO_2; R′ = CH_3
6, R = *p*-NO_2; R′ = CH_3CO
7, R = *m*-NO_2; R′ = CH_3

The observation by Murase[3] that *o*-aminophenol gave a cyclic product with glyoxal led us to investigate the similar reaction of glyoxal with *o*-aminobenzoic acid. In this reaction, a 45% yield of 2,2′-bis(1,2-dihydro-4-oxo-3,1-benzoxazine), **8**, is realized in which self incorporation of the hydroxylic moiety takes place.



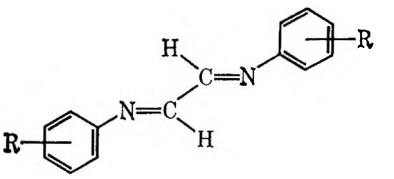
8

Schiff base formation was the primary mode of reaction for the other aromatic primary amines noted in this study. Thus, *o*-toluidine (**9**, 70% yield), *p*-toluidine (**10**, 26% yield), *p*-anisidine (**11**, 58% yield), *p*-hydroxyaniline[3] (**12**, 37% yield), and *p*-chloroaniline (**13**, 78% yield) all gave the corresponding 1,2-diimine when the reaction was carried out in either methanol or isopropyl alcohol.



9, R = *o*-CH_3
10, R = *p*-CH_3
11, R = *p*-OCH_3
12, R = *p*-OH
13, R = *p*-Cl

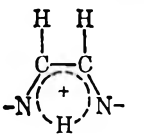
There is considerable evidence that aromatic aldimines in which the carbon–nitrogen double bond is conjugated with an aromatic ring exist preferentially in the *E*[11] conformation.[12,13] This observation is paralleled in the case of diimines **9–13**. An inspection of molecular models of compound **9**, for example, shows that only the *E-s-cis-E* or *E-s-trans-E* conformations allow for coplanarity of the aromatic rings with the two carbon–nitrogen double bonds, thereby extending the conjugated system. This fact, coupled with the greater stability associated with the *s-trans* configuration in 1,3-diene systems leads to the conclusion that these diimines should all exist in the *E-s-trans-E* conformation, **14**.



14

The nmr spectra of compounds **9–12** support this conclusion and have been discussed previously.[1a] The behavior of compounds **9–13** toward 0.1 *N* perchloric acid in acetic acid complements their conformational assignments. Thus, we find that compounds **10–13** all titrate for one molar equivalent of nitrogen, whereas, compound **9** titrates for two.

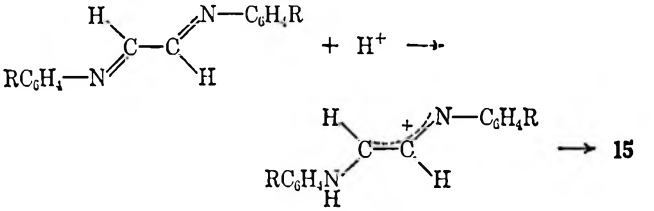
We have proposed that in the case of aliphatic 1,2-diimines, monobasic behavior towards perchloric acid is due to formation of a five-membered, highly stabilized, planar ring system[1] such as **15**.



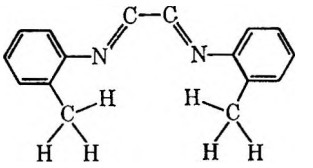
15

Such highly stabilized systems are only possible if the 1,2-diimine can assume an *E-s-cis-E* conformation (*Z-s-cis-Z* and *E-s-cis-Z* being too sterically hindered to allow a single proton to interact with both nitrogens).

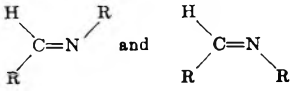
The analogous situation exists with compounds **10–13**. The only conformation which allows for protonation followed by rotation to the planar, cyclic *s-cis* configuration is the *E-s-trans-E* structure (the *E-s-cis-E* would already be in the proper configuration).



An inspection of molecular models of compound **9** demonstrates why it is, on the other hand, dibasic toward perchloric acid. The bulkiness of the *o*-methyl group is such that, when it assumes a planar *E-s-cis-E* conformation, the nitrogens are blocked from interaction with the proton. The molecule cannot, then,



(11) J. E. Blackwood, *et al.*, *J. Amer. Chem. Soc.*, **90**, 510 (1968); *i.e.*,

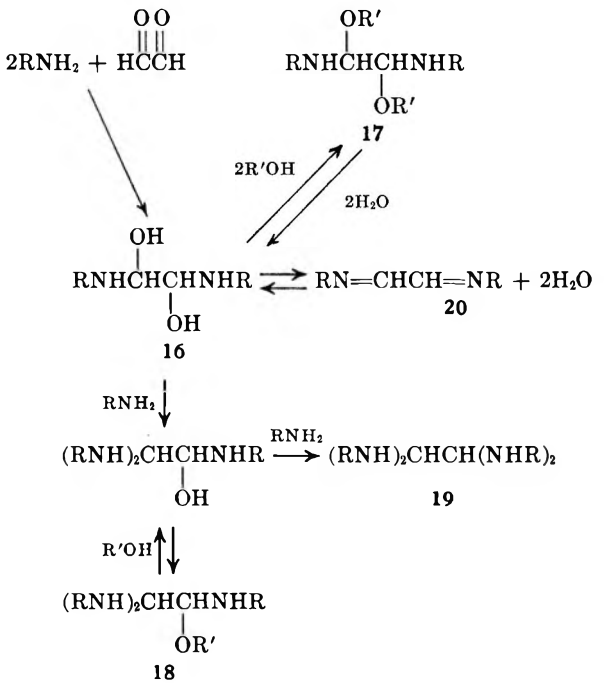


are *E* and *Z*, respectively, while *s-cis* and *s-trans* refer to tortional isomers around the central carbon–carbon bond of the 1,3-diene.

(12) V. De Gouck and R. J. W. LeFevre, *J. Chem. Soc.*, 741 (1938).

(13) D. G. Anderson and G. Wettermark, *J. Amer. Chem. Soc.*, **87**, 1433 (1965).

SCHEME I



assume the five-membered ring configuration and should act as a "normal" diimino compound[14] and take up the second mole of perchloric acid.

The ultraviolet spectra of these Schiff bases are in agreement with the proposed structures and are given in Table I.

TABLE I
UV SPECTRA OF 1,2-DIIMINES[a]

Compd	λmax, mμ (log ε)		
9	242 (4.06)	273 (3.99)	380 (4.25)
10	235 (4.23)	300 (3.88)	380 (3.93)
11	240 (4.12)	290 (3.99)	350 (4.19)
12	235 (4.10)	300 (3.81)	387 (4.29)
13	255 (4.41)	290 (3.81)	430 (3.32)

[a] 95% EtOH.

It is difficult to completely understand what the driving forces are for formation of the observed products in these reactions. The large number of variables coupled with differences in reaction condition and incomplete product balances makes speculation hazardous. One set of equilibria that would explain the products which we observed is as follows in Scheme I.

Experimental Section[15]

1,1',2,2'-Tetrakis(phenylamino)ethane (1).—Glyoxal, 14.5 g, aqueous 40%, 0.10 mol, was added slowly at 0–10° to aniline, 37.2 g, 0.40 mol, dissolved in 100 ml of isopropyl alcohol. In about 15 min the total reaction mixture became a white paste. Filtering and drying the product *in vacuo* gave a white solid, 20.0 g, mp 87–92°, 50% yield. Recrystallization from isopropyl alcohol gave 17.5 g material, 47% yield, with a melting point of 101–102°.

Anal. Calcd for $C_{26}H_{26}N_4$: C, 79.17; H, 6.64; N, 14.20. Found: C, 78.88; H, 6.85; N, 14.30.

The infrared spectrum (KBr) had a band at 2.97 μ (NH) and no bands indicating the presence of OH or C=N.

1,2-Bis(phenylamino)-1,2-dihydroxyethane (2).—When the reaction forming compound 1 above was conducted with 0.21 mol of aniline, 19.5 g, and 0.10 mol of glyoxal, 14.5 g, aqueous 40%, the major product was compound 2, 13.0 g, mp 106°, after recrystallization from cyclohexane, 54% yield.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.80; H, 6.60; N, 11.46. Found: C, 69.02; H, 6.53; N, 11.44.

The infrared spectrum (KBr) of this compound had bands at 3.02 μ (NH), 3.15 (OH), and 9.97, 10.1 (C–OH).

1,1',2,2'-Tetrakis(*o*-chlorophenylamino)ethane (3).—Glyoxal, 14.5 g, aqueous 40%, 0.10 mol, was added dropwise to *o*-chloroaniline, 64.0 g, 0.5 mol, with vigorous stirring. After several hours a water layer separated and the mixture was put on a rotary evaporator and water removed *in vacuo*. Distillation of the dark brown mixture afforded only unreacted *o*-chloroaniline, 7.0 g, 27° (0.05 mm), $\eta^{25}D$ 1.5863, leaving a semisolid residue. Trituration of this with isopropyl alcohol gave a yellow solid which was collected on a filter, 24.9 g, mp 131–133° dec, 47% yield.

Anal. Calcd for $C_{26}H_{22}N_4Cl_4$: C, 58.65; H, 4.14; N, 10.52; Cl, 26.69. Found: C, 58.79; H, 3.86; N, 10.20; Cl, 27.08.

The infrared spectrum (KBr) had the following major bands: 2.93 and 2.97μ (NH), 6.64 (arom and NH), and 13.45 (4 adjacent aromatic hydrogens).

1,1',2-Tris-(*o*-methoxyphenylamino)-2-isopropoxyethane (4).—Glyoxal, 21.8 g, aqueous 40%, 0.15 mol, was added dropwise to a hot, stirred solution of *o*-anisidine, 36.9 g, 0.30 mol, in 200 ml of isopropyl alcohol. After several days a dark orange solid precipitated which was collected by filtration and recrystallized from isopropyl alcohol to give 18.4 g of dark solid. This was crushed in a mortar and dried *in vacuo*, mp 70–71°. The yield was 41%.

Anal. Calcd for $C_{26}H_{33}N_3O_4$: C, 69.18; H, 7.32; N, 9.31. Observed: C, 68.82; H, 7.63; N, 9.20.

The infrared spectrum (KBr) had bands at 2.9 μ (NH), 3.52 (OCH_3), 8.05 and 8.17 (Ph–O–), 8.50 ($CH(CH_3)_2$), 8.93 (aliphatic C–O–C), 9.73 (OCH_3), and 13.55 (4 adjacent aromatic hydrogens).

1,2-Bis(*p*-nitrophenylamino)-1,2-dimethoxyethane (5).—Glyoxal, 36.3 g, aqueous 40%, 0.25 mol, was added dropwise to a stirred, refluxing solution of *p*-nitroaniline, 69.0 g, 0.50 mol, in 500 ml of methyl alcohol. After addition was complete the solution was allowed to cool to room temperature and was filtered giving 5.4 g of an olive colored solid, mp 172–174°. The mother liquors were reduced in volume by one-half and cooled. Filtering and washing with ether gave 23.5 g of a bright yellow solid, mp 172–173°. Total yield was 32%.

Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 4.97; N, 15.46. Found: C, 52.64; H, 4.95; N, 15.42.

The nmr spectrum (DMF) exhibited the following peaks in ppm from TMS: 3.45 (s, 6.1 H), 5.17 (d, J = 8.0 cps, 1.8 H), 7.45 (d, J = 8.0 cps, 1.8 H), 7.60 (8 for typical *p*-subst, 8.0 H). The infrared spectrum (KBr) had bands at 2.93 μ (NH), 3.50 (OCH_3), and 8.99 (aliphatic C–O–C), besides typical aromatic bands.

1,2-Bis(*p*-nitrophenylamino)-1,2-diacetoxyethane (6).—Glyoxal, 5.37 g, aqueous 40%, 0.037 mol, in 5 ml of glacial acetic acid was added to a hot solution of *p*-nitroaniline, 10.1 g, 0.073 mol, in 150 ml of hot acetic acid. The resultant mixture was heated to reflux and filtered. Upon cooling a solid precipitated. Filtration and drying gave 5.6 g of a dark brown solid, mp 237–240° dec. The mother liquors were reduced in volume by one-half and the solution cooled. This afforded upon filtration 0.83 g of additional solid. The total yield was 77%.

Anal. Calcd for $C_{18}H_{18}N_4O_8$: C, 51.67; H, 4.31; N, 13.40. Found: C, 52.02; H, 4.13; N, 13.71.

The nmr spectrum (DMSO) was not definitive; however, acetoxy methyl protons were clearly evident. The infrared spectrum showed bands at 2.97 μ (NH), 3.24 (aromatic), 5.83 (C=O), in addition to other aromatic and nitro peaks.

1,2-Bis(*m*-nitrophenylamino)-1,2-dimethoxyethane (7).—Glyoxal, 21.8 g, aqueous 40%, 0.15 mol, was added dropwise to a hot, stirred solution of 41.4 g, 0.30 mol of *m*-nitroaniline in 300 ml of methyl alcohol. After addition was complete the resultant solution was heated to reflux and then cooled in a refrigerator (−15°). Filtration of the resulting mixture afforded 25.2 g yellow solid, mp 163–164°. A small portion was recrystallized from methanol–

(14) For example, N,N'-dibenzylidineethylenediamine adds 2 mol of perchloric acid.

(15) Melting points and boiling points are uncorrected. Infrared, ultraviolet, nuclear magnetic resonance, and mass spectra were obtained in Perkin-Elmer Model 21 and Bairde Model 4SS, Cary Model 14, Varian A60, and AIC MS-9 spectrophotometers by Messrs. W. H. Joyce, C. M. Lovell, C. B. Strow, Jr., and B. E. Wilkes. Microanalyses were performed by Mr. S. Gottlieb and his associates.

nitrobenzene giving yellow crystals, mp 167–168°. The yield of this reaction was 47%.

Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.03; H, 4.97; N, 15.47. Found: C, 52.87; H, 4.93; N, 15.17.

The nmr spectrum (DMSO) showed the following peaks in ppm from TMS: 3.32 (s, ≈6 H), 4.94 (m, ≈2 H), 6.95 (m, ≈2 H), and 7.53 (m, ≈8 H). The infrared spectrum (KBr) had the following bands: 2.88 μ (NH), 3.22 (aromatic CH), 3.36 (CH_3), 3.5 (OCH_3), 6.15 (C=C), 6.52 and 7.48 (NO_2), 6.73 (aromatic C=C), 8.93 (C–O–C), 9.5 (OCH_3), 11.6 (isolated arom. hydrogen), 12.6 (3 adjacent aromatic hydrogens), and 13.63 (aryl NO_2).

2,2′-Bis(1,2-dihydro-4-oxo-3,1-benzoxazine) (8).—Glyoxal, 21.8 g, aqueous 40%, 0.15 mol, was added dropwise to a hot solution of 41.1 g, 0.30 mol of *o*-aminobenzoic acid in 150 ml of hot dioxane. Cooling to room temperature and collecting several crops of white solid on a filter gave 19.8 g of product, mp 183–184°. The yield was 45%.

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.05; N, 9.46. Found: C, 64.74; H, 4.06; N, 9.16.

The infrared spectrum (KBr) was consistent with the assigned structure showing bands at 3.0 μ (NH), 5.83 (C=O), 6.65 (NH), 9.2 (C–O), and 13.4 (4 adjacent aromatic hydrogens).

N,N′-Bis(*o*-tolyl)ethylenediimine (9).—*o*-Toluidine, 32.1 g, 0.30 mol, was added dropwise to a stirred, warmed solution of glyoxal, 21.8 g, aqueous 40%, 0.15 mol, in 300 ml of methanol. Upon cooling a solid precipitated. Filtering and drying gave 18.6 g of yellow solid, mp 122–124° [lit.[3] 126.5–127.5°]. A second crop, 1.1 g, mp 122–124°, was afforded upon further cooling. The yield was 58%.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86. Found: C, 81.50; H, 6.77; N, 11.51.

The nmr spectrum ($CDCl_3$) exhibited the following peaks in ppm from TMS: 2.38 (s, 2.9 H), 7.20 (m, 4.2 H), 8.32 (s, 0.9 H). The infrared spectrum (KBr) had no NH or OH bands but had a strong band at 6.21 μ (C=N).

N,N′-Bis(*p*-tolyl)ethylenediimine (10).—Glyoxal, 14.3 g, aqueous 40%, 0.10 mol, was added dropwise to a cooled (0–10°) solution of *p*-toluidine, 21.4 g, 0.20 mol, in 100 ml of isopropyl alcohol. The resultant yellow solid was collected on a filter and quickly recrystallized from isopropyl alcohol. The recrystallized material was collected by filtration giving 6.2 g of yellow needles, mp 164–165°. The yield was 26%.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86. Found: C, 81.54; H, 6.55; N, 12.00.

The nmr spectrum ($CDCl_3$) had the following peaks in ppm from TMS: 2.37 (s, 3.2 H), 7.70 (s, 3.8 H), 8.38 (s, 0.9 H). The infrared spectrum (KBr) had a strong band at 6.20 μ (C=N).

N,N′-Bis(*p*-anisyl)ethylenediimine (11).—Glyoxal, 36.3 g, aqueous 40%, 0.25 mol, was added dropwise to a hot solution of 61.5 g, 0.50 mol, of *p*-anisidine in 300 ml of methyl alcohol. A solid soon precipitated and isopropyl alcohol was added and methanol distilled until solution occurred. Cooling to room temperature gave needles, which were collected on a filter and dried, 3.92 g, mp 153–154° [lit.[5] 159°], yield 58%.

The nmr spectrum ($CDCl_3$) shows the following peaks in ppm from TMS: 3.82 (s, 5.6 H) 7.13 (q of typical *p*-subst, 8.2 H), 8.42 (s, 2.0 H). The infrared spectrum (KBr) had a strong band at 6.23 μ (C=N).

N,N′-Bis(*p*-hydroxyphenyl)ethylenediimine (12).—Glyoxal, 72.5 g, aqueous 40%, 0.508 mol, was added dropwise to a stirred solution of *p*-aminophenol, 109.0 g, 1.0 mol, in 900 ml of refluxing methanol. A yellow precipitate soon formed and the mixture was cooled and filtered. The yellow solid thus collected was washed with methanol and dried giving 93.1 g of material, mp 185–186° dec. A small portion was recrystallized from isopropyl alcohol giving tan needles, mp 186° dec [lit.[3] 213–214°]. The yield was 86%.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67; mol wt, 240.0899. Found: C, 70.07; H, 4.86; N, 11.40; mol wt, 240.0884 (mass spec.).

The nmr spectrum (DMSO) shows the following peaks in ppm from TMS: 7.18 (q, typical *para*-substituted, 7.8 H), 8.40 (s, 2.0 H), 9.75 (s, unresolved). The infrared spectrum (KBr) shows bands at 3.25 μ (hydrogen bonded OH), 6.21 (C=N), 7.9 and 8.07 (Ph–OH), and 12.3 (2 adjacent aromatic hydrogens).

N,N′-Bis(*p*-chlorophenyl)ethylenediimine (13).—A mixture of glyoxal, 14.5 g, aqueous 40%, 0.10 mol, and *p*-chloroaniline, 64.0 g, 0.5 mol, was stirred at 75° for 10 hr. The dark mixture was put on a rotary evaporator and water removed *in vacuo*. The resultant dark solid was then subjected to distillation at reduced pressure [80–90° (0.3 mm)] and unreacted *p*-chloroaniline was removed. The residue was taken up with hot isopropyl alcohol and cooled to give upon filtration 10.2 g of a purple solid, mp 107–110° dec. The yield was 37%.

Anal. Calcd for $C_{14}H_{10}N_2Cl_2$: C, 60.65; H, 3.61; N, 10.11; Cl, 25.63. Found: C, 60.74; H, 3.83; N, 9.80; Cl, 24.11.

The infrared spectrum (KBr) had bands at: 5.18 μ (C=N), 9.17 (*p*-Cl–Ph), 9.9 (*para*-substituted), and 12.3 (2 adjacent aromatic hydrogens). All the peaks in the nmr spectrum appeared as a complex multiplet in the aromatic region.

Perchloric acid titrations were carried out in the usual manner.[1b] The results were: compound (nitrogen equivalents per mole) 9 (2.02), 10 (1.15), 11 (1.17), 12 (1.03), 13 (0.91).

Registry No.—1, 4378-77-2; 2, 24978-34-5; 3, 24978-35-6; 4, 25024-01-5; 5, 24978-36-7; 6, 24978-37-8; 7, 24978-38-9; 8, 24978-39-0; 9, 24978-40-3; 10, 24978-41-4; 11, 24978-42-5; 12, 24978-43-6; 13, 24978-44-7; glyoxal, 107-22-2.

3-Nitromethylphthalide and 2-Phenyl-3-nitromethylphthalimidine

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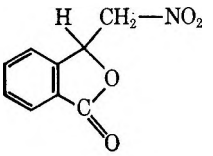
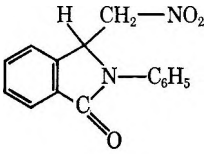
Received February 24, 1970

The product from the base-catalyzed condensation of *o*-phthalaldehydic acid and nitromethane, reported to be *o*-carboxy-β-nitrostyrene,[2] has been shown from its nuclear magnetic resonance (nmr) spectrum to be 3-nitromethylphthalide (I) as previously reported.[3,4] In a similar manner, the product from the condensation of 3-nitromethylphthalide and aniline, reported to be *o*-(2-nitrovinyl)benzanilide,[2] has been identified as 2-phenyl-3-nitromethylphthalimidine (II) from its nmr and infrared (ir) spectra.



I



II

The compound obtained from the condensation of *o*-phthalaldehydic acid and nitromethane was a white, colorless solid rather than the characteristic yellow of the unsaturated β-nitrostyrenes, its nmr spectrum in acetone lacked vinylic and carboxylic proton signals, and its ir spectrum lacked the OH stretching band. The nmr spectrum gives three sets of quartets attributed to nonaromatic protons centered at δ 6.29, 5.43, and 4.91 with each integrating to one proton relative to the aromatic proton signal (δ 7.81). The quar-

(1) (a) Public Health Service Predoctoral Fellow 5-F01-GM-34,830; (b) abstracted in part from the Ph.D. Dissertation of B. D. Whelton, University of Washington, 1970; (c) to whom correspondence should be addressed.

(2) T. Hashimoto and S. Nagase, *Yakugaku Zasshi*, **80**, 1637 (1960); *Chem. Abstr.*, **55**, 7415*d* (1962).

(3) B. B. Dey and T. K. Srinivasan, *Arch. Pharm.* (Weinheim), **275**, 397 (1937).

(4) G. E. Ullyot, J. J. Stehle, C. L. Zirkle, R. L. Shriner, and F. J. Wolf, *J. Org. Chem.*, **10**, 429 (1945).

tets have been interpreted as arising from H-3, the hydrogen β to the nitro, and the two magnetically nonequivalent methylene protons α to the nitro group in 3-nitromethylphthalide. The nonequivalence results from unequal time average population of rotamers. The quartet at δ 6.29 results from the coupling of H-3 to the α protons by 7.8 and 3.0 Hz. Geminal coupling between the two nonequivalent α hydrogens is 14.3 Hz. Of these two, that which is downfield is then coupled to H-3 by 3.0 Hz and that which is upfield is coupled to H-3 by 7.8 Hz. The difference in coupling constants results from unequal average dihedral angles because of unequal time average populations of rotamers.

In an attempt to isolate the β-nitrostyrene, the work of Hashimoto and Nagase[2] was repeated for the synthesis of their reported *o*-(2-nitrovinyl)benzanilide. The product from the condensation of 3-nitromethylphthalide and aniline was recovered as a white, colorless solid. Its nmr displayed no vinylic or amide hydrogen signals and its ir lacked the amide NH stretching band. The same general nmr signal pattern was observed for this derivative in acetonitrile as was seen in the case of 3-nitromethylphthalide, and it has been concluded that the correct structure of this compound is 2-phenyl-3-nitromethylphthalimidine. Once again the α-methylene protons are magnetically nonequivalent being separated by ~0.27 ppm. They give two slightly overlapping quartets centered at δ 4.76 and 5.03 resulting from a geminal coupling of 13.5 Hz, and from a coupling of the α proton at lower field to H-3 by 4.3 Hz and that at higher field to H-3 by 4.6 Hz. The methine H-3 gives a triplet-like pattern at δ 5.83 resulting from coupling with the α hydrogens. The aromatic protons are observed as a complex multiplet centered at δ 7.56. Partial deuterium exchange of the α protons employing deuterium oxide and a catalytic amount of anhydrous potassium carbonate results in collapsing the signal attributed to H-3 to a singlet and in virtually eliminating the signal of the two α hydrogens. This confirms the assignment of the α-methylene hydrogens and the five-membered ring lactam. The result of the deuterium exchange on II also substantiates the structure of I because of the similarity in chemical shifts and multiplicities of the signals of the methine and methylene hydrogens in the two compounds.

Experimental Section[5]

3-Nitromethylphthalide.[2]—To a solution of 176.3 g (1.175 mol) of *o*-phthalaldehydic acid,[6] 72.4 g (1.18 mol) of nitromethane, and 885 ml of methanol cooled to −15° was added dropwise and with stirring a solution of 112 g (2.78 mol) of sodium hydroxide in 400 ml of distilled water. After addition of the base, the solution was allowed to warm to 25° and stirred for 2.5 hr. The solution was then poured into 710 ml of 5 *N* hydrochloric acid with stirring. The product crystallized and was filtered and washed with distilled water. Additional cooling of the reaction mixture resulted in more crystalline material. The combined product was dissolved in 2-propanol and recrystallized to give 140.4 g (61%) of white crystals: mp 129–131° (Fisher-Johns) (lit. mp 129–130°,[2] 130°,[3] 130–131°[4]); ir (KBr) 1560 (NO_2), 1755 (lactone C=O), 2980 (aliphatic CH), and 3040 cm^{-1} (aromatic CH).

2-Phenyl-3-nitromethylpythalimidine.[2]—A solution of 5.0 g (26.0 mmol) of 3-nitromethylphthalide and 4.65 g (50.0 mmol) of aniline was refluxed in 10 ml of anhydrous toluene for 18 hr. The reaction mixture was diluted with benzene and extracted three times with 0.6 *N* hydrochloric acid. After washing the organic layer with distilled water to pH 5.5 and drying over anhydrous sodium sulfate, the solvents were evaporated and the remaining oil dissolved in 2-propanol. Repeated recrystallization gave 4.6 g (66%) of white crystals: mp 158.0–159.0° (Kofler) (lit.[2] mp 151–153°); ir (KBr) 1380 and 1540 (NO_2), 1685 (lactam C=O), 2920 (aliphatic CH), and 3060 cm^{-1} (aromatic CH).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.03; H, 4.38; N, 10.64.

Registry No.—I, 3598-68-3; II, 25097-57-8.

(5) All nmr spectra were recorded on a Varian A-60 spectrometer at operating temperature of about 37° utilizing ~20% solutions of compound with tetramethylsilane (TMS) as the internal reference. Infrared spectra were determined using a Beckman IR 5-A infrared spectrophotometer. All melting points are uncorrected.

(6) R. L. Shriner and F. J. Wolf, "Organic Syntheses," Col. Vol. III, Wiley, New York, N. Y., 1955, p 737.

Basicity of N-Ylides[1]

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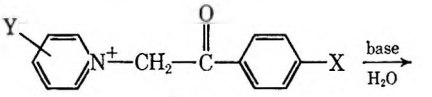
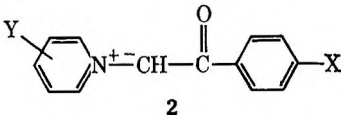
Received March 5, 1970

Although nitrogen ylides were isolated and characterized by Krohnke[2] over 30 years ago, no systematic study of the basicities of these ylides has been reported. The basicity trends are significant in that they suggest to some extent the expected nucleophilic reactivity and delineate the factors which are important in this respect in ylide structures. Also nitrogen ylides are unique in that they can derive no stabilization by d-orbital carbanion delocalization, a usually important factor in the better known sulfur and phosphorus ylides. We have determined the pK_a's of a number of pyridinium (1) and ammonium salts in order to determine to some extent the significant factors affecting the stability and reactivity of the corresponding ylide (2).



1



2

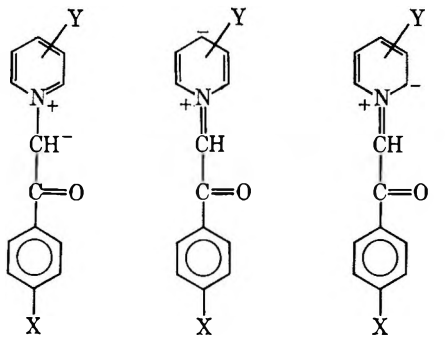
The pK_a's of a number of pyridinium salts are listed in Table I. In cases where the pyridinium salt was not acidic enough to conveniently titrate with aqueous sodium hydroxide solution, the pK_a was determined by titrating the isolated ylide with aqueous hydrochloric acid. In preparative runs, the ylides were isolated by employing sodium carbonate as the base (see Table II).

Table III summarizes the results of the $\sigma\rho$ treatments of the pK_a's. When the phenacyl substituent X is held at H, NO_2, or halogen and the pyridine substituent Y is varied, ρ is fairly constant and equals an average of 2.9. This indicates that electron-withdrawing substituents on the pyridine nucleus tend to stabilize the ylide. An inductive effect is certainly one reason for the moderately high ρ value. An additional

(1) For a previous paper in this series, see W. G. Phillips and K. W. Ratts, *Tetrahedron Lett.*, 1383 (1969).

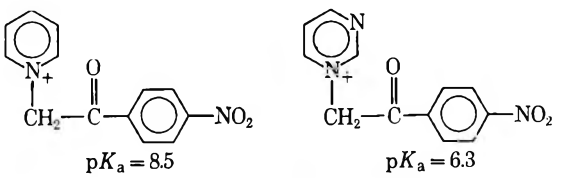
(2) F. Krohnke, *Chem. Ber.*, **68**, 1177 (1935).

explanation involves the resonance stabilization shown below in which the negative charge is delocalized into the pyridine ring.



3

The pK_a's of pyrimidinium, pyridazinium, and pyrazinium salts (**5**, **6**, and **7**) are less than that for the pyridinium salt (**4**). Accordingly, the replacement of carbon with a nitrogen atom in the aromatic ring is a stabilizing factor since nitrogen is more electronegative than carbon (**8**). However, the comparative order of basicities for **5**, **6**, and **7** involves more complicating

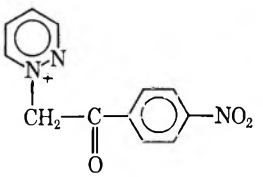


$pK_a = 8.5$

4

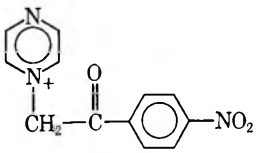
$pK_a = 6.3$

5



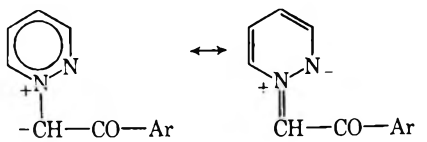
$pK_a = 5.4$

6



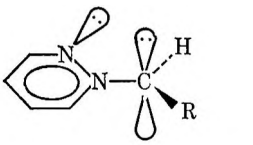
$pK_a = 4.1$

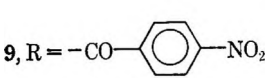
7



8

factors. Those ylides where the negative charge can be resonance delocalized on nitrogen (**6** and **7**) are more stable than the pyrimidinium ylide where this possibility does not exist. The fact that **7** has a lower pK_a than **6** may indicate that repulsion between the electron pairs as depicted in **9** raises the ground-state energy of **8**.[3]

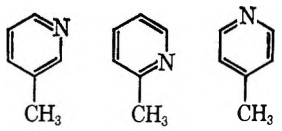




9, R = —CO—C$_6$H$_4$—NO$_2$

(3) We are indebted to Professor P. Beak for making this suggestion.

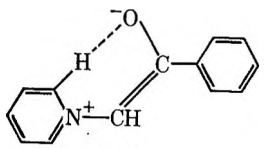
In this connection the relative rates of exchange of the isomeric picolines are noteworthy.[4] Results in the



Relative rate of exchange	1	46	164

analogous benzene series suggest that the relative rates reflect the relative acidities of hydrocarbons.[5] Since 4-picoline exchanges faster than 2-picoline, this same type of steric effect may be operative here.

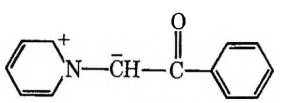
As seen in Tables I and II, the α-protons of the pyridine ring in the ylide are shifted downfield as compared to the α-protons of the pyridine ring in the starting salt. An attractive explanation involves deshielding of the α-hydrogens by the carbonyl function as depicted in **10**.



10

Here a six-membered ring is formed and the α-hydrogen is partially polarized in a resonance structure possessing considerable electron density at oxygen. Evidence for the carbonyl possessing considerable electron density was obtained by Henrick[6a] who noted that pyridinium ylides showed strong carbonyl absorption at low frequency.

Henrick[6b] in a recent paper has noted a similar nmr effect but prefers to attribute this to a deshielding of the α-proton resulting from resonance structure **11**. In light of our basicity studies, this explanation now appears unlikely.[7]



11

In additional pK_a studies of structure **1**, when Y is held constant and X is varied, $\rho = +2.3$. Thus it is clear that substitutents on the phenacyl aromatic ring which are electron withdrawing tend to stabilize the nitrogen ylide **2** by inductive effects. This value is consistent with similar ρ values obtained for sulfur and phosphorus salts. Ratts and Yao[8] found ρ to be +2.1

(4) N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *Zh. Obshch. Khim.*, **33**, 2705 (1963); *Dokl. Akad. Nauk SSSR*, **154**, 148 (1964).

(5) A. Streitwieser and D. E. Van Sickle, *J. Amer. Chem. Soc.*, **84**, 249 (1962).

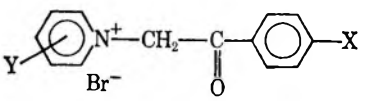
(6) (a) C. A. Henrick, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **20**, 2455 (1967); (b) *ibid.*, 2441 (1967).

(7) An additional explanation involves an electric-field effect. Buckingham has reported calculations which show that a C–H proton is deshielded by the electric field of a nearby charge: A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).

(8) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966).

TABLE I

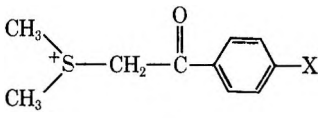
N-PHENACYLPYRIDINIUM SALTS[a]



Y[b]	X	Registry no.	Mp, °C, dec	% yield	pK_a	Nmr (SO_2 solvent, τ,[c] multiplicity[d]) α-Pyridine	β- + γ-pyridine	Methylene	Aromatic	Y	X
H	H	a	194.5–197	64	9.7	s, 1.2	m, 2.0	s, 3.6	m, 2.0		
H	Br	b	242–243[e]	75	9.4						
CH_3	H	c	159–161	92	10.5	d, 1.4	m, 2.0	s, 3.7	m, 2.0	s, 7.1	
CN	H	d	236–237	60	7.0	d, 0.9	d, 1.5	s, 3.4	m, 2.1		
C_2H_5	H	e	236–238	93	10.3	d, 1.4	m, 2.1	s, 3.7	m, 2.1	q, 6.9	
CN	NO_2	f	220–222	99	5.1	d, 0.8	m, 2.1	s, 3.2	m, 1.4	t, 8.6	
CN	Cl	g	259–261	26	6.45	d, 0.9	d, 1.4	s, 3.4	q, 2.2		
H	NO_2	h	255–257	65	8.5	d, 1.0	m, 1.5	s, 3.3	m, 1.5		
CH_3	NO_2	i	242–243	89	8.8	d, 1.4	d, 2.0	s, 3.6	s, 1.7	s, 7.2	
CH_3	Cl	j	242–243	65	9.9	d, 1.4	d, 2.4	s, 3.7	m, 2.0	s, 7.1	
t-C_4H_9	H	k	247–248	84	10.4	d, 1.4	d, 2.3	s, 3.8	m, 1.9	s, 8.5	
CH_3CO	H	l	214–215	25	8.3	d, 0.9	d, 1.3	s, 3.6	m, 1.9	s, 7.1	
H	OCH_3	m	208–210	78	10.8	m, 1.2–3.0[f]	m, 1.2–3.0	s, 3.6	q, 2.4		s, 6.1
CN	OCH_3	n	230–231	55	7.5	d, 1.1	d, 1.5	s, 3.6	q, 2.5		s, 6.1
3-CN	H	o	195–196	43	7.7	m, 1.6	m, 1.6	s, 3.5	m, 1.6		
3-Br	H	p	114–117	28	9.15	m, 1.0–2.6[f]	m, 1.0–2.6	s, 3.5	m, 1.0–2.6		

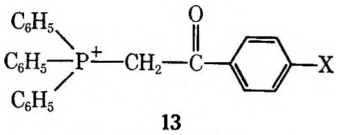
[a] Satisfactory analyses (±0.35% for C and H) were reported for all compounds except the salt with Y = CN, X = NO_2, which tended to decompose upon standing. Ed. [b] The substituent is in the 4 position unless indicated otherwise. [c] Internal TMS. [d] s = singlet, d = doublet, m = unresolved multiplet, q = quartet, t = triplet; all integrations were in accord with theory. [e] Lit. mp 235°: F. Krohnke, *Ber. Deut. Chem. Ges.*, 68, 177 (1935). [f] The phenyl and pyridine protons were not well resolved here.

for series 12. Fliszar, Hudson, and Salvadori[9] found ρ to be +2.3 for series 13.



12

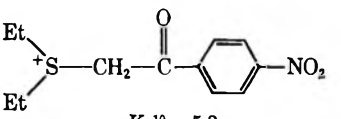
X = H, C_6H_5, Br, NO_2



13

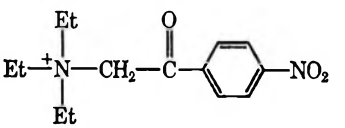
X = OCH_3, H, NO_2

An examination of pK_a's of 14 through 19 reveals that nitrogen ylides are more basic than corresponding sulfur, phosphorus, or arsenic ylides. Thus sulfur, phosphorus, and arsenic ylides have a stabilizing factor which is deprived from nitrogen ylides. Since electronegativity differences and bond length differences favor the stability of N-ylides, one can conclude that back donation of electrons in d orbitals accounts for the increase in stability of phosphorus, sulfur, and arsenic ylides over nitrogen ylides. No conclusions regarding the degrees of d-orbital participation in 16, 17, and 18 can be made since electronegativity differences and bond length differences can equally as well explain the pK_a trends.



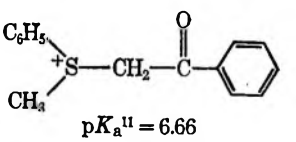
pK_a[10] = 5.3

14



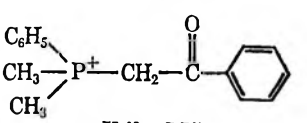
pK_a = 9.1

15



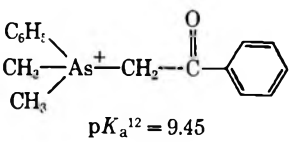
pK_a[11] = 6.66

16



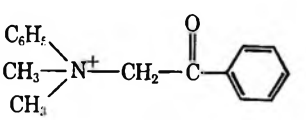
pK_a[12] = 7.75

17



pK_a[12] = 9.45

18



pK_a[13] = 9.8

19

Experimental Section

Synthesis of Pyridinium Salts.—The pyridinium salts employed were synthesized by the action of the appropriate pyridine on the appropriate phenacyl bromide in benzene. The results are summarized in Table I.

(9) S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, 1580 (1963).

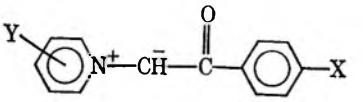
(10) Since the 4-Br analog was more accessible, its pK_a was determined and found to be 6.44. The value of 5.3 shown was calculated by using a ρ of +2.1.

(11) A. W. Johnson and R. T. Amel, *Can. J. Chem.*, 46, 461 (1968).

(12) G. Aksnes and J. Sonstad, *Acta Chem. Scand.*, 18, 655 (1964).

(13) Since the 4-Br analog was more accessible, its pK_a was determined and found to be 9.3. The value of 9.8 shown was calculated by using a ρ of +2.3. It also should be noted that different solvents were used.

TABLE II
PYRIDINIUM YLIDES



Y	X	Registry no.	Mp, °C, dec	% yield	Nmr (CDCl₃ solvent, τ,[c] multiplicity[d]) Y	α-Pyridine	β- + γ-pyridine	Methine	Aromatic	Neut equiv[e]
H	H	a	89–92[a]	85		m, 0.4	m, 2.2	Not seen	m, 2.7	212 (197)
H	Br	b	133–136[b]	93		m, 0.9	m, 2.2	Not seen	m, 2.2	
CH_3	H	c	110–113		s, 7.3	d, 0.3	m, 2.1	s, 3.2	m, 3.3	214 (211)
CN	H	d	114–118	Quant		d, 0.6[f]	m, 2.0	s, 3.2	m, 2.0	216 (222)
C_2H_5	H	e	103–106	83	q, 7.4 t, 8.8	d, 0.5	m, 2.0	s, 3.2	m, 2.7	
CN	NO_2	f	187–189		[g]					
CN	Cl	g	148–150	32		d, 0.9[f]	m, 2.2	d, 3.3	m, 2.2	265 (257)
H	NO_2	h	Slow dec	Quant		m, 0.3	m, 2.5	s, 3.2	q, 1.9	239 (242)
CH_3	NO_2	i	Slow dec	95	s, 7.5	d, 0.5	m, 2.7	Not seen	q, 1.9	236 (256)
CH_3	Cl	j	86–89	87	s, 7.6	d, 0.6	d, 2.3	s, 3.4	m, 2.8	262 (246)
t-C_4H_9	H	k	155–162		s, 8.7	d, 0.5	m, 2.2	s, 3.2	m, 2.6	
CH_3CO	H	l	93–98		[g]					
H	OCH_3[h]	m	103–107	56		m, 0.4	m, 2.8	Not seen	q, 2.6	233 (227)
CN	OCH_3[i]	n	128–131	Quant		d, 1.0[f]	d, 2.9	s, 3.4	m, 1.8	260 (252)
3-CN	H	o	143–147	82		m, 1.8–2.9[j]	m, 1.8–2.9		m, 1.8–2.0	
3-Br	H	p	118–120	88		s, 0.0 d, 1.0	m, 2.2	Not seen	m, 2.8	274 (276)

[a] Lit.[2] mp 93–96°. [b] Lit.[2] mp 135–136°. [c] Internal TMS. [d] m = unresolved multiplet (the integrations were all consistent with theory), d = doublet, s = singlet, q = quartet, t = triplet. [e] Theoretical values are in parentheses. [f] SO_2 was solvent here. [g] A nmr spectrum was not obtained because of solubility difficulties. [h] The methoxy gives raise to a nmr absorption at τ 6.2 (s). [i] The methoxy gives raise to a nmr absorption at τ 6.1 (s). [j] The phenyl and pyridine protons overlapped here.

TABLE III
RESULTS OF $\sigma\rho$ TREATMENT OF pK_a'S[a]

X varied	Y = H	ρ = +2.3
X varied	Y = CN	ρ = +2.3
X varied	Y = CH_3	ρ = +2.2
X = H	Y varied	ρ = +2.6
X = NO_2	Y varied	ρ = +3.1
X = Br or Cl	Y varied	ρ = +2.9

[a] σ constants are those for substituted benzoic acids except for Y = 4-CN and 4-$COCH_3$, where σ was employed.

Synthesis of Pyridinium Ylides.—The method of Krohnke was followed.[2] An aqueous solution of 10% sodium carbonate was added to an aqueous solution of the pyridinium salt. The ylide was then filtered off and dried. In cases where the ylide was soluble in water, the solution was extracted with chloroform. Table II is a summary of the results. In some cases, the methine proton was not seen in the nmr because of exchange with $CDCl_3$.

Measurement of pK_a Values.—The pK_a values were determined by the method given in ref 14. The ρ's were determined by a least-squares treatment of the data.

N-(4-Nitrophenacyl)pyridazinium Bromide.—To 29.3 g (0.125 mol) of 4-nitrophenacyl bromide in benzene was added 10.0 g (0.125 mol) of pyrazine. After stirring overnight, 30.1 g of a precipitate was filtered off, mp 226–227°.

Anal. Calcd for $C_{12}H_{10}BrN_3O_3$: C, 44.46; H, 3.11; N, 12.96. Found: C, 44.62; H, 3.30; N, 12.75.

N-(4-Nitrophenacyl)pyrimidinium Bromide.—To 6.1 g (0.025 mol) of 4-nitrophenacyl bromide in 300 ml of benzene was added 2.0 g (0.025 mol) of pyrimidine. After heating overnight on a steam bath, 1.5 g of a precipitate which formed was filtered off, mp 187–188°.

Anal. Calcd for $C_{12}H_{10}BrN_3O_3$: C, 44.46; H, 3.11; N, 12.96. Found: C, 44.59; H, 3.18; N, 12.79.

N-(4-Nitrophenacyl)pyrazinium Bromide.—To 30 g of 4-nitrophenacyl bromide in benzene was added 10.0 g (0.125 mol) of pyrazine. After stirring overnight, 4.5 g of a precipitate was filtered off, mp 208–209°.

Anal. Calcd for $C_{12}H_{10}BrN_3O_3$: C, 44.46; H, 3.11; N, 12.96. Found: C, 44.62; H, 3.11; N, 12.99.

(14) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **85**, 2790 (1963).

Registry No.—Table I—a, 16883-69-5; b, 17282-37-0; c, 7250-28-4; d, 25357-39-5; e, 16844-13-6; f, 25407-29-8; g, 25357-41-9; h, 25407-30-1; i, 25357-42-0; j, 25357-43-1; k, 25357-44-2; l, 25357-45-3; m, 25407-31-2; n, 25407-32-3; o, 25357-46-4; p, 6299-99-6; Table II—a, 17282-43-8; b, 17282-45-0; c, 25357-50-0; d, 25357-51-1; e, 25407-33-4; f, 25357-52-2; g, 25357-53-3; h, 25357-54-4; i, 25357-55-5; j, 25357-56-6; k, 25357-57-7; l, 25357-58-8; m, 25357-59-9; n, 25357-60-2; o, 25357-61-3; p, 25357-62-4; N-(4-nitrophenacyl)pyridazinium bromide, 25357-63-5; N-(4-nitrophenacyl)pyrimidinium bromide, 25357-64-6; N-(4-nitrophenacyl)pyrazinium bromide, 25357-65-7.

Methyl Aryl Ether Cleavage in Benzazole Syntheses in Polyphosphoric Acid

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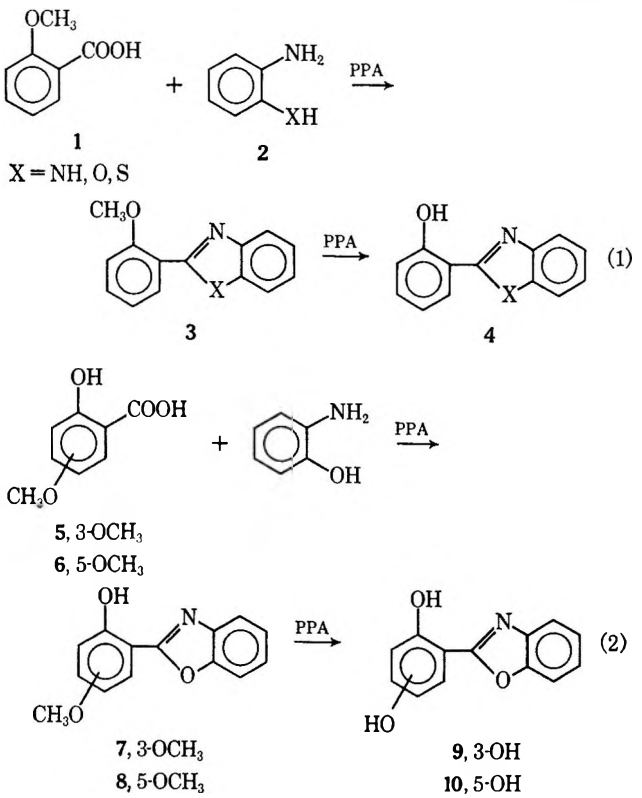
The polyphosphoric acid method[1] has been extensively employed as a general synthesis of benzazole compounds. As part of some recent studies, a number of substituted 2-phenylbenzazoles have been prepared in PPA, and we now wish to report an interesting ether cleavage reaction accompanying benzazole formation using this method.

The condensation reactions of *o*-methoxybenzoic acid

(1) (a) D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Amer. Chem. Soc.*, **79**, 427 (1957). (b) D. W. Hein, R. J. Alheim, and J. J. Leavitt, American Cyanamid Company, U. S. Patent 2,985,611; *Chem. Abstr.*, **57**, 11203c (1962).

(1) with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol in PPA at 180–200° proceeded with methyl ether cleavage resulting in the formation of the corresponding 2-(2-hydroxyphenyl)benzazoles (**4**). However, the reaction of **1** with *o*-phenylenediamine in PPA at 135° has been reported to give only the 2-(2-methoxyphenyl)benzimidazole (**3**, X = NH).[2] We have similarly observed the formation of **3** (X = S) as the major product in the condensation of **1** with *o*-aminothiophenol in PPA at 160°. Extended heating of the same reaction mixture at 200° resulted only in the isolation of the ether cleavage product 2-(2-hydroxyphenyl)benzothiazole (**4**, X = S).

Similar demethylations were also observed in the reactions of 3- and 5-methoxysalicylic acids (**5** and **6**) with *o*-aminophenol in PPA at 185 to 195°. The products isolated under these conditions were the corresponding isomeric 2-(dihydroxyphenyl)benzoxazoles (**9** and **10**). In analogy with reactions of *o*-methoxybenzoic acid described above, it is probable that the benzoxazoles (**7** and **8**) were initially formed in the reactions of the isomeric methoxysalicylic acids and were subsequently demethylated under the experimental conditions. Methyl ether cleavage has been observed for the structurally analogous 2-(2-hydroxy-5-methoxyphenyl)benzothiazole in PPA at 170°. In general, demethylation accompanies benzazole formation from methoxy aromatic carboxylic acids in PPA from 170 to 200°, but ether cleavage does not occur below 150°.



Several attempts to extend the ether cleavage in PPA to carbocyclic systems such as β-methoxynaphthalene and 4-methoxybiphenyl were unsuccessful. Numerous examples of chemical reactions in PPA involving methoxy-substituted aromatic compounds have been described.[3] It would appear that the possibility of methyl aryl ether cleavage in these reactions must be given consideration.

(2) M. Dunnenberger, A. E. Siegrist, and E. Maeder, Ciba Ltd., Swiss Patent 350,763; *Chem. Abstr.*, **55**, 19973a (1961).

Experimental Section

All melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Infrared and ultraviolet spectra were recorded on the Perkin-Elmer Model 137 and Cary Model 14 spectrophotometers, respectively.

Materials.—Polyphosphoric acid (practical grade) was obtained from Matheson Coleman and Bell, East Rutherford, N. J. 2-(2,5-Dihydroxyphenyl)benzoxazole (mp 207–209°) and 2-(2,5-dihydroxyphenyl)benzothiazole (mp 195–196°) were prepared from the reactions of 5-hydroxysalicylic acid with *o*-aminophenol and *o*-aminothiophenol in PPA, respectively.

3Methoxysalicylic acid (mp 142–144°) was prepared by the oxidation of the corresponding aldehyde according to the procedure described in "Organic Syntheses."[4]

Reaction of o-Methoxybenzoic Acid in PPA. A. With *o*-Phenylenediamine.—A mixture of 3.04 g (0.02 mol) of *o*-methoxybenzoic acid, 2.16 g (0.02 mol) of *o*-phenylenediamine, and 60 g of PPA was heated at 130° for 15 hr and for an additional 48 hr at 185–190°. The reaction mixture was cooled, poured into 300 ml of water, and neutralized with 50% aqueous sodium hydroxide solution. The precipitate was removed by filtration, washed with water, and dried under vacuum. Vacuum sublimation of the crude product gave 2-(2-hydroxyphenyl)benzimidazole, 0.6 g (14%), mp 239–240° (lit.[1a] mp 241.6–242.2°). The infrared spectrum of this product was identical with that of 2-(2-hydroxyphenyl)benzimidazole prepared by the literature method.[1a]

B. With *o*-Aminophenol.—A mixture of 2.18 g (0.02 mol) of *o*-methoxybenzoic acid, 2.72 g (0.02 mol) of *o*-aminophenol, and 120 g of PPA was heated at 200° for 24 hr. Work-up as above gave 2-(2-hydroxyphenyl)benzoxazole, 0.3 g (7%), mp 121–123° (lit.[5] mp 123°). The infrared spectrum of this product was identical with that of 2-(2-hydroxy)benzoxazole prepared by the literature method.[5]

C. With *o*-Aminothiophenol.—A mixture of 1.52 g (0.01 mol) of *o*-methoxybenzoic acid, 1.25 g (0.01 mol) of *o*-aminothiophenol, and 75 g of PPA was heated at 200° for 16 hr. Work-up as above in A gave 2-(2-hydroxyphenyl)benzothiazole, 0.5 g (22%), mp 130–132° (lit.[6] mp 131–132°). The infrared spectrum of this product was identical with that of 2-(2-hydroxyphenyl)benzothiazole prepared by the literature method.[6]

The same reaction mixture, when heated at 160° for 16 hr, gave 1 g of a white solid which was established by vpc analysis (4-ft silicone rubber column, 210°) as a 4 to 1 mixture of 2-(2-methoxyphenyl)- and 2-(2-hydroxyphenyl)benzothiazoles, respectively.

Reaction of 3-Methoxysalicylic Acid with *o*-Aminophenol in PPA.—A mixture of 3.4 g (0.02 mol) of 3-methoxysalicylic acid, 2.2 g (0.023 mol) of *o*-aminophenol, and 120 g of PPA was heated at 150° for 2 hr and then at 195° for 14 hr. Work-up as above in A followed by recrystallization from 95% ethanol gave pale pink needles of 2-(2,3-dihydroxyphenyl)benzoxazole, 1.5 g (33%), mp 163–163.5°: ν^{KBr} 3380, 1630, 1245, cm^{-1}; $\lambda_{max}^{95\%\ C_2H_5OH}$ mμ (ε), 330 sh (7880), 304 (25,500), 293 (25,800), and 269 sh (12,500).

Anal. Calcd for $C_{13}H_9NO_3$ (mw 227.21): C, 68.71; H, 3.99; N, 6.17. Found: C, 68.40; H, 4.0; N, 6.24.

Reaction of 5-Methoxysalicylic with *o*-Aminophenol in PPA.—A mixture of 0.6 g (3.6 mmol) of 5-methoxysalicylic acid, 0.39 g (3.6 mmol) of *o*-aminophenol, and 60 g of PPA was heated at 185° for 20 hr. Work-up as above in A was followed by recrystallization from 95% ethanol gave pale yellow needles of 2-(2-hydroxyphenyl)benzoxazole, 0.28 g (33%): mp 206–207°; ν^{KBr} 3400, 3350, 1640, 1245 cm^{-1}; $\lambda_{max}^{95\%\ C_2H_5OH}$ mμ (ε), 350 (11,300), 301 (18,200), 288 (19,200), 280 (19,200), 282 (14,600), and 265 sh (11,400).

Anal. Calcd for $C_{13}H_9NO_3$ (mw 227.21): C, 68.71; H, 3.99; N, 6.17. Found: C, 68.50; H, 4.10; N, 6.10.

(3) (a) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958); (b) F. Uhlig and H. R. Snyder *Advan. Org. Chem.*, **1**, 35 (1960).

(4) "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 972.

(5) S. Skraup and M. Moser, *Chem. Ber.*, **55B**, 1080 (1922).

(6) M. T. Bogert and H. B. Corbitt, *J. Amer. Chem. Soc.*, **48**, 783 (1926).

Reaction of 2-(2-Hydroxy-5-methoxyphenyl)benzothiazole in PPA.—A mixture of 0.4 g (1.55 mmol) of 2-(2-hydroxy-5-methoxyphenyl)benzothiazole and 60 g of PPA was heated at 170° for 15 hr. Work-up as above in A gave 2-(2,5-dihydroxyphenyl)benzothiazole, 0.12 g (30%), mp 193–196°. An infrared spectrum of the product was identical with that of 2-(2,5-dihydroxyphenyl)benzothiazole prepared from 5-hydroxysalicylic acid and *o*-aminothiophenol in PPA.

Registry No.—**4** (X = O), 835-64-3; **9**, 24978-46-9; 2-(2,5-dihydroxyphenyl)benzothiazole, 24978-47-0.

A Convenient Method of Esterification of Polyphosphonic Acids

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Unlike carboxylic acids, phosphonic acids cannot be esterified by direct reaction with alcohols. Esterification is usually accomplished by converting the phosphonic acid to the corresponding acid chloride which will react with an alcohol in the presence of base to yield the phosphonate ester.[2]

In the course of a recent study it became of interest to synthesize a series of esters from methylenediphosphonic acid (MDP). Siddall and Prohaska[3] have prepared tetra(3-methyl-2-butyl) methylenediphosphonate in 50% yield from methylenediphosphonic tetrachloride and the alcohol in the presence of pyridine. Methylenediphosphonic tetrachloride is also obtained in 50% yield[4] so that the overall conversion from MDP to its tetraalkyl ester proceeds in low yield and involves two rather difficult steps.[3,4]

This note describes a one-step method of esterification of MDP which results in 70–90% yields of the tetraalkyl esters. The method is not limited to MDP but has been shown to be applicable to esterifications of *vic*-tri- and tetraphosphonic acids as well as 1-hydroxy-1,1-diphosphonic acids.

Three literature reports led us to attempt the esterification of polyphosphonic acids with esters of orthoformic acid. Trialkyl orthoformates are known[5] to effect the esterification of carboxylic acids in up to 95% yield. Fitch[6] has prepared alkyl hypophosphites from hypophosphorous acid and trialkyl orthoformates. Finally a 1960 patent[7] describes the esterification of benzenephosphonic acid with triethyl orthoformate.

MDP was found to react at elevated temperatures with trialkyl orthoformates to yield tetraalkyl methylenediphosphonates, along with the corresponding alcohol and alkyl formate (eq 1). It was necessary to

$$H_2O_3PCH_2PO_3H_2 + 4(RO)_3CH \xrightarrow{\Delta} R_2O_3PCH_2PO_3R_2 + 4ROH + 4HC(O)OR \quad (1)$$

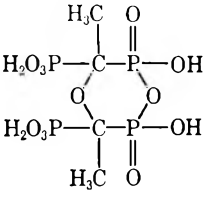
continuously remove the lower boiling alcohols and formates (reduced pressure is required when R = $C_{18}H_{37}$) so that higher reaction temperatures could be obtained. Tetramethyl, tetraethyl, tetraallyl, and tetrakis(octadecyl) methylenediphosphonates were successfully prepared *via* this procedure. Their ^{31}P nmr chemical shifts are given in Table I.

To broaden the scope of this esterification method, the recently reported[8] vicinal tri- and tetraphosphonic acids were allowed to react with triethyl orthoformate. Esterification proceeded as described above and hexaethyl propane-1,2,3-triphosphonate and octaethyl butane-1,2,3,4-tetraphosphonate were isolated by distillation. In this case the polyphosphonic acid halides are unknown so that an alternative method of esterification is not available. Phosphorus nmr chemical shifts are given in Table I.

Another class of polyphosphonic acids for which the acid halides are unknown is the alkyl-1-hydroxy-1,1-diphosphonic acids. An attempt was made[9] to esterify ethane-1-hydroxy-1,1-diphosphonic acid with diazomethane. The tetramethyl ester was perhaps prepared initially but completely rearranged to the phosphate-phosphonate.[10a] Under the conditions used,[9] the tetramethyl ester of ethane-1-methoxy-1,1-diphosphonic acid always accompanied the phosphate–phosphonate in the final product.

Reaction of ethane-1-hydroxy-1,1-diphosphonic acid with trimethyl orthoformate was found to produce the corresponding tetramethyl ester which was isolated in about 70% yield by crystallization. This ester proved to be identical with authentic tetramethyl ethane-1-hydroxy-1,1-diphosphonate prepared by a combination of the methods of Fitch and Moedritzer[10a] and Pudovik, *et al.*[10b]

It is known[11] that ethane-1-hydroxy-1,1-diphosphonic acid can dimerize to a very stable cyclic condensate containing C–O–C and P–O–P linkages (compound I). This condensate was easily converted to the hexamethyl ester by reaction with trimethyl orthoformate. As reported elsewhere,[11] the ester was utilized in establishing the structure of I.



I

An attempt to esterify ethane-1-hydroxy-1,1,2-triphosphonic acid with trimethyl orthoformate resulted in partial esterification with concomitant rearrangement to the phosphate–diphosphonate as shown by ^{31}P nmr. To further characterize the course of the re-

(1) (a) To whom correspondence should be addressed. (b) Retired, Nov 1, 1966.

(2) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, pp 139–140.

(3) T. H. Siddall, III, and C. A. Prohaska, *Inorg. Chem.*, **4**, 783 (1965).

(4) J. J. Richard, K. E. Burke, J. W. O'Laughlin, and C. V. Banks, *J. Amer. Chem. Soc.*, **83**, 1722 (1961).

(5) H. Cohen and J. D. Mier, *Chem. Ind. (London)*, 349 (1965).

(6) S. J. Fitch, *J. Amer. Chem. Soc.*, **86**, 61 (1964).

(7) J. Preston and H. G. Clark, U. S. Patent 2,928,859 (1960).

(8) W. A. Cilley, D. A. Nicholson, and D. Campbell, *J. Amer. Chem. Soc.*, **92**, 1685 (1970).

(9) D. F. Kuemmel, private communication.

(10) (a) S. J. Fitch and K. Moedritzer, *J. Amer. Chem. Soc.*, **84**, 1876 (1962); (b) A. N. Pudovik, I. V. Konovalova, and L. V. Dedova, *Dokl. Akad. Nauk SSSR*, **153**, 616 (1963); *Chem. Abstr.*, **60**, 8060a (1964).

(11) J. B. Prentice and O. T. Quimby, manuscript submitted for publication on the preparation of condensates of ethane-1-hydroxy-1,1-diphosphonic acid.

TABLE I

Compd	Registry no.	Bp/mm, (mp)	δ (^{31}P nmr)[a]	Calcd, % C	Calcd, % H	Calcd, % P	Calcd, % mol wt	Found, % C	Found, % H	Found, % P	Found, % mol wt[b]	% yield
$[(CH_3)_2O_3P]_2CH_2$	16001-93-7	87–90°/0.05	−23.0	25.9	6.1	26.7	232	25.9	6.2	26.7	235	70–90[c]
$[(C_2H_5)_2O_3P]_2CH_2$	1660-94-2	90–94°/0.1	−19.0	37.5	7.7	21.5	288	37.4	7.8	21.8	280	70–90[c]
$[(CH_2{=}CHCH_2)_2O_3P]_2CH_2$	25091-05-8	...[d]	−20.0	46.4	6.6	18.4	336	46.5	6.6	17.6	355	99[e]
$[(C_{18}H_{37})_2O_3P]_2CH_2$	25091-06-9	(60–62°)[f]	−19.5	73.9	12.8	5.2	1156	73.1	12.7	5.0	1110	86[e]
$(C_2H_5)_2O_3P{-}CH_2$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH_2$	25091-07-0	170°/0.1	−28.5[g]	39.8	7.8	20.5	452	39.2	8.1	20.6	425	72
$(C_2H_5)_2O_3P{-}CH_2$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH_2$	25091-08-1	...[h]	−30.3[g]	39.9	7.7	20.6	603	39.8	7.6	20.6	580	79
$[(CH_3)_2O_3P]_2C(OH)CH_3$	15207-88-2	(67–70°)[i]	−22.0	27.4	6.1	23.7	262	27.3	6.1	24.9	265	70
$(CH_3)_2O_3P{-}C(H_3C)(O){-}P(=O){-}OCH_3$ O $(CH_3)_2O_3P{-}C(H_3C)(O){-}P(=O){-}OCH_3$	16218-84-1	(141–144°)[j]	−15.8[k] −6.5[k]	26.1	5.3	26.9	460	26.4	5.5	26.0	458	62

[a] Chemical shifts are reported in ppm shift from 85% H_3PO_4. [b] Average of three determinations. [c] Range of yields from several experiments. [d] CAUTION!! Attempted vacuum distillation of this material resulted in violent decomposition. Purification was accomplished by chromatography on acid-washed alumina. [e] Based on crude yield of alcohol and formate. [f] Recrystallized from hexane–petroleum ether. [g] ^{31}P nmr resonances for "end" and "middle" phosphonate groups have been shown to be degenerate. See ref 8. [h] It was necessary to molecularly distill the crude ester. [i] Recrystallized from acetone–hexane. [j] Recrystallized from ethyl acetate–ethyl ether. [k] The resonance at −15.8 ppm has been shown to arise from the dangling phosphonate groups, and that at −6.5 ppm from phosphorus atoms in the ring. See ref 11.

arrangement, this esterification was driven to completion and the resulting product hydrolyzed to the acid. After neutralization with base, the tetrasodium salt of ethane-1-hydroxy-1,2-diphosphonic acid was isolated by crystallization. Structure elucidation was accomplished *via* ^{31}P and ^{1}H nmr decoupling experiments. The probable reaction pathway is shown in Scheme I.

SCHEME I

$$H_2O_3PCH_2C(OH)(PO_3H_2)_2 \xrightarrow{(CH_3O)_3CH} (CH_3)_2O_3PCH_2C(OH)[PO_3(CH_3)_2]_2 \xrightarrow{\Delta} (CH_3)_2O_3PCH_2CH[OPO_3(CH_3)_2][PO_3(CH_3)_2] \xrightarrow[H_2O]{H^+} H_2O_3PCH_2CH(OH)(PO_3H_2) + H_3PO_4$$

Experimental Section[12]

Methylenediphosphonic acid (MDP) was prepared by pyrolyzing (180°) a sample of tetraisopropyl methylenediphosphonate.[13,14] Propane-1,2,3-triphosphonic acid and butane-1,2,3,4-tetraphosphonic acid were prepared by literature methods[8] as were ethane-1-hydroxy-1,1-diphosphonic acid,[15] its condensate (I),[11] and ethane-1-hydroxy-1,1,2-triphosphonic acid.[16] Trimethyl and triethyl orthoformate were purchased from the Aldrich Chemical Company. Triallyl and tris(octadecyl) orthoformate were purchased from Kay–Fries Chemicals.

All esterifications were performed by combining the polyphosphonic acid with an excess of trialkyl orthoformate, heating, and removing alcohol and alkyl formate by distillation as they were formed. The preparation of tetramethyl methylenediphosphonate is considered typical and is given in detail. Yields, physical measurements, and analytical data for the other esters prepared in this study are collected in Table I.

Tetramethyl Methylenediphosphonate.—MDP (1 equiv) and trimethyl orthoformate (6 equiv) were combined and heated to reflux for 1 hr. The acid was not significantly soluble in trimethyl orthoformate necessitating rapid stirring to assure intimate contact of the two phases. Excess trimethyl orthoformate (100%) was added and the methyl formate and methanol, formed *in situ*, were continuously removed by distillation thereby allowing the reaction temperature to rise. Heating was continued until only one phase remained and trimethyl orthoformate began to distill (bp 99–101°). Removal of excess trimethyl orthoformate left a colorless liquid. This liquid was vacuum distilled to yield pure tetramethyl methylenediphosphonate.

Attempted Preparation of Hexamethyl Ethane-1-hydroxy-1,1,2-triphosphonate.—The reaction temperature was not allowed to exceed 90° in this preparation. Even after extended heating at this temperature esterification was incomplete as evidenced by ^{31}P and ^{1}H nmr. Nevertheless, approximately 18% of the triphosphonate had rearranged to the phosphate–diphosphonate.

Tetrasodium Ethane-1-hydroxy-1,2-diphosphonate.—The above reaction was repeated without temperature control. The maximum reaction temperature (105°) was maintained for 10 hr. After removing volatile products, concentrated HCl was added and the mixture was refluxed 6 hr. Excess HCl was removed and 4 equiv of NaOH (based on starting acid) was added. The title compound was precipitated by addition of methanol and was recrystallized from methanol–water, yield 61%.

Anal. Calcd for $C_2H_4O_7P_2Na_4$ (dihydrate): C, 7.3; P, 18.8; Na, 27.9; H_2O, 10.9. Found: C, 7.6; P, 19.2; Na, 29.0; H_2O, 10.7.

Registry No.—MDP, 1984-15-2.

Acknowledgments.—The authors would like to express their appreciation to Dr. T. J. Flautt for aid in obtaining and interpreting the nmr spectra, and to Messrs. D. Campbell, H. L. Vaughn, and P. Vanden Eynden for technical assistance.

(12) All melting and boiling points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. Phosphorus nmr spectra were recorded on a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm and are measured from an external 85% H_3PO_4 reference. Molecular weights were determined on a Model 302 Mechrolab osmometer.

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Cleavage of Single Amino Acid Residues from Merrifield Resin with Hydrogen Chloride and Hydrogen Fluoride

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Anhydrous HF-containing anisole is being used for the removal of the resin and side-chain blocking groups in the final step of Merrifield solid-phase peptide synthesis,[1c,2,3] and HCl hydrolysis is being used for the preparation of samples for amino acid analysis during the course of Merrifield solid-phase peptide synthesis.[1c,3-5] We have performed some experiments in order to determine the optimal conditions for these two reactions. The determined conditions have been used routinely in our laboratory for the past 2 years during several hundred cycles of Merrifield solid-phase peptide synthesis with good results.

HF Reaction.—For it we use 5000 μmol of anisole in 5 ml of anhydrous HF at 0° for 0.50 hr. Trifluoroacetic acid or toluene decreases the overall recovery of the single amino acids, and the use of only 500 μmol of anisole in 5 ml of anhydrous HF decreases the recovery of the amino acids even if the total amino acids to be recovered in the reaction mixture is less than 20 μmol. The resin itself serves as a scavenger for blocking groups but is not usually present in high enough concentration to prevent attack on the amino acid side chains themselves. Recoveries without any anisole are about two-thirds complete for most amino acids but are very low for Tyr, Trp, Phe, and Met.

AsN and GIN are deamidated in some peptides during this procedure.[6]

HCl Reaction.—For it we use an "anaerobic" mixture of 0.5 ml of 6 *N* HCl in H_2O and 0.5 ml of propionic acid at 130° for 2 hr (see Table I). We use 10–50 mg of resin–peptide. This mixture gives more clean, consistent, and complete recoveries of the 20 amino acids than do similar mixtures in which propionic acid has been substituted by H_2O, dioxane, dimethyl sulfoxide, dimethylformamide, formic acid, or acetic acid. Valeric acid and propionic acid give the same results, but propionic acid is more pleasant. This procedure has been used extensively in our laboratory with resin–peptides with good results.

In addition, our rate experiments have shown that the effect of improper solvation of the Merrifield resin is to close off completely the less accessible sites on the resin, rather than generally to decrease rates of reaction at all the sites by similar amounts. This is illustrated by Figure 1, which shows the rates of cleavage of ε-CBZ-*t*-BOC-lysine from Merrifield resin in the mixture reacted with HCl–H_2O–acetic acid and HCl–H_2O–propionic acid. This closing off is responsible for the fact that Merrifield synthesis itself yields such excellent products even when quantitative analysis during the synthesis is sometimes discouraging. During the synthesis, of course, the particular structure of the peptide being synthesized also has an important effect on solvation of the resin–peptide surface.

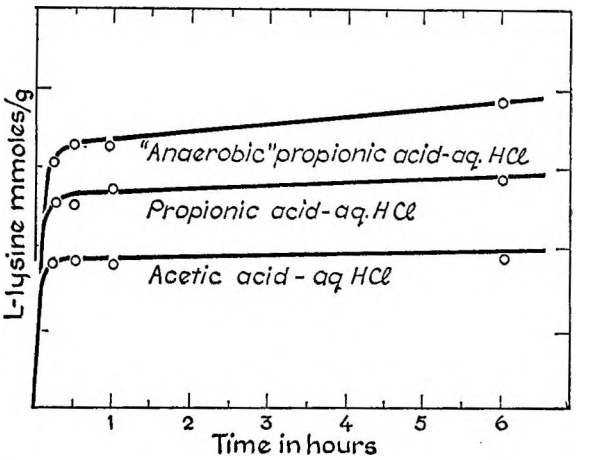

Figure 1.—Recovery of L-lysine from the hydrolysis mixture *vs.* time. Variations in solvent change the total accessible resin sites.

TABLE I
RECOVERY OF AMINO ACIDS BY HCl AND HF

Compd	"Anaerobic" HCl—H_2O–propionic acid, mmol/g: 2 hr at 130°[a]	"Anaerobic" HCl—H_2O–propionic acid, mmol/g: Maximum recovery at 130° (hr)	5 ml of HF-5000, μmol of anisole, 30 min at 0°
BOC-L-Ala-resin	0.48	0.48 (2)	0.48
BOC-nitro-L-Arg-resin	0.25[b]	0.26 (12)	0.16
BOC-β-BZL-L-Asp-resin + BOC-L-AsN-resin	0.41	0.41 (2)	0.43
BOC-S-*p*-methoxybenzyl-L-Cys-resin	0.11	0.13 (1)	0.07
BOC-γ-L-Glu-resin + BOC-L-GIN-resin	0.47	0.47 (2)	0.43
BOC-Gly-resin	0.45	0.45 (2)	0.38
BOC-L-Lleu-resin	0.48	0.48 (2)	0.53
BOC-L-Leu-resin	0.47	0.47 (2)	0.44
BOC-ε-CBZ-L-Lys-resin	0.32	0.39 (12)	0.43
BOC-L-Met-resin	0.29	0.29 (2)	0.28
BOC-L-Phe-resin	0.47	0.47 (2)	0.44
BOC-L-Pro-resin	0.48	0.50 (1)	(0.7 ± 0.3)[c]
BOC-O-BZL-L-Ser-resin	0.35	0.39 (1)	0.50
BOC-O-BZL-L-Thr-resin	0.44	0.44 (2)	0.46
BOC-L-Trp-resin	0.06[d]		0.10
BOC-O-BZL-L-Tyr-resin	0.34	0.35 (1)	0.34
BOC-L-Val-resin	0.46	0.47 (12)	0.49

[a] Each value in the table is an average for ten rate experiments like that illustrated in Figure 1. Error of each analysis was ±7%, hence the table values are ±3%. [b] Recovery is of Arg. Very little ornithine and nitroarginine are observed with the propionic acid hydrolysis procedure. [c] The modified amino acid analyses (K. Dus and R. Smith) used for these experiments gave very poor analysis of Pro. [d] Trp is destroyed by hydrolysis. Probably a few drops of some reducing agent would prevent this.

Experimental Section

Copolystyrene–2% divinylbenzene was obtained from Bio-Rad Laboratories and was washed and chloromethylated in the usual way.[1c] Volhard titration after boiling in pyridine for 1 hr

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(2) J. Lenard and A. B. Robinson, *ibid.*, **89**, 181 (1967).
(3) B. Gutte and R. B. Merrifield, *ibid.*, **91**, 501 (1969).
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(5) A. Marglin and R. B. Merrifield, *J. Amer. Chem. Soc.*, **88**, 5051 (1966).
(6) A. B. Robinson, J. McKerrow, and P. Cary, *PNAS*, July 1970.

showed 1.15 mmol of chloride per gram of resin. BOC[7] derivatives of L-Ala, nitro-L-Arg, β-BZL-L-Asp, S-*p*-methoxy-BZL-L-Cys, γ-BZL-L-Glu, L-Gly, L-Ileu, L-Leu, ε-CBZ-L-Lys, L-Met, L-Phe, L-Pro, O-BZL-L-Ser, O-BZL-L-Thr, L-Trp, O-BZL-L-Tyr, and L-Val were esterified to the resin by refluxing 20 g of chloromethylated resin, 20 mmol of derivative, 18 mmol of triethylamine, and 50 ml of ethanol for 46 hr. An equal weight mixture of all of the resin-derivative preparations was treated with acetic acid–anhydrous HCl (1 *M*) for 30 min and washed extensively and dried from ethanol. This mixture was used for all experiments, so that a representative collection of blocking groups was always present. The hydrolyses were performed in sealed glass tubes which were frozen by liquid nitrogen and thawed several times on a vacuum line before sealing. These "anaerobic" conditions seem to give higher recoveries of all of the amino acids. HF reactions were carried out in the apparatus described by Robinson and Kamen[8] which is similar to that described by Sakakibara, *et al.*[9]

Registry No.—Hydrogen chloride, 7647-01-0; hydrogen fluoride, 7664-39-3.

Acknowledgment.—We are grateful to Paul Cary for the preparation of many of the amino acid derivatives and to Paul Cary and Professor R. B. Merrifield for their suggestions. Financial support for this research by U. S. Public Health Service, Grant No. T1-GM-1045 to Professor M. D. Kamen, in whose laboratory the experiments were performed, is gratefully acknowledged.

(7) Abbreviations: BOC = *t*-butyloxycarbonyl, CBZ = carbobenzyloxy, BZL = benzyl (ethers and esters).

(8) A. B. Robinson and M. D. Kamen, Symposium on Cytochromes, Osaka, Japan, 1967.

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Synthesis of *trans*-3,*cis*-5-Tetradecadienoic Acid (Megatomoic Acid), the Sex Attractant of the Black Carpet Beetle, and Its Geometric Isomers[1]

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The sex attractant of the black carpet beetle, *Attagenus megatoma* (Fabricius), was identified[2] as *trans*-3,*cis*-5-tetradecadienoic acid (I), to which we assign the trivial name, megatomoic acid. The synthesis of megatomic acid and its geometric isomers, *cis*-3,*cis*-5- (II), *cis*-3,*trans*-5- (III), and *trans*-3,*trans*-5-tetradecadienoic acid (IV) is described herein.

$C_8H_{17}CH{=}CH{-}CH{=}CHCH_2COOH$

trans-3,*cis*-5 (I)
cis-3,*cis*-5 (II)
cis-3,*trans*-5 (III)
trans-3,*trans*-5 (IV)

Megatomic acid was synthesized by the sequence shown in Scheme I based on the procedure described by Celmer and Solomons.[3] The *cis*-3,*cis*-5 isomer (II) also resulted.

(1) (a) Supported by the U. S. Department of Agriculture under Contract No. 12-14-100-7786(51). (b) Department of Chemistry, State University College of Forestry at Syracuse University, Syracuse, N. Y. 13210.

(2) R. M. Silverstein, J. O. Rodin, W. E. Burkholder, and J. E. Gorman, *Science*, **157**, 85 (1967).

The sequence in Scheme II produced *cis*-3,*cis*-5-tetradecadienoic acid (II) and *cis*-3,*trans*-5-tetradecadienoic acid (III).

trans-3,*trans*-5-Tetradecadienoic acid (IV) was prepared by isomerization with iodine[3] of the *trans*-3,*cis*-5- or *cis*-3,*trans*-5-methyl esters, followed by hydrolysis.

Since none of the isomers (II–IV) nor the by-products resulting from the synthesis of megatomic acid masked its attractiveness, the crude mixture was submitted for large-scale field testing. Analytical samples of all the isomeric acids were prepared by mild alkaline hydrolysis of the corresponding methyl esters, which were isolated by gas chromatography and shown to be homogeneous on several substrates of different polarities. The acids were re-esterified with diazomethane to verify that only a negligible amount of isomerization occurred during the hydrolysis.

Experimental Section

The spectra were recorded on the following instruments unless otherwise noted: ir, Perkin-Elmer 137; uv, Perkin-Elmer 202; mass, CEC 103; nmr, Varian T 60 (60 Mc). The nmr spectra were obtained in CCl_4 and the chemical shifts are in τ values using TMS as an internal standard. The abbreviations "s, d, q, and m" denote "singlet, doublet, quartet, and multiplet," respectively. Gas chromatography (glc) was done on a Varian Aerograph 205 equipped with a hydrogen flame detector; a 1:20 splitter and N_2 make-up gas were used for preparative runs. Glc substrates were obtained from Applied Science Laboratory, Inc., State College, Pa.

1-*n*-Tridecen-4-yn-3-ol (V).—This compound was prepared in 56% yield from 1-decyne and acrolein according to the procedure of Celmer and Solomons.[3] The crude product was distilled at 114–117° (0.9 mm). Ir (λ^{film}, μ) 3.0 (OH), 3.25 (olefinic CH) 4.45 (C≡C), 6.03 (C=C), 9.8 (C—OH), 10.1 and 10.8 (vinyl).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.4. Found: C, 80.0; H, 11.5.

1-Bromo-*cis*- and -*trans*-2-tridecen-4-yne (VI).—A mixture of 3-bromo-1-tridecen-4-yne and 1-bromo-2-tridecen-4-yne resulted from the reaction of V with phosphorus tribromide according to the procedure of Celmer and Solomons.[3] Ir (λ^{film}, μ) 4.5 (C≡C), 10.15 and 10.8 (vinyl), 10.5 (*trans* -CH=CH-).

The 3-bromo compound was converted to VI when the mixture was heated under nitrogen at 117° for 75 min. Distillation though a Claisen head at 0.15 mm (bath temp 95–110°) afforded a 75% yield of VI.

Anal. Calcd for $C_{13}H_{21}Br$: C, 60.7; H, 8.2. Found: C, 61.0; H, 8.5.

The *cis* and *trans* isomers of VI were obtained in a ratio of 1:2 by glc fractionation (SE 30, 4% on Chromosorb G, 60–80 mesh, 0.9 m × 7 mm i.d. Pyrex, 160°, 50 cm³ He/min) with fractions collected: at 20 min ir (λ^{film}, μ) 4.50 (C≡C), 8.3, 13.1 (*cis*-CH=CH-); and 25 min ir (λ^{film}, μ) 4.50 (C≡C), 8.3 and 10.5 (*trans* -CH=CH-).

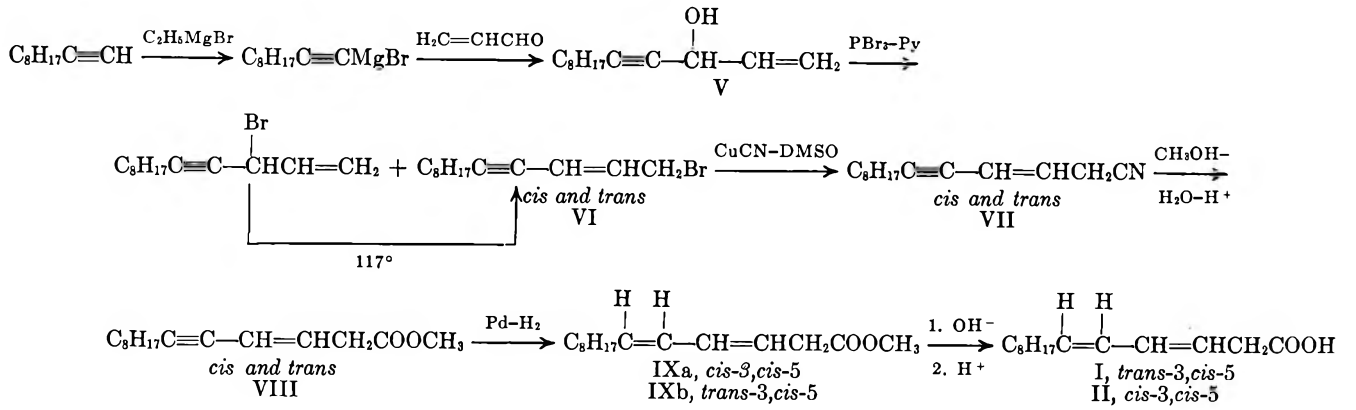
1-Cyano-2-*cis*- and -*trans*-tridecen-4-yne (VII).—A solution of 140 g (0.54 mol) of VI in 70 ml of dimethyl sulfoxide (dried over Linde 4X molecular sieves) was added dropwise over 20 min to a stirred suspension of 55.7 g (0.62 mol) of cuprous cyanide in 300 ml of dimethyl sulfoxide. The reaction mixture was stirred without external heating for 1 hr, at 40° for 1 hr, and finally at 85° for 2 hr. After cooling, the mixture was diluted with water and extracted with hexane. The extract was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was distilled through a Claisen head at 0.1 mm (bath temp 110–130°) to give 72 g (66% yield) of VII.

Anal. Calcd for $C_{14}H_{21}N$: N, 6.9. Found: N, 6.9.

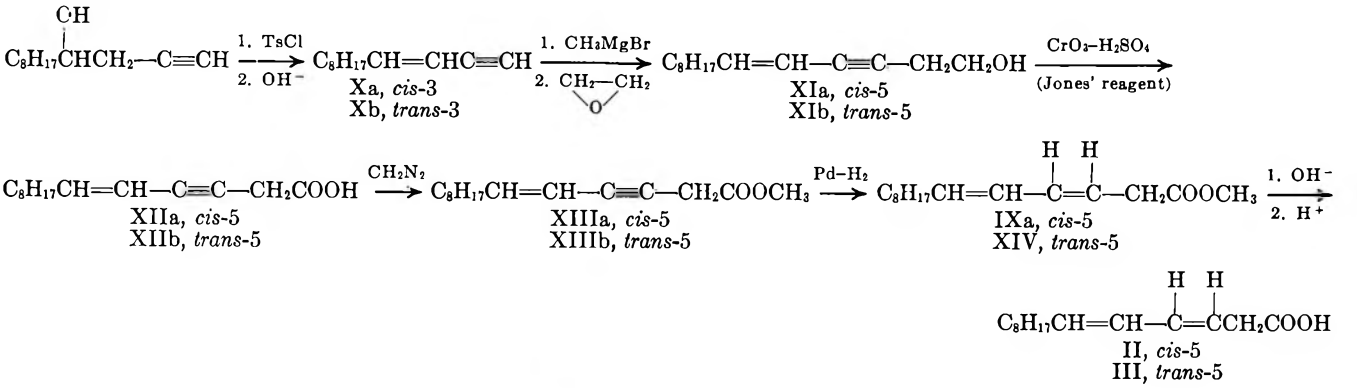
The *cis* and *trans* isomers of VII were obtained in a ratio of 1:2 by glc fractionation (Carbowax 20M, 10% on Gas Chrom Q, 60–80 mesh, 0.6 m × 8 mm i.d. Pyrex, 170°, 100 cm³ He/min) with fractions collected at 45 min and 100 min. The 45 min peak showed: ir (λ^{film}, μ) 4.44 and 4.51 (C≡C) and 13.7 (broad. *cis* -CH=CH-); nmr 4.3 (m, CH=CH) and 6.7 (d, $-CH_2CN$).

(3) W. D. Celmer and I. A. Solomons, *J. Amer. Chem. Soc.*, **75**, 3430 (1953).

SCHEME I



SCHEME II



The 100 min peak showed ir (λ^{film}, μ) 4.44 and 4.51 (C≡C) and 10.5 (*trans* -CH=CH-); nmr 4.2 (m, -CH=CH-) and 6.9 (d, $-CH_2CN$).

Methyl *cis*- and *trans*-3-Tetradecen-5-ynoate (VIII).—A slow stream of hydrogen chloride was bubbled into a solution of 32 g (0.157 mol) of VII in 84 ml of methanol and 6 ml of water. The resulting heat of solution caused the solvent to reflux. After the temperature had subsided (10 min), the reaction solution was treated with 15 ml of water, warmed on a steam bath for 15 min, and poured into an excess of cold water. The solution was extracted with pentane. The extract was washed successively with water, sodium bicarbonate solution, and water, dried over sodium sulfate, and concentrated under reduced pressure. The product was distilled through a Claisen head at 0.1 mm (bath temp 90–130°) to give 32 g (86% yield) of VIII.

The *cis* and *trans* isomers of VIII were obtained in one fraction by glc fractionation (Carbowax 20M, 10% on Gas Chrom Q, 60–80 mesh, 0.6 m × 8 mm i.d. Pyrex, 170°, 100 cm^3 He/min, R_t 50–80 min). This fraction comprised 80% of the total. Ir (λ^{film}, μ) 4.51 (C≡C), 5.74 (C=O), 8.0, 8.3, 8.6 (C—O, methyl ester), 10.45 (*trans* -CH=CH-).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2 Found: C, 76.6; H, 10.7.

Methyl *cis*- and *trans*-3,*cis*-5-Tetradecadienoate (IXa and IXb).—A mixture of 20.0 g (0.085 mol) of VIII (distillate), 2.7 g of Lindlar catalyst (Engelhardt Industries, Inc.), and 210 ml of hexane containing 1.5 ml of pyridine was stirred at 25° under a hydrogen atmosphere. After 2180 ml (0.091 mol) of hydrogen was absorbed (2 hr), the hydrogenation was stopped, the mixture filtered, and the filtrate concentrated to give 20.2 g of product.

Compounds IXa and IXb were obtained pure by glc fractionation (HIEFF-IBP, 10% on Gas Chrom Q, 60/80 mesh, 6 m × 4 mm i.d. Pyrex, 174°, 46 cm^3 He/min). IXb was collected at 52–57 min and IXa at 62 to 66 min. These two peaks comprised 65% of the total fraction.

The following data were obtained on IXb: ir (λ^{film}, μ) 3.32 (C=CH), 5.74 (C=O), 6.03, 6.18 (weak, C=C conjugated), 8.00, 8.35, 8.60 (C—O, methyl ester), 9.85, 10.18, 10.54 (characteristic pattern for *cis,trans* conjugated double bonds; the 9.85 band is very weak),[4] 13.90 (weak CH_2 rock); uv ($\lambda_{max}^{pentane}$, mμ) 231.5 (ϵ 29,000); nmr (100 MHz, CCl_4, τ) 3.55–4.90 (4 H, m, conjugated olefinic), 6.41 (3 H, s, $COOCH_3$), 6.98 (2 H, d, J = 7 Hz $=CHCH_2COOCH_3$), 7.88 (2 H, distorted q, CH_2-CH_2CH=), 8.72 [12 H, $(CH_2)_6$], 9.11 (3 H, distorted t, CH_2-CH_2); mass, *m/e* 238 (M^+), 207 (M^+ minus OCH_3), 206 (M^+ minus CH_3OH), 179 (M^+ minus $COOCH_3$), 74 (CH_2COOCH_3 + H). The above spectra of IXb were congruent with those of the methyl ester of megatomoic acid isolated from *Attagenus megatoma*.[2]

The following data were obtained on IXa: the infrared spectrum was essentially the same as IXb except for the absence of the 10.18 and 10.54 μ bands. This is consistent with absorption of *cis,cis* conjugated double bonds:[4] uv ($\lambda_{max}^{pentane}$, mμ) 234 (ϵ 29,000).

***cis*- and *-trans*-3,*cis*-5-Tetradecadienoic Acid (II and I).**—A solution of 20.8 g (0.087 mol) of the esters IXa and IXb (distillate) in 340 ml of 0.9 *M* potassium hydroxide in methanol containing 10% water was stirred at 25° for 2.5 hr. The solution was diluted with 300 ml of cold water and extracted thrice with 200-ml portions of pentane. The aqueous solution was cooled to 0°, acidified with 6 *N* hydrochloric acid to pH 1.5, and extracted twice with pentane. The pentane solution was washed with water, dried over sodium sulfate, and concentrated under reduced pressure to 12.4 g (64%) of a viscous oil. Ir (λ^{film}, μ) 3.0 to 4.2 (characteristic COOH absorption), 5.83 (C=O), 10.15, 10.5 (characteristic pattern for *cis,trans* conjugated double bonds), 10.7 (broad, carboxylic acid dimer).

A sample of the hydrolysate was methylated with diazomethane in ethyl ether solution. Glc analysis (Carbowax 20 M, 5% on Gas Chrom Q, 3 m × 3 mm aluminum tubing, 170°; 30 cm^3 He/min) showed major peaks at 11.3 and 12 min (50% and 22%) which coincided with IXb and IXa, respectively. A sample of the methylated material was fractionated by glc (same conditions as for IXa and IXb) collecting the two major peaks as a single fraction at 50–70 min. The ir spectrum was identical with a mixture of IXa and IXb. This glc fraction was hydrolyzed by the procedure used above and the hydrolysate was evaporatively distilled at 120° (0.05 mm). The distillate gave the following data: ir (λ^{film}, μ) 3.0 to 4.2, 5.83, 6.17 (weak), 6.85, 7.1, 7.8, 8.2, 10.2, 10.5, 10.7 (broad), 12.1, and 13.9; uv (λ_{max}^{hexane}, mμ) 233 (ϵ 25,000).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.0; H, 10.8. Found: C, 75.1; H, 10.9.

(4) A. Butenandt, E. Hecker, M. Hopp, and W. Koch, *Justus Liebigs Ann. Chem.*, **658**, 39 (1962).

cis-3- and *trans*-3-Dodecen-1-yne (X).—A solution of 32 g (0.095 mol) of *p*-toluenesulfonic esters of 1-dodecyn-4-ol and 1,2-dodecadien-4-ol (prepared from nonanal and propargyl bromide by the method of Butenandt, *et al.*[4]), 7 g of potassium hydroxide, 30 ml of water, and 150 ml of ethanol was refluxed under nitrogen for 75 min, cooled, and extracted twice with 200-ml portions of pentane. The pentane solution was washed with water, dried over sodium sulfate, and concentrated to give 14 g (90%) of yellow oil. This product was flash-distilled at 5 mm and fractionated by glc [Carbowax 20M, 20% on Chromosorb P, 10–60 mesh, 2.4 m × 12.7 mm (i.d.) stainless steel tubing, 115°, 350 cm³ helium per min] to give 6.2 g of *cis*-3-dodecen-1-yne (Xa) at 46 to 66 min (99.8% pure) which had ir (λ^{film}_{max}, μ) 3.1 (C≡CH), 3.32 (C=CH), 13.5 (*cis* -CH=CH-). The yield of *trans*-3-dodecen-1-yne (Xb) was (2.4 g) (98% pure) at 67–87 min and had ir (λ^{film}_{max}, μ) 3.1 (C≡CH), 3.32 (C=CH), 10.4 (*trans* -CH=CH-).

Anal. Calcd for $C_{12}H_{20}$, Xa: C, 87.7; H, 12.3. Found: C, 88.0; H, 12.4. Xb: C, 87.7; H, 12.3. Found: C, 87.6; H, 12.4.

cis-5-Tetradecen-3-yn-1-ol (XIa).—A mixture of 1.25 g (0.0076 mol) of *cis*-3-dodecen-1-yne (Xa), 2 ml of anhydrous ethyl ether, and 2.8 ml (0.0084 mol) of methylmagnesium bromide (3 *M* in ethyl ether) was refluxed under N_2 with stirring for 1.5 hr with ethyl ether added at intervals to compensate for evaporation. The reaction mixture was cooled with an ice bath and a solution of 0.9 ml (0.02 mol) of ethylene oxide in 4 ml of ethyl ether was added. After 5 min, 15 ml of benzene was added to the gel that had formed, the ethyl ether was boiled off, and the mixture was refluxed for 2 hr under nitrogen, during which time the gel disappeared and a dark red solution resulted. The solution was cooled and poured into ice water containing 2 g of ammonium chloride. The mixture was extracted twice with ethyl ether. The organic solution was washed with water, dried over magnesium sulfate, and concentrated. The residue was distilled evaporatively at 105° (0.05 mm), and 0.8 g of distillate was collected. A portion of this was fractionated (Carbowax 20 M, 5% on Chromosorb G, 60–80 mesh, 0.9 m × 9.4 mm aluminum tubing, 177°, 100 cm³ He/min) and the major peak (90%) was collected at 10 to 18 min. Ir (λ^{film}_{max}, μ) 3.05, 3.32, 9.55, 13.5.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.7; H, 11.6. Found: C, 80.4; H, 11.7.

trans-5-Tetradecen-3-yn-1-ol (XIb).—This was prepared from Xb with the same procedure used to prepare XIa. The distillate had ir (λ^{film}_{max}, μ) 3.05, 3.32, 9.55, and 10.4 (*trans* -CH=CH-).

Methyl *cis*-5-Tetradecen-3-ynoate (XIIIa).—Chromic acid solution[5] (1.1 ml) was added dropwise (2 min) to a stirred solution of 0.40 (2.0 mmol) of *cis*-5-tetradec-3-yn-1-ol (XIa) in 10 ml of acetone at 15°. Stirring was continued under nitrogen for 10 min, and 25 ml of pentane was added. The pentane solution was decanted, washed twice with water, and extracted twice with sodium carbonate solution. The sodium carbonate solution was acidified with 1 *N* hydrochloric acid and extracted with ethyl ether. The ether solution was washed twice with water, dried over magnesium sulfate, and concentrated to give 0.30 g of *cis*-5-tetradecen-3-yn-oic acid (XIIa). Ir (λ^{film}_{max}, μ) 2.9 to 4.1 (characteristic COOH pattern), 4.5 and 4.6 (weak doublet, C≡C), 5.8 (C=O), 6.15 (weak, C=C), 10.7 (COOH dimer), and 13.6 (*cis* -CH=CH-).

A solution of diazomethane (4 mmol) in 10 ml of ethyl ether was added to a cold solution of 0.3 g (1.5 mmol) of XIIa in 5 ml of ethyl ether. After 5 min at 0°, the solution was concentrated to give 0.3 g of product. A portion of this was fractionated (Carbowax 20 M, 10% on Gas Chrom Q, 60–80 mesh, 0.6 m × 8 mm i.d. Pyrex, 170°, 100 cm³ He/min), and the major peak (30 to 40 min) was collected. Ir (λ^{film}_{max}, μ) 3.33 (C=CH), 4.5 (very weak, C≡C), 5.83 (C=O), 9.85, 13.5 (broad, *cis* -CH=CH-).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2. Found: C, 76.3; H, 10.7.

Methyl *trans*-5-Tetradecen-3-ynoate (XIIIb).—This was prepared from XIb using the same procedure used to prepare XIIIa. Compound XIIIb had ir (λ^{film}_{max} μ) 2.9–4.1 (characteristic COOH pattern), 4.5 and 4.6 (weak doublet, C≡C), 5.81 (C=O), 6.15 (weak, C=C), 10.45 (*trans*-CH=CH-), 10.7 (shoulder, COOH dimer). XIIIb: ir (λ^{film}_{max}, μ) 3.33 (C=CH), 4.5 (very weak, C≡C), 5.83 (C=O), 9.85, 10.4 (*trans* -CH=CH-).

Methyl *cis*-3,*cis*- and -*trans*-5-Tetradecadienoate (IXa and XIV).—These dienoic esters were prepared from their corresponding enyne compounds (XIIIa and XIIIb) using the procedure for the preparation of IXa and IXb. Spectra for IXa synthesized by both sequences were congruent.

The data obtained on the *cis*-3,*trans*-5 isomer (XIV) were very similar to those obtained on the *trans*-3,*cis*-5 isomer (IXb). Subtle differences in the nmr and ir spectra were observed. The main distinguishing feature was the 9.8 μ ir band, which was very weak in IXb and moderate in XIV where it is as strong as the 10.5 μ band. The uv spectra were indistinguishable as were the retention times on 3 m × 3 mm columns with the following substrates: Carbowax 20 M, Versamid 900, STAP, EGSS-X, CHDMS, PDEAS, HI-EFF-IBP, ECNSS-S.

Methyl *trans*-3,*trans*-5-Tetradecadienoate (XV).—A solution of 10 mg of methyl *cis*-3,*trans*-5-tetradecadienoate in 0.3 ml of carbon tetrachloride containing ~1 μmol of iodine in a sealed Pyrex tube was irradiated with a 250-W lamp for 16 hr. The solvent and iodine were removed under reduced pressure, and the residue was tube-distilled at 100° and 0.02 mm pressure to give 7 mg of distillate. Ir (λ^{film}_{max}, μ) 3.32, 5.73, 8.0, 8.35, 8.60, 10.1 (*trans*, *trans* -CH=CHCH=CH-); uv (λ^{hexane}_{max}, mμ) 229 (ϵ 28,000).

Glc data on the 4 isomeric esters (Carbowax 20 M, 4% on Chromosorb G 60–80 mesh, 3 m × 3 mm aluminum tubing, 160°, 20 cm³ He min), IXb, XIV, IXa, XV, showed retention times of 28.5, 28.5, 30.2, and 34 min, respectively.

Synthesis of Megatomoic Acid Isomers (II, III, and IV).—In each case, 1-mg samples of the ester (a glc fraction, 98 to 99% pure) was hydrolysed as described for megatomoic acid. The products showed the following uv data (λ^{hexane}_{max}, mμ): II, 235; III, 233; IV, 229. A portion of each acid solution was reesterified and analyzed by glc (conditions described above).

Registry No.—I, 23400-52-4; II, 25091-12-7; III, 17022-64-9; IV, 25091-14-9; V, 25091-15-0; *cis*-VI, 25091-16-1; *trans*-VI, 25091-17-2; *cis*-VII, 25091-18-3; *trans*-VII, 25091-19-4; *cis*-VIII, 25091-20-7; *trans*-VIII, 25091-21-8; IXa, 25091-22-9; IXb, 25091-23-0; Xa, 25091-24-1; Xb, 25091-25-2; XIa, 25091-26-3; XIb, 25091-27-4; XIIIa, 25091-28-5; XIIIb, 25091-29-6; XV, 25091-30-9.

(5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., p 142.

Studies on Resin Acids. VI. Synthesis of (+)-4-Epidehydroabietic Acid[1]

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(+)-4-Epidehydroabietic acid (callitrisic acid, abieta-8,11,13-trien-19-oic acid) (1) has recently been isolated as a natural product by several workers[2] and its synthesis from agathic acid has been reported.[3] In addition, the total synthesis of racemic 1 has been reported by several groups.[3a,4]

An obvious synthetic approach to 4-epidehydroabietic is its preparation from podocarpic acid (2) *via* methyl 12-methoxy abieta-8,11,13-trien-19-oate (3).[5] This general approach was attempted by Chuah and

(1) Part V: J. W. Huffman, *J. Org. Chem.*, **35**, 478 (1970). This work was supported in part by Career Development Award GM-5433 from the National Institutes of Health.

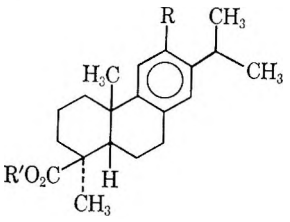
(2) (a) R. M. Carman and H. C. Deeth, *Aust. J. Chem.*, **20**, 2789 (1967); (b) L. J. Gough, *Tetrahedron Lett.*, 295 (1968); (c) Y. S. Chuah and A. D. Wood, *Aust. J. Chem.*, **22**, 1333 (1969).

(3) (a) R. M. Carman, H. C. Deeth, R. A. Marty, K. Mori, and M. Matsui, *Tetrahedron Lett.*, 3359 (1968); (b) R. C. Carman and R. A. Marty, *Aust. J. Chem.*, **22**, 2696 (1969).

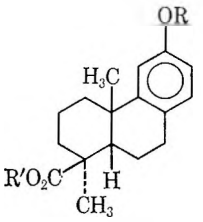
(4) (a) R. D. Haworth and R. L. Barker, *J. Chem. Soc.*, 1299 (1939); (b) M. Sharma, U. R. Ghatak, and P. C. Dutta, *Tetrahedron*, **19**, 985 (1963).

(5) W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **62**, 1287 (1940).

Wood;[2c] however the hydrogenolysis of the benzoxazolyl ether derived from **3** (**4**) failed even under extreme conditions.[6] In our hands, however, a modification of this procedure affords a convenient synthesis of 4-epidehydroabietic acid.



1, R, R′ = H
3, R = OCH_3; R′ = CH_3
4, R = OC_7H_4NO; R′ = CH_3
6, R = OH; R′ = CH_3
7, R = $OC_7H_5N_4$; R′ = CH_3
8, R = H; R′ = CH_3



2, R, R′ = H
5, R, R′ = CH_3

The conversion of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**5**) to **3** was carried out essentially as described by Campbell and Todd.[5] However, the reaction of podocarpic acid (**2**) with dimethyl sulfate and base gave **5** as the major product, rather than the corresponding acid as described previously.[7] Demethylation of **3** with boron tribromide[8] gave methyl 12-hydroxy-abieta-8,11,13-trien-19-oate (**6**) in 85% yield.[9] The attempted conversion of **6** to the phenyltetrazolyl ether (**7**) by the published method[10] gave only recovered starting materials; however, the interaction of the preformed anion of **6** with 2 equiv of 1-phenyl-5-chlorotetrazole in dimethyl formamide gave **7** in 68% yield. The hydrogenolysis of **7** proceeded smoothly under mild conditions to afford methyl abieta-8,11,13-trien-19-oate (methyl 4-epidehydroabietate, **8**) which was identical with the methyl ester of the natural product.[11] The hydrolysis of **8** to give **1** has been described previously.[2a,c] Since the total synthesis of (+)-podocarpic acid has been described,[12] this work constitutes a formal total synthesis of (+)-4-epidehydroabietic acid.

Experimental Section[13]

12-Methoxypodocarpa-8,11,13-trien-19-oic Acid and Methyl 12-Methoxypodocarpa-8,11,13-trien-19-oate.—The methylation of podocarpic acid was carried out essentially as described by Bennett and Cambie;[7] however, in contrast to the results reported by these authors, the principal product was methyl 12-methoxypodocarpa-8,11,13-trien-19-oate, rather than the corresponding acid. From 55.74 g of podocarpic acid, 78 ml of dimethyl sulfate, and 33.4 g of sodium hydroxide in 100 ml of water, there was obtained 43.50 g of hexane soluble material, mp 105–108°, and only a trace of hexane insoluble brown gum. The hexane soluble material was suspended in 400 ml of 10% aqueous potassium hydroxide and the insoluble material was collected and recrystallized from hexane to give 27.81 g (43%) of methyl ester (**5**), mp 125–126° (lit. mp 127–128°). Acidification of the basic solution gave 10.97 g (18%) of 12-methoxypodocarpa-8,11,13-trien-19-oic acid, mp 154–156° (lit. mp 157–158°), as off-white needles from aqueous ethanol.[14]

Methyl 12-Methoxyabieta-8,11,13-trien-19-oate (3).—This material, mp 105–107° (lit.[5] mp 109°), was prepared from methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**5**) by the method of Campbell and Todd.[5] The infrared spectrum of this compound showed $\lambda_{C=O}$ 5.81 μ and nmr signals at 1.03 (s, C-10 methyl), 1.19 (d, J = 7 Hz, isopropyl), 1.27 (s, H-18), 3.62 (s, CO_2CH_3), 3.78 (s, CH_3O), and 6.72, 6.86 (br s, Ar H).

Methyl 12-Hydroxyabieta-8,11,13-trien-19-oate (6).—To a solution of 5.50 g of methyl 12-methoxyabieta-8,11,13-trien-19-oate (**3**) in 200 ml of methylene chloride was added 2.0 ml of boron tribromide. The reaction mixture was stirred at room temperature overnight and concentrated to dryness on the steam bath, and the dark brown residue was taken up in 250 ml of methanol and 20 ml of water. This mixture was heated at reflux for 4 hr, concentrated to a small volume, taken up in ether, and washed with saturated aqueous sodium bicarbonate and water. After drying, the solvent was removed leaving a brown crystalline mass. Recrystallization from aqueous methanol gave 4.47 g (85%) of off-white needles, mp 178–179° (lit.[9] mp 178–180°), λ_{OH} 2.93 μ, $\lambda_{C=O}$ 5.86 μ, and nmr signals at 1.00 (s, C-10 methyl), 1.21 (d, J = 6 Hz, isopropyl), 1.27 (s, H-18), 3.62 (s, CO_2CH_3), and 6.58, 6.75 (br s, Ar H). An analytical sample, mp 180–181°, was prepared by recrystallization from aqueous methanol.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.15; H, 9.12.

Phenyltetrazolyl Ether of Methyl 12-Hydroxyabieta-8,11,13-trien-10-oate (7).—To a suspension of 0.60 g of sodium hydride (50% suspension in mineral oil, washed with four portions of hexane and dried at 1 mm and room temperature) in 80 ml of anhydrous dimethyl formamide was added 2.00 g of methyl 12-hydroxyabieta-8,11,13-trien-19-oate (**6**). The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere until the evolution of hydrogen ceased (approximately 30 min), and 1.47 g of 1-phenyl-4-chlorotetrazole was added. The temperature was gradually raised to 50° and the mixture stirred under nitrogen at this temperature for 4 hr. The mixture was cooled, an additional 1.47 g of tetrazole added, and heating with stirring under nitrogen continued for 20 hr. The reaction mixture was cooled, water was added cautiously to destroy any excess hydride, and the solution was poured into water. After acidification with 10% hydrochloric acid, the aqueous mixture was extracted with two portions of ether. The ethereal extracts were washed with water and dried, and the solvent was removed to give a pale brown semisolid mass. Two recrystallizations from methanol gave 1.94 g (68%) of **7** as white crystals, mp 157–159°. The analytical sample, mp 161–162°, was crystallized from methanol and showed nmr signals at 1.04 (s, C-10 methyl), 1.20 (d, J = 7 Hz, isopropyl), 1.28 (s, H-18), 3.65 (s, CO_2CH_3), 7.03, 7.22 (Ar H), and 7.67 (m, C_6H_5).

Anal. Calcd for $C_{28}H_{34}N_4O_3$: C, 70.86; H, 7.22; N, 11.80. Found: C, 71.16; H, 7.41; N, 11.96.

The attempted preparation of this compound by using Musliner and Gates procedure (potassium carbonate in acetone) gave only recovered phenol and tetrazole. The above method using 1 equiv of chlorotetrazole gave the ether in only 16% yield, and the product could be isolated only after chromatography on Merck alumina and elution with benzene.

Methyl Abieta-8,11,13-trien-19-oate (8).—A solution of 2.28 g of tetrazolyl ether (**2**) in 275 ml of ethanol was hydrogenated at 40 psig and 40° using 2.20 g of 5% palladium on carbon for 20 hr. The catalyst was filtered off, the ethanol removed at reduced pressure, and the residue taken up in ether. The ethereal extracts were washed with two portions of 5% aqueous sodium hydroxide to remove the 1-phenyltetrazolone and dried, and the solvent was removed to give a colorless oil which slowly crystal-

(6) W. L. Meyer and C. W. Sigel, *Tetrahedron Lett.*, 2485 (1967), reported, without comment, the hydrogenolysis of a 7-oxo 4-epimer of **4**.

(7) C. R. Bennett and R. C. Cambie, *Tetrahedron*, **23**, 927 (1967).

(8) J. F. McOmie, M. L. Watts, and D. E. West, *ibid.*, **24**, 2289 (1968), and references therein.

(9) S. M. Bocks, R. C. Cambie, and T. Takahashi, *ibid.*, **19**, 1109 (1963), have carried out this conversion in two steps from **3**.

(10) W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

(11) We would like to thank Dr. R. M. Carman of the University of Queensland for a sample of this material.

(12) (a) E. Wenkert and A. Tahara, *J. Amer. Chem. Soc.*, **82**, 3229 (1960); (b) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964).

(13) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer, and nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Signals are given in parts per million relative to this standard. Rotations were determined using a Rudolph Model 70 polarimeter and analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(14) Bennett and Cambie (ref 7) reported that this procedure gives a 5% yield of methyl ester and 64% of the acid.

lized. Recrystallization from aqueous methanol gave 1.01 g (59%) of material: mp 79–80° (lit. mp 79,[2b] 80–81°[2a]); $[\alpha]^{23}D$ +140° (C=O, 557, ethanol) (reported +137°,[2b] +140°[2a]). An additional 0.01 g (0.6%) of material, mp 73–76°, could be obtained by concentration of the mother liquors. The infrared spectrum of this material, mp 79–80°, was identical with that of an authentic sample: lit.[11] mp 78.5–79.5°; mmp 79–80°. The nmr spectrum of the ester showed signals at 1.03 (s, C-10 methyl), 1.22 (d, J = 7 Hz, isopropyl), 1.27 (s, H-18), 3.67 (s, CO_2CH_3), 6.91 (br s, H-14), 7.00 (q, J_{ortho} = 7.5 Hz, J_{meta} = 2 Hz, H-12), and 7.24 (d, J = 7.5 Hz, H-11).

Registry No.—**1**, 18045-62-0; **6**, 25356-78-9; **7**, 25454-68-6; **8**, 18045-63-1.

Griseofulvin Analogs. VII.[1] 5′-Formyl-, 5′-Alkoxalyl-, and 5′-Halogriseofulvins

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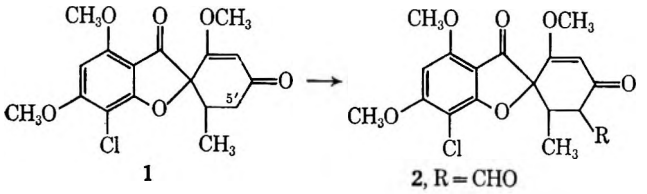
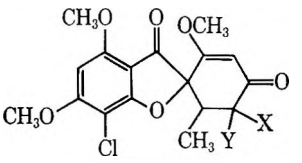
Although a large number of griseofulvin analogs have been prepared involving a variety of positions,[2,3] the 5′ position has not heretofore been manipulated except for the preparation of 5′-hydroxygriseofulvin by microbiological oxidation[4a] and 5,5′-dichlorogriseofulvin.[4b] We have now succeeded in activating the 5′ position of griseofulvin (**1**) by formylation in very high yield (and in much inferior yield by alkoxalylation) thus making it amenable to extensive manipulation. We describe here the preparation of the bromo, chloro, iodo, and fluoro derivatives and present some interesting aspects of their chemistry.

Formylation of griseofulvin (**1**) to form the 5′-formyl derivative **2** was accomplished in 94% yield by simply stirring griseofulvin in a large excess of neat methyl formate in the presence of a molar excess of sodium methoxide for 40 hr. Although methoxalylation and ethoxalylation of the 5′ position were also effected to give **3** and **4**, respectively, the poor yields in which they were obtained precluded their suitability for further transformations.



1 → **2**, R = CHO; **3**, R = $COCO_2CH_3$; **4**, R = $COCO_2Et$

The formyl derivative **2** underwent facile bromination with N-bromosuccinimide in chloroform at room temperature to give 5′-bromo-5′-formyl griseofulvin (**5**) as a mixture of isomers A and B separable by fractional crystallization.[5] The bromo–formyl mixture **5** underwent rapid deformylation to the 5′-bromo derivative **6**



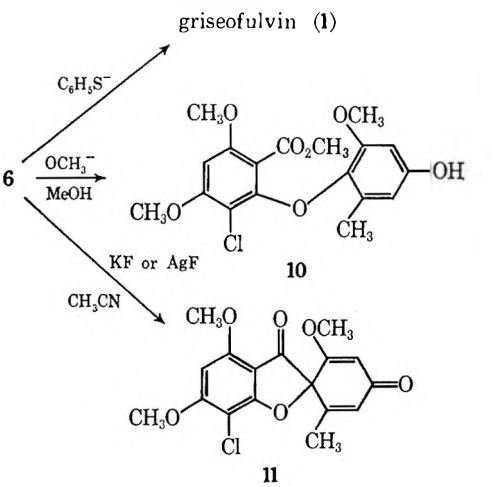
5a, X = Br; Y = CHO
5b, X = CHO; Y = Br
6, X = Br; Y = H
7, X = Cl; Y = H
8, X = I; Y = H
9, X = F; Y = H

with methanolic methoxide. In fact, the two steps could be conveniently combined and **6** isolated directly. In a similar manner, using N-chlorosuccinimide and N-iodosuccinimide, the corresponding 5′-chloro analog **7** and 5′-iodo analog **8** were prepared.

The 5′-fluoro derivative **9** was obtained by treating the sodium salt of **2** in methanol with perchloryl fluoride. Formation of **9** was accompanied by hydrolysis of the enol ether moiety to give 5′-fluorogriseofulvic acid (**9a**) (OH in place of OCH_3 on ring C in **9**) in *ca.* equivalent yield.[6,7]

It has been anticipated that 5′-bromogriseofulvin (**6**) would be a most suitable substrate for introducing a variety of substituents *via* simple displacement. It, however, quickly became apparent that this was not to be the case.

Thus, with even as ideal a nucleophile as thiophenolate ion, **6** underwent preferential reduction to griseofulvin (**1**) rather than displacement. With methoxide in methanol, **6** was converted to the diphenyl ether **10**[8] and with potassium fluoride or silver fluoride in acetonitrile to dehydrogriseofulvin **11**.[9]



(1) See ref 3 for previous papers in this series.

(2) J. F. Grove, *Progr. Chem. Org. Natur. Prod.*, **22**, 203 (1964).

(3) H. Newman and R. B. Angier, *J. Org. Chem.*, **34**, 3484 (1969), and previous publications cited there.

(4) (a) W. Andres, W. McGahren, and M. Kunstmann, *Tetrahedron Lett.*, 3777 (1969). See also the patent application filed July 1, 1968 (Serial No. 741,328), by H. Newman, P. Shu, and W. Andres in which the microbiological reduction of the ring B sulfur analog of dehydrogriseofulvin[4c] is described. The products obtained there were the ring B sulfur analog of griseofulvin and the ring B sulfur analog of 5′-hydroxygriseofulvin, the latter presumably arising by the microbiological oxidation of the former. (b) D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 3344 (1963). (c) H. Newman and R. B. Angier, *ibid.*, **34**, 1463 (1969); see ref 11 cited there.

(5) The very much lower optical rotation exhibited by isomer A compared with isomer B and the other 5′-halogriseofulvins (see Experimental Section) would appear to suggest that the configuration of the halogen in A is different than it is in the others. Nmr spectroscopy indicates a *trans* diequatorial relationship between the 6′-CH_3 and the 5′-halogen in the 5′-halogriseofulvins (*cf. ca.* 13 Hz coupling constant between the 6′ and 5′ protons). In isomer A, therefore, these substituents would appear to be *cis* oriented.

(6) It is extremely unlikely that fluorination followed hydrolysis, since the expected product would then be the 3′-fluoro derivative.

(7) See, W. A. Sheppard, *Tetrahedron Lett.*, 83 (1969), for a discussion of the mechanism of fluorination with perchloryl fluoride.

(8) E. Kyburz, J. Wursch, and A. Brossi, *Helv. Chem. Acta*, **45**, 813 (1962).

(9) D. Taub, C. H. Kuo, H. L. Slates, and N. C. Wendler, *Tetrahedron*, **19**, 1 (1963).

TABLE I[a,b]

Compd	Aromatic H	Vinyl H	Aromatic OCH_3	Vinyl OCH_3	5′-H	6′-H	6′-CH_3	Other
5′-Formyl **2**	6.13	5.52	4.02, 3.95	3.67	None	3.42 m	1.05 d, J = 6 Hz	OH ← 13.9 d, J = 11 Hz; =C; H ← 7.08 d, J = 11 Hz
5′-Methoxalyl **3**	6.15	5.50	4.03, 3.98	3.65	4.85 d, J = 13 Hz	Not clearly delineated	0.88 d, J = 6 Hz	$-COCOOCH_3$ ← 3.90
5′-Ethoxalyl **4**	6.15	5.51	4.03, 3.98	3.65	4.85 d, J = 13 Hz	Not clearly delineated	0.88 d, J = 6 Hz	4.33 q, 1.38 t; $-COCOOCH_2CH_3$
5′-Bromo-5′-formyl **5a**	6.18	5.70	4.03, 3.98	3.70	None	Not clearly delineated	1.23 d, J = 6 Hz	−CHO 9.58
5′-Bromo-5′-formyl **5b**	6.18	5.80	4.03, 3.98	3.68	None	3.32 m	1.33 d, J = 6 Hz	−CHO 9.52
5′-Bromo **6**	6.15	5.67	4.05, 4.02	3.67	5.20 d, J = 13 Hz	3.2–2.7 m	1.17 d, J = 6 Hz	
5′-Chloro **7**	6.15	5.67	4.05, 4.02	3.67	5.10 d, J = 12 Hz	3.1–2.7 m	1.17 d, J = 6 Hz	
5′-Iodo **8**	6.15	5.67	4.05, 3.99	3.66	5.47 d, J = 13 Hz	3.2–2.9 m	1.18 d, J = 6 Hz	
5′-Fluoro **9**[c]	6.35	5.60[d]	4.05, 4.02	3.70	5.3[e]	Not clearly delineated	1.03 d, J = 6 Hz	
5′-Fluorogriseofulvic acid **9a**[f]	6.50	5.42[d]	4.07, 3.95	None	5.4[g]	Not clearly delineated	0.99 d, J = 6 Hz	
5′-Tosyloxy **12**	6.15	5.47	4.03, 3.99	3.60	5.70 d, J = 12 Hz	Not clearly delineated	1.00 d, J = 6 Hz	7.85 d, J = 9 Hz → H; H ← 7.30 d, J = 6 Hz; $-OSO_2$; CH_3 ← 2.43; H H

[a] Chemical shift values are in ppm (δ) from tetramethylsilane. Spectra were determined in chloroform unless otherwise indicated. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Solvent $CDCl_3$–d_6-DMSO. [d] Poorly resolved doublet, J_{HF} = 2 Hz. [e] The C-5′-H was just barely discernible as a quartet centered about δ 5.3, $J_{5'H,F}$ = 26 Hz, $J_{5'H,6'H}$ = *ca.* 12 Hz. [f] Solvent d_6-DMSO. [g] The C-5′-H appeared as a quartet with further fine splitting centered about 5.4, $J_{5'H,F}$ = 26 Hz, $J_{5'H,6'H}$ = 10 Hz.

The possibility of displacing halogen in the 5′-chloro and 5′-iodo derivatives (**7** and **8**, respectively) was also briefly investigated with the following results: **7** was recovered unchanged from the reaction with thiophenolate under conditions which converted **6** to **1**. **8** was converted to **1** exclusively with thiophenolate, at a rate much faster than **6**.

8 was recovered virtually unchanged from 17 hr of refluxing with potassium acetate in acetone and was, quite unexpectedly, converted to griseofulvin **1** when heated under reflux (6 hr) in potassium acetate in acetic acid.

The result of the reaction of **6** with thiophenolate in which reduction was found to be favored over displacement made it of interest to investigate a case in which the former reaction pathway is significantly suppressed relative to the latter, thus creating a more favorable situation for observing the latter. 5′-Tosyloxygriseofulvin (**12**) was therefore prepared (from 5′-hydroxygriseofulvin and tosyl chloride–pyridine), since it is known that tosylate and bromide exhibit roughly equivalent leaving potentials.[10] Reaction of **12** with sodium thiophenolate under the conditions employed for **6** except that the reaction time was doubled, left it unchanged.

The resistance to displacement exhibited by the 5′-halo griseofulvin derivatives and 5′-tosyloxygriseofulvin while initially unexpected is, in retrospect, not too surprising. The halogen substituent in these derivatives is in an extremely hindered environment both sterically and electronically. There is a π-electron cloud positioned in close proximity on the opposite side of the 6-membered ring, an axial substituent in a 1,3 relationship (the spiro junction) and an equatorial substituent in a 1,2 relationship (6′-CH_3) to it. A displacement reaction, which would necessarily involve an even greater increase in the steric and electronic crowding is thus disfavored in competition with reaction pathways which can relieve this strain such as reduction to griseofulvin, elimination to dehydrogriseofulvin, and ring opening of ring B.

Nmr Spectra.—In Table I are listed the nmr spectral data of the various 5′-griseofulvin analogs discussed above.

Experimental Section[11]

5′-Formylgriseofulvin (2).—Sodium methoxide (4.3 g, 80 mmol) was cautiously added, with stirring and external cooling, to 150 ml of methyl formate. Griseofulvin (14.0 g, 40 mmol) was added portionwise over a 15-min period and the resultant thick white slurry was stirred at room temperature. After 1 hr the reaction mixture began turning yellow. After 40 hr the bright yellow reaction mixture was concentrated to dryness *in vacuo*. The residual solid was thoroughly mixed with 150 ml of water and

(10) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 82. See also, H. M. R. Hoffman, *J. Chem. Soc.*, 6753, 6762 (1965).

(11) Melting points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer. Ultraviolet spectra were measured on a Cary 11MS spectrophotometer. Magnesium sulfate was used for drying. Thin layer chromatograms were run on phosphor-containing silica gel plates (Anal. Tech. Wilmington, Del.) using benzene–ethyl acetate (1:1) for development; thick layer chromatograms were run on 2-mm silica gel plates (E. Merck Agr., Darmstadt, Germany; distributed by Brinkmann Instrument Inc., Westbury, N. Y.).

filtered. The insoluble material (5.1 g) was identified by tlc (PhH–EtOAc 1:1) and infrared as unreacted griseofulvin. The alkaline filtrate was cooled in an ice bath and 10 ml of glacial acetic acid was added with vigorous stirring. The pale yellow crystals which precipitated were collected by filtration, washed with water, and dried *in vacuo* over P_2O_5 at 60°. The yield of analytically pure 5′-formylgriseofulvin (based on unrecovered starting material) was 9.0 g (94.1%): mp 192°; λ_{max}^{MeOH} 291 nm (ϵ 24,765); λ_{max}^{KBr} 5.81, 6.17, and 6.27 μ; $[\alpha]^{25}D$ +199° (c, 1.01 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{17}ClO_7$ (380.8): C, 56.78; H, 4.62; Cl, 9.11. Found: C, 56.77; H, 4.50; Cl, 9.31.

5′-Methoxalylgriseofulvin (3).—Sodium hydride (50% suspension in oil, 1.6 g, 32 mmol) was added to a slurry of griseofulvin (5.6 g, 16 mmol) in 40 ml of sodium-dried benzene. After 30 min., dimethyl oxalate (3.8 g, 32 mmol) was added and the reaction mixture was stirred at room temperature for 72 hr. The yellow slurry was diluted with 60 ml of benzene, cooled in an ice bath, and acidified by the cautious addition of 6 ml of glacial acetic acid. Unreacted starting material (identified by tlc and ir) was removed by filtration and the yellow filtrate was extracted thrice with 30-ml portions of 1 *N* sodium hydroxide. The combined alkaline extracts were washed with ether and acidified by the addition of 12 ml of glacial acetic acid. The gummy pale yellow solid which precipitated was extracted into methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to a yellow solid *in vacuo*. Recrystallization from methanol yielded 560 mg of white, crystalline 5′-methoxalylgriseofulvin: mp 205–208; λ_{max}^{KBr} 5.73, 5.82, 6.02, 6.15, and 6.25 μ; λ_{max}^{MeOH} 325 nm (ϵ 7240) and 292 (25,900); $[\alpha]^{25}D$ +312° (c 0.51 in $CHCl_3$).

Anal. Calcd for $C_{20}H_{19}ClO_9$ (438.8): C, 54.79; H, 4.37; Cl, 8.12. Found: C, 54.51; H, 4.34; Cl, 8.42.

5′-Ethoxalylgriseofulvin (4).—The 5′-ethoxalyl derivative was obtained essentially as described in the previous experiment using diethyl oxalate. The analytical sample obtained by recrystallization from methanol melted at 209–212: λ_{max}^{KBr} 5.75 (sh), 5.83, 6.02, 6.18, and 6.27 μ; λ_{max}^{MeOH} 330 nm (ϵ 6100) and 291 (18,500); $[\alpha]^{25}D$ +302 (c 0.64 in $CHCl_3$).

Anal. Calcd for $C_{21}H_{21}ClO_9$ (452.8): C, 55.70; H, 4.67; Cl, 7.83. Found: C, 55.81; H, 4.53; Cl, 7.89.

5′-Bromo-5′-formylgriseofulvin (5).—N-Bromosuccinimide (2.92 g, 16.4 mmol) was added to a solution of 5′-formylgriseofulvin (5.71 g, 15 mmol) in 45 ml of chloroform. An exothermic reaction occurred and the solution was cooled to room temperature and stirred for 40 min. The small amount of white solid which had precipitated was removed by filtration and discarded. The filtrate was washed twice with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to an off-white solid. The crude product was crystallized in the following manner. The total crude was refluxed in 200 ml of *ethanol* for 15 min. The suspension was filtered while hot and the white crystalline bromoaldehyde (isomer A) was dried *in vacuo* at 60° over P_2O_5: yield 450 mg, mp 228–229° w/evol of gas; λ_{max}^{KBr} 5.77, 6.01 (w), 6.14, and 6.25 μ; λ_{max}^{MeOH} 325 nm (ϵ 5750) and 291 (26,450); $[\alpha]^{25}D$ +93° (c 0.45 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{16}BrClO_7$ (459.7): C, 47.03; H, 3.51; Br, 17.38; Cl, 7.71. Found: C, 47.38; H, 3.65; Br, 17.50; Cl, 7.76.

The filtrate from isomer A was concentrated to 30 ml and cooled in an ice bath. The white crystals which separated were collected on a filter and dried *in vacuo* at 60° over P_2O_5. The nmr spectrum of this material (1.09 g, mp 213–218° w/evol of gas) indicated that it was a mixture of the isomeric bromoaldehydes.

In another run, the total crude product (324 mg from 381 mg of 5′-formylgriseofulvin) was recrystallized from 5 ml of *methanol* to yield 135 mg of pure isomer B: mp 218–220° w/evol of gas; λ_{max}^{KBr} 5.85, 6.17, and 6.24 μ; λ_{max}^{MeOH} 325 nm (ϵ 5750) and 292 (25,300); $[\alpha]^{25}D$ +241° (c 0.48 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{16}BrClO_7$ (459.7): C, 47.03; H, 3.51; Br, 17.38; Cl, 7.71. Found: C, 46.65; H, 3.70; Br, 17.74; Cl, 7.87.

We thus have the interesting situation of a change in relative solubilities of the two isomers in going from ethanol to methanol.

5′-Bromogriseofulvin (6).—A solution of 1.9 g (0.0050 mol) of 5′-formylgriseofulvin in 15 ml of chloroform was treated with 0.98 g (0.0055 mol) of N-bromosuccinimide at room temperature. After keeping at room temperature for 1 hr, ice and water were added, followed by some 2 *N* NaOH and methylene chloride. The organic phase was extracted to remove the succinimide formed, dried, and concentrated to small volume. Methanol (10 ml) was added, followed by 1.0 ml of 1 *M* methanolic sodium methoxide. A new solid rapidly separated. After stirring the suspension at room temperature for 15 min, the solid was collected by filtration and washed with methanol, yield (colorless solid) 1.4 g (64%), mp 193–196°. Recrystallization from methanol furnished the analytical sample: mp 207–210°; λ_{max}^{KBr} 5.85 (s), 5.93 (m), and 6.20 μ (vs); λ_{max}^{MeOH} 325 nm (plateau) (ϵ 6500), 293 (28,000), 252 (plateau) (17,000), 235 (22,800), 217 (infl) (25,000), and 210 (27,000); $[\alpha]^{25}D$ +322° (c 0.37 in $CHCl_3$). (The nmr spectra of the product before and after recrystallization were identical.)

Anal. Calcd for $C_{17}H_{16}ClBrO_6$ (431.67): C, 47.29; H, 3.72; Br, 18.51; Cl, 8.21. Found: C, 47.23; H, 3.72; Br, 18.73; Cl, 8.31.

5′-Chlorogriseofulvin (7).—A solution of 1.9 g (0.0050 mol) of 5′-formylgriseofulvin in 15 ml of chloroform was treated with 0.7 g (0.0053 mol) of N-chlorosuccinimide, and the reaction mixture was processed as described for the preparation of the 5′-bromo analog. A 1.45 g (76%) yield of crude product was obtained as a colorless solid melting at 198–203°. Recrystallization from methanol furnished the analytical sample: mp 203–207°; λ_{max}^{KBr} 5.83 (s), 5.91 (m), and 6.20 μ (vs); λ_{max}^{MeOH} 328 nm (plateau) (ϵ 5800), 293 (27,000), 250 (infl) (17,500), 236 (23,000), 217 (23,000), and 210 (24,000); $[\alpha]^{25}D$ +354° (c 0.41 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}Cl_2O_6$ (387.21): C, 52.73; H, 4.17; Cl,18 .31. Found: C, 52.76; H, 4.19; Cl, 18.46.

5′-Iodogriseofulvin (8).—A solution of 1.9 g (0.005 mol) of 5′-formylgriseofulvin and 1.3 g (0.0058 mol) of N-iodosuccinimide in 15 ml of chloroform was kept for 1 hr and then diluted with methylene chloride and washed with cold dilute sodium hydroxide. The organic solution was washed, dried, and concentrated to small volume. Methanol (10 ml) was added, followed by 2 ml of 1 *M* methanolic sodium methoxide. (In contrast to the preparation of the 5′-bromo and 5′-chloro analogs, the addition of 1 ml of the methanolic methoxide raised the pH of the medium only to *ca.* 8, which was not basic enough for rapid deformylation.) The solid which separated was collected after 15 min and washed with methanol, yield (ivory colored solid) 1.5 g (63%), mp 214–219° dec. The analytical sample was obtained by heating the product partially suspended in boiling methanol: mp 216–220° dec; λ_{max}^{KBr} 5.85 (s), 6.10 (w), and 6.2 μ (vs); λ_{max}^{MeOH} 327 nm (plateau) (ϵ 6400), 293 (28,500), 255 (plateau) (15,000), 233 (plateau) (21,500), 217 (infl) (27,400), and 210 (28,500); $[\alpha]^{25}D$ +303° (c 0.61 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}ClIO_6$ (478.66): C, 42.65; H, 3.37; Cl, 7.41, I, 26.51. Found: C, 42.30; H, 3.25; Cl, 7.44; I, 26.63.

5′-Fluorogriseofulvin (9) and 5′-Fluorogriseofulvic Acid (9a).—A methanolic solution of 0.0026 mol of the sodium salt of 5′-formylgriseofulvin [prepared from 1 g (0.0026 mol) of 2, 2.6 ml of 1 *M* methanolic sodium methoxide (0.0026 mol) in 20 ml of methanol] was cooled (ice–water) and a rapid stream of perchloryl fluoride was bubbled through for *ca.* 30 sec. The pH of the solution at this point was essentially neutral. Gas passage was discontinued and the metanolic solution was immediately poured into ice–water. The colorless solid which separated was collected by filtration, washed with water, and while still wet, was transferred to a beaker and stirred with cold dilute ($\leq$2 *N*) NaOH for 5 min, and then collected by filtration. (The filtration proceeded slowly because of the fine particle size of product; it took *ca.* 10–15 min to separate the basic supernatant.) The yield of dull white solid obtained was 260 mg (27%). It showed a single spot, R_f *ca.* 0.5, on tlc (silica gel, PhH–EtOAc 1:1). Recrystallization from MeOH–CH_2Cl_2 furnished analytically pure 5′-fluorogriseofulvin: mp 231–233° (wetting 228°); λ_{max}^{KBr} 5.82 (s), 5.98 (s), 6.15, and 6.3 μ (s); λ_{max}^{MeOH} 372 nm (plateau) (ϵ 5900), 292 (25,000), 250 (infl) (17,500), 236 (24,000), 217 (pleateau) (22,000), and 210 (23,000); $[\alpha]^{25}D$ +283° (c 0.08 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}ClFO_6$ (370.76): C, 55.07; H, 4.35; Cl, 9.56; F, 5.12. Found: C, 54.86; H, 4.32; Cl, 9.91; F, 4.87.

Acidification of the original filtrate from which the initial colorless solid was separated gave 260 mg (28%) of yellow solid which was converted to the colorless crystalline 5′-fluorogriseofulvic acid (9a): mp 270–272° dec (with effervescence) on trituration with methanol; λ_{max}^{KBr} 2.9 (m), 5.85 (m–s), 5.95 (m–s), 6.02 (s),

and 6.17 μ (vs); λ_{max}^{MeOH} 325 nm (plateau) (ϵ 5500), 291 (29,000), 235 (38,000), and 211 (23,000). 9a was soluble in aqueous bicarbonate.

Anal. Calcd for $C_{16}H_{14}ClFO_6$ (356.73): C, 53.90; H, 3.96; Cl, 9.94; F, 5.33. Found: C, 53.56; H, 3.72; Cl, 9.77; F, 4.92.

5'-Tosyloxygriseofulvin (12).—A mixture (suspension) of 369 mg (0.001 mol) of 5'-hydroxygriseofulvin[4a,12] and 380 mg (0.002 mol) of tosyl chloride in 2.5 ml of dry pyridine was stirred at room temperature for 27 hr. An additional 190 mg (0.001 mol) of tosyl chloride was then added to the still heterogeneous reaction mixture and stirring continued for another 25 hr. A completely homogeneous reaction mixture formed which was poured into ice–water to precipitate the solid 5'-tosyloxy derivative. The aqueous mixture was made strongly basic (pH $\geq$ 13) with 2 *N* NaOH and stirred at room temperature for 20 min (to destroy excess tosyl chloride) before collecting the product, yield 410 mg (79%), mp 207–212°. Heating the mixture suspended in boiling methanol raised the melting point to 211–214°, λ_{max}^{KBr} 5.85 μ.

Anal. Calcd for $C_{24}H_{23}O_9SCl$ (522.95): C, 54.12; H, 4.43; Cl, 6.78; S, 6.13. Found: C, 54.45; H, 4.30; Cl, 7.08; S, 6.11.

Dehydrogriseofulvin (11) from 5'-Bromogriseofulvin and Silver Fluoride or Potassium Fluoride in Acetonitrile.—A solution of 0.59 g (0.0013 mol) of 5'-bromogriseofulvin in 10 ml of acetonitrile was heated under reflux (protected from light by wrapping the flask in aluminum foil) with 0.5 g (0.004 mol) of AgF (Alfa Inorganic Inc., Beverly, Mass.) for 17 hr and then filtered through Celite. The filtrate was evaporated and 200 mg of the residue obtained was thick-layer chromatographed (developing solvent PhH–EtOAc 1:1). Two somewhat overlapping zones were obtained which were eluted with acetone containing some MeOH. The faster of the two (37 mg) was identified as starting 5'-bromogriseofulvin by melting point and ir and tlc. The slower one (58 mg, mp 270–274° dec) was recrystallized from methanol to give material melting at 282–285° dec.

Anal. Calcd for $C_{17}H_{15}ClO_6$ (350.75): C, 58.17; H, 4.31; Cl, 10.10. Found: C, 57.49; H, 4.47; Cl, 10.36.

The infrared and nmr spectra of the compound were identical with those of authentic dehydrogriseofulvin.

Dehydrogriseofulvin was also the exclusive product obtained from the treatment of 5'-bromogriseofulvin with a large excess of potassium fluoride dihydrate in refluxing acetonitrile (18 hr).

Treatment of 5'-Bromogriseofulvin with Methanolic Methoxide. Formation of 2-Carbomethoxy-2',3,5-trimethoxy-4'-hydroxy-6-chloro-6'-methyldiphenyl Ether (10).—A suspension of 100 mg (0.23 mmol) of 5'-bromogriseofulvin in 1 ml of methanol was treated with 0.23 ml of *ca.* 1 *M* sodium methoxide in methanol (0.23 mmol), and the mixture was stirred at room temperature for 16 hr. Ice–water and methylene chloride were added and the mixture was extracted with dilute sodium hydroxide. Acidification of the basic extract gave 34 mg of a colorless solid A. Drying and evaporating the methylene chloride solution gave 24 mg of a yellow solid B.

Solid A melted at 195–199°. The analytical sample, obtained by recrystallization from methanol, melted at 194–199°: λ_{max}^{KBr} 3.0 (m), 5.75 (sh, m), and 5.85 μ (s); λ_{max}^{MeOH} 285 nm (ϵ 5400).

Anal. Calcd for $C_{18}H_{19}O_7Cl$ (382.79): C, 56.48; H, 5.00; Cl, 9.26. Found: C, 56.20; H, 4.82; Cl, 9.55.

The physical constants cited are in excellent agreement with those reported for **10** by Kyburz, *et al.*[8]

Solid B was identified as starting 5'-bromogriseofulvin (after recrystallization from MeOH) by melting point and mixture melting point, and tlc and infrared spectroscopy.

10 was also the exclusive transformation product when the reaction was conducted in refluxing methanol (1 hr).

Reaction of 5'-Bromogriseofulvin (6) and Sodium Thiophenolate.—To a solution of 0.46 mmol of sodium thiophenolate in 3 ml of methanol [prepared by adding 70 mg (0.64 mmol) of thiophenol to 0.46 ml of 1 *M* sodium methoxide in methanol] was added 0.2 g (0.46 mmol) of 5'-bromogriseofulvin **6**. The resulting suspension was stirred at room temperature for 26 hr and diluted with water, and the solid was collected, yield 110 mg, mp 120–197°. Tlc and nmr spectroscopy indicated the product to be mainly griseofulvin contaminated by some unreacted **6**.

(12) Prepared by Mr. M. Dann of these laboratories.

Registry No.—**2**, 25357-21-5; **3**, 25357-22-6; **4**, 25357-23-7; **5**, 25350-64-5; **6**, 25350-65-6; **7**, 25350-66-7; **8**, 25350-67-8; **9**, 25350-68-9; **9a**, 25350-69-0; **10**, 25357-24-8; **11**, 25357-25-9; **12**, 25357-26-0.

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Structure of Kutkin, the Bitter Glucoside of *Picrorhiza kurroa* Royle ex Benth

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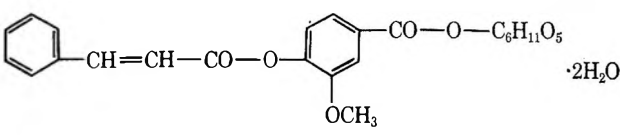
Picrorhiza kurroa Royle ex Benth (Scrophulariaceae)[1c] is a wild plant which grows from Kashmir to Sikkim at an altitude of 5000 to 10,000 ft. The roots are extremely bitter and extensively used in the indigenous system of medicine as an antiperiodic, stomachic, cathartic, and cholagogue. Rastogi, *et al.*,[2,3] previously isolated from the roots a bitter glucoside, kutkin, $C_{23}H_{24}O_{10}\cdot 2H_2O$, mp 211°, $[\alpha]^{41}D$ −165°, together with D-mannitol, vanillic acid, and several uncharacterised products. Kutkin, on hydrolysis, yielded vanillic acid, cinnamic acid, and glucose, on the basis of which they put forward structure I for kutkin. In view of the reported



I

uses of the drug in the indigenous and modern systems of medicine,[4,5] we became interested in the chemistry of kutkin which appeared to be the active principle of the drug. Moreover, the structure I proposed for kutkin by Rastogi, *et al.*, is not consistent with the biogenetic principles applicable to lignins,[6] known to be derived from C_6–C_3 and D-glucose precursors. Again, the facile hydrolysis of kutkin to glucose and other fragments in protic solvents, even at ordinary temperatures, also militates against the assumption[2] that the phenolic and sugar entities are joined in an ester linkage as shown in I.

Experimental Section

Kutkin, isolated from the roots of *Picrorhiza kurroa* (3 kg) following essentially the method of Rastogi, *et al.*,[2] crystallized

(1) (a) Department of Medicinal Chemistry, Post Graduate Institute of Indian Medicine; (b) Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-5, India; (c) R. N. Chopra, S. L. Nayar, and I. C. Chopra, "Glossary of Indian Medicinal Plants," CSIR, New Delhi, 1956, p 192.

(2) R. P. Rastogi, V. N. Sharma, and S. Siddiqui, *J. Sci. Ind. Res., Sect. B*, **8**, 173 (1949).

(3) R. P. Rastogi and M. L. Dhar, *ibid.*, **18**, 219 (1959).

(4) P. K. Das and M. K. Raina, *J. Res. Ind. Med.*, **1** (2), 213 (1967).

(5) H. S. Bajpai, S. S. Hospital, Banaras Hindu University, Varanasi-5, personal communication.

(6) W. J. Schubert, "Lignin Biochemistry," Academic Press, New York, N. Y., 1965, p 54.

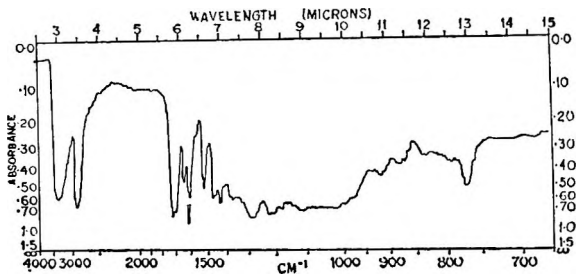


Figure 1.—Infrared spectrum of component A.

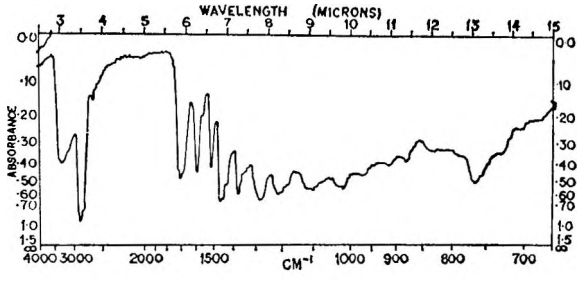


Figure 2.—Infrared spectrum of component B.

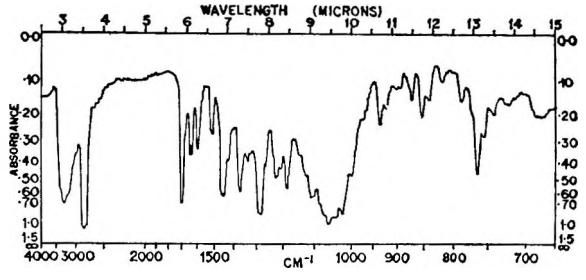


Figure 3.—Infrared specturm of kutkin.

from absolute alcohol as clusters of small needles: mp 214–216° (13 g); infrared λ_{max}^{Nujol} 3300 (OH), 1700 (-CH=CHCO-), 1650 (dissolved H_2O), 765 cm^{-1} (4 adjacent aromatic H).

Anal. Calcd for $C_{24}H_{28}O_{11}\cdot 2H_2O$: C, 54.54; H, 6.06. Found: C, 54.54, 54.81, 54.65; H, 5.55, 5.86, 5.81. Calcd for Rastogi's formula, $C_{23}H_{24}O_{10}\cdot 2H_2O$ (I): C, 55.6; H, 5.6. Found:[2] C, 55.0; H, 5.3.

Acid Hydrolysis of Kutkin to Glucose and Two Aglycones A and B.—Kutkin (1 g) in aqueous hydrochloric acid (2–3%, 30 ml) was kept at room temperature for 24 hr. Within 30 min the color of the solution changed to green which gradually faded away. The mixture was repeatedly extracted with chloroform and the chloroform extract was washed until free from acid and dried. On removal of solvent, a pale yellow amorphous compound B (0.1303 g) was obtained. Attempts to crystallize B from different solvents failed. It showed a single spot at R_f 0.87 (Whatman paper No. 1, *n*-butyl alcohol–pyridine–water, 30:15:22.5 v/v, Tollens reagent). The spot turned pink when sprayed with an alcoholic solution of 2,4-dinitrophenylhydrazine, followed by 10% KOH solution,[7] indicating its aldehydic character.

The acidic solution, after separation of B, was repeatedly extracted with isoamyl alcohol. The organic layer was processed in the above way, when another component A was obtained as a brown amorphous material (0.6188 g). On papergram, A showed two spots at R_f 0.77 (intense), no color with DNP reagent,[7] and R_f 0.87 (faint, due to B). The aqueous mother liquor left showed only one spot at R_f, 0.26 (D-glucose). Compound A was purified by repeated extraction with chloroform, followed by isoamyl alcohol. Attempts to dry a pure sample of A over dehydrating agents (concentrated H_2SO_4, P_2O_5) resulted in a mixture of A and B. On further hydrolysis, both A and B afforded a mixture of vanillic and cinnamic acids.

A fresh aqueous solution of kutkin did not exhibit any reducing spot on papergram, but on standing or warming exhibited only two spots at R_f, 0.26 (D-glucose) and 0.77 (A), but no spot at R_f, 0.87 (B), which appeared only in protic solvents along with the other two spots.

Periodic Acid Oxidation of Compound A.—A mixture of a yellow colored suspension of A (0.2 g) and periodic acid (1 g) in water (5 ml) was kept at room temperature for 20 hr. The product was steam distilled. The distillate was led to a saturated solution of dimedone in water. The resulting precipitate was filtered, washed with water, and dried, mp 189–190°, mixture melting point (with formaldehyde dimedone, mp 189–190°) remained undepressed.

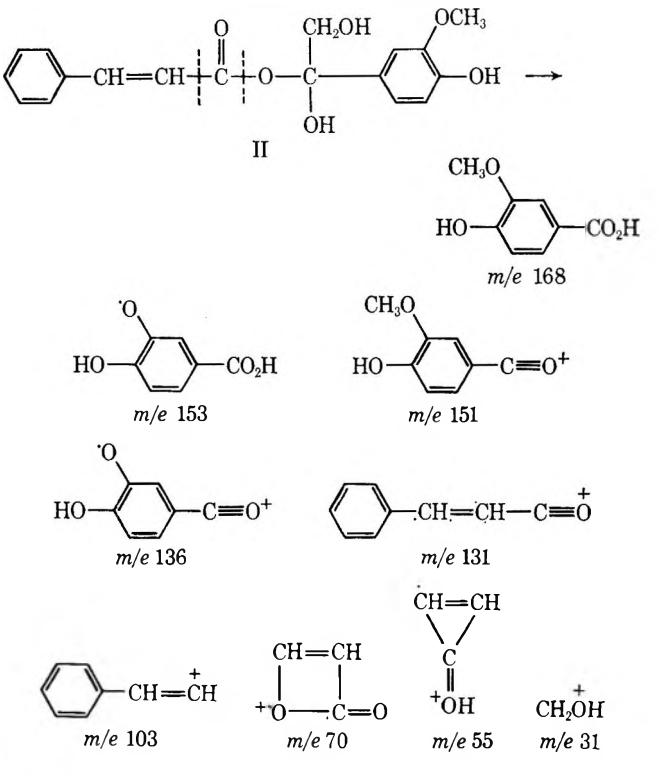
From the mother liquor, vanillin was isolated and characterized through the DNPH.

Results and Discussion

The compound A, $C_{18}H_{18}O_6$ (on the basis of integral proton count and by difference of the sugar component from the parent compound, $C_{24}H_{28}O_{11} + H_2O - C_6H_{12}O_6$), showed significant infrared absorption bands at 1700 (α,β-unsaturated ester carbonyl) and at 1650 cm^{-1} (due to dissolved water in polyhydroxy systems).[8] It did not show the molecular ion peak in its mass spectrum, but instead intense fragment ions appeared at *m/e* 168, 153, 151, 148, 147, 136, 131, 125, 103, 97, 77, 71, 70, 57, 55, and 31, consistent with structure II for A (Scheme I).

SCHEME I

MASS SPECTRAL FRAGMENTATION PATTERN OF A



In contrast to a one sharp band at 1700 cm^{-1} in the infrared spectra of kutkin and A, component B, $C_{18}H_{16}O_5$ (M^+, *m/e* 312), showed a twin peak at 1710 (CHO) and 1700 cm^{-1} (α,β-unsaturated ester). Again, the band at 1650 cm^{-1} ascribed to dissolved water in polyhydroxy systems[8] is completely absent in B. The location of the aldehyde function in B, associated with a OCH—CH= grouping, was confirmed from its nmr spectrum, which exhibited a doublet at δ 9.8 (J = 4

(7) E. Lederer and M. Lederer, "Chromatography," Elsevier, New York, N. Y., 1957, pp 169–170.

(8) G. Eglinton in "Physical Methods in Organic Chemistry," J. C. P. Schwarz, Ed., Olive & Boyd, Edinburg and England, 1964, p 106.

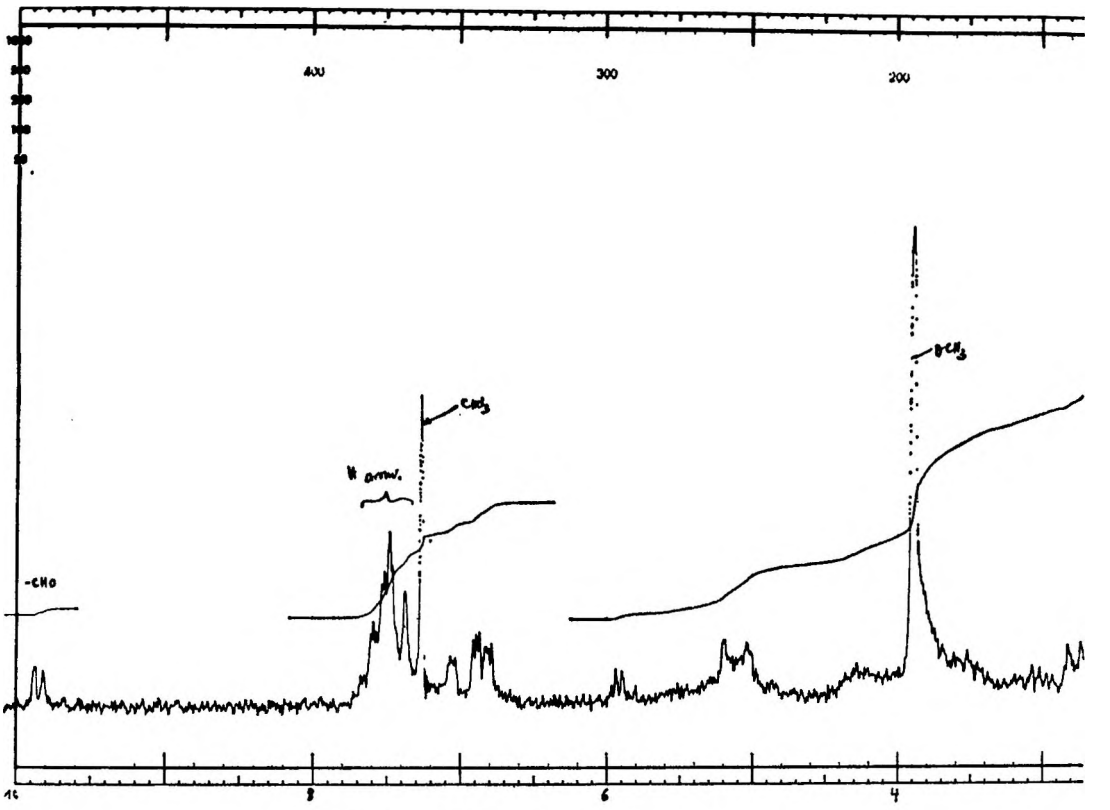
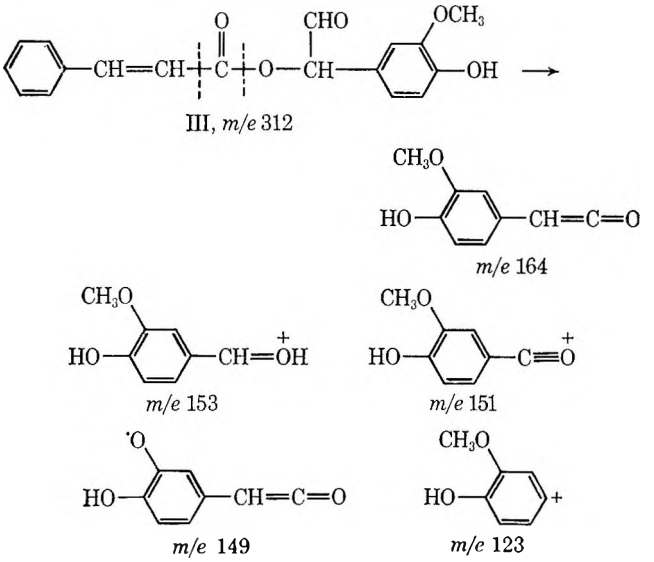


Figure 4.—Nmr spectrum of component B.

cps). These evidences together with the mass spectral fragmentation pattern (Scheme II), significant peaks at *m/e* 164, 153, 151, 149, and 123, indicate structure III for B.

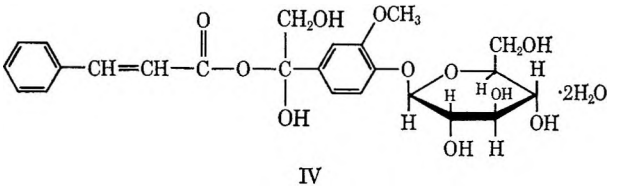
SCHEME II

MASS SPECTRAL FRAGMENTATION PATTERN OF B



See Figures 1–3 for infrared spectra of A, B, and kutkin. Figure 4 shows the nmr spectrum of B.

On the basis of structures II and III for the two major degradation products, we propose the following revised structure IV for the glucoside, kutkin. The physical data (nmr[9] and ir spectra, high optical rotation,[2] and analyses, *loc. cit.*) are consistent with the structure IV for kutkin. The observed hydrolysis of kutkin with emulsin indicates its β-glucosidic linkage.



IV

Registry No.—IV, 25356-80-3.

Acknowledgment.—K. B. is grateful to the Ministry of Health, Government of India, for the award of a Research Fellowship. Financial assistance from the ICMR (CDRS), New Delhi, is thankfully acknowledged.

(9) Dr. U. Scheidegger, Varian AG Research Laboratory, Switzerland, also opined, on the basis of nmr data, for the above structural assignments of kutkin and its two major degradation products, for which the authors are indebted.

Synthesis of 2-(2-Nitroalkyl)benzoates[1]

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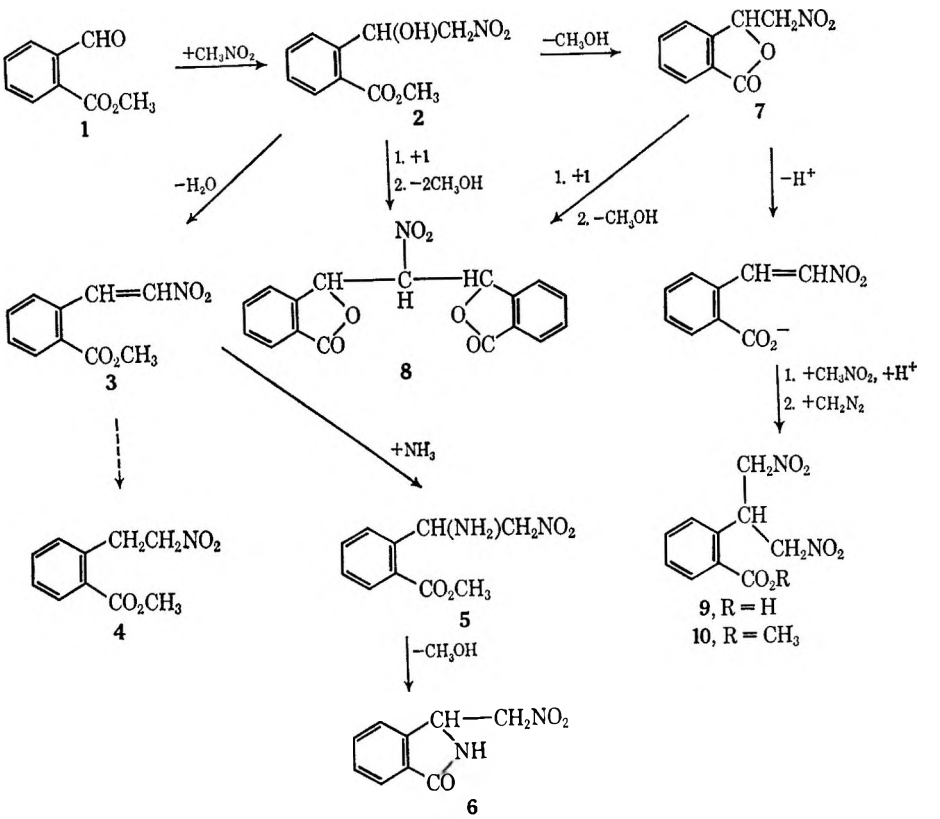
Received December 19, 1969

Methyl 2-(2-nitroethyl)benzoate (**4**) was required for a synthesis[2] of 2-nitroindanone. A possible approach seemed to be selective hydrogenation of methyl 2-(2-nitrovinyl)benzoate (**3**). The latter compound was thought to be accessible by applying the β-nitro-

(1) Taken from the Ph.D. Thesis of S. R. Naik, University of Ottawa, 1967.

(2) H. H. Baer and S. R. Naik, *J. Org. Chem.*, **35**, 2927 1970.

SCHEME I



styrene synthesis[3] to methyl phthalaldehydate (1), provided that, for the nitromethane condensation, conditions not affecting the ester grouping were found.[4] Examining a variety of conditions, we obtained the hitherto unknown products **6**, **8**, **9**, and **10**, but **3** could not be isolated.

When the reaction was performed in refluxing acetic acid in the presence of ammonium acetate,[5] the lactam **6** was isolated in poor yield. Presumably it arose by way of amination of intermediate **3** followed by internal aminolysis (**1** → **2** → **3** → **5** → **6**). Substitution of sodium acetate for ammonium acetate, as well as triethylamine-catalyzed reaction in methanolic solution at room temperature, led to a compound $C_{17}H_{11}NO_6$ which exhibited infrared and ultraviolet absorptions very similar to those reported for the known[4,6] 3-phthalidylnitromethane (**7**). The product was therefore formulated as bis(3-phthalidyl)nitromethane (**8**). It obviously arose by combination of two molecules of **1** with one molecule of nitromethane, with lactone formation from intermediate hydroxy esters, in the sequences **1** → **2** → **7** → **8** or **1** → **2** → **8**. Performance of the reaction at 0° using nitromethane as the solvent and benzyltrimethylammonium hydroxide as the catalyst gave 2-(1,3-dinitro-2-propyl)benzoic acid (**9**) which yielded the methyl ester (**10**) by the action of diazomethane. The formation of **9** may be envisioned as proceeding *via* **2** and **7**. The latter compound is known[4] to undergo lactone opening by β elimination induced by strong base, and in the presence of excess nitromethane this process is evidently accompanied by a Michael addition leading to the dinitro acid. See Scheme I.

Attempts at synthesizing **3** from **1** and nitromethane, with sodium methoxide, sodium hydrogen carbonate, dimethylamine, piperidine, or pyridine as the catalyst and methanol or benzene as the solvent, resulted in the recovery of starting material and (or) the formation of unidentifiable products. The sodium bisulfite procedure[7] also failed. Therefore, an alternate route to **4** was elaborated.

2-(2-Bromoethyl)benzoic acid (**11**), obtained from isochroman-1-one[8] by fission with hydrogen bromide,[8b] was converted into its (liquid) methyl ester (**12**) by diazomethane. It was observed that distillation of **12** requires carefully controlled conditions as this ester tends to suffer thermal cleavage, thereby reverting to isochroman-1-one.[9] Treatment of **12** with sodium nitrite in dimethyl sulfoxide[10] gave the nitro ester **4** in about 60% yield. The bromo acid (**11**) was converted into its phenyl ester (**13**) *via* the acid chloride, and

(3) B. Priebs, *Ber.*, **16**, 2591 (1883); *Justus Liebigs Ann. Chem.*, **225**, 319 (1884). J. Thiele, *Ber.*, **32**, 1293 (1899). H. Knoevenagel, *ibid.*, **37**, 4502 (1904). F. W. Hoover and H. B. Hass, *J. Org. Chem.*, **12**, 501 (1947). V. V. Perekalin, "Unsaturated Nitro Compounds," translated by L. Mandel, Israel Service of Scientific Translations, Ltd., Jerusalem, 1964.

(4) It was known that the free acids corresponding to intermediate **2** and to **3** spontaneously cyclize to 3-phthalidylnitromethane (**7**); see H. H. Baer and F. Kienzle, *Can. J. Chem.*, **43**, 190 (1965).

(5) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953). S. Byrdy, Z. Eckstein, and J. Plenkiewicz, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, **9**, 627 (1961). See also M. G. S. Rao, C. Srikantia, and M. S. Iyengar, *Helv. Chim. Acta*, **12**, 581 (1929).

(6) T. Széki, *Ber. Ung. Pharm. Ges.*, **13**, 680 (1937); *Chem. Abstr.*, **31**, 6644 (1937). B. B. Dey and T. K. Srinivasan, *Arch. Pharm. (Weinheim)*, **275**, 397 (1937). G. E. Ullyot, J. J. Stehle, C. L. Zirkle, R. L. Shriner, and F. J. Wolf, *J. Org. Chem.*, **10**, 429 (1945). H. H. Baer and B. Achmatowicz, *ibid.*, **29**, 3180 (1964).

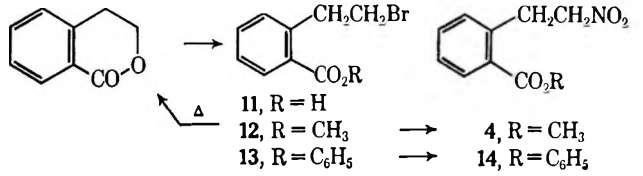
(7) J. Kamlet, U. S. Patent No.2,151,517 (1939); *Chem. Abstr.*, **33**, 5003 (1939).

(8) (a) J. Cologne and P. Boisde, in "Les Hétérocycles Oxygénés," Centre National de la Recherche Scientifique, Paris, 1957, p 177; (b) P. Maitte, *ibid.*, p 197.

(9) Possibly this is caused by attack of the carbonyl oxygen on the bromo carbon atom, resulting in displacement of bromide ion and formation of a resonance-stabilized cyclic oxonium salt which collapses to isochromanone and methyl bromide.

(10) N. Kornblum, *Org. React.*, **12**, 101 (1962).

treatment of **13** with sodium nitrite produced a crystalline substance that appeared to be a mixture of the expected nitro ester **14** and starting **13**. Pure **14** was separated by preparative thin layer chromatography. The cyclization of **4** and **14** to 2-nitroindanone is disclosed elsewhere.[2]



Experimental Section[11]

Methyl Phthalaldehydate (1).[12]—A solution of commercial phthalaldehydic acid (15.0 g, 0.1 mol) in warm water (100 ml) was cooled to room temperature, and a solution of potassium carbonate (6.91 g, 0.05 mol) in water (15 ml) was added gradually. A small amount of insoluble matter was filtered off, and to the heated (70°) and vigorously stirred filtrate was added a hot solution of silver nitrate (17.88 g, 0.105 mol) in water (25 ml). The mixture was allowed to cool in the dark, and the white silver phthalaldehydate was filtered off, washed thoroughly with water, and then with ethanol. After drying at 80° the salt was suspended in ether (200 ml) containing methyl iodide (21.4 g) and refluxed for 2 hr. The insoluble matter was filtered off and washed with ether, and the filtrate was dried (Na_2SO_4) and evaporated to leave a pale yellow oil. Distillation at 13 Torr gave 12.9 g (78.6%) of colorless **1** collected at 136–138° [lit.[12,13] bp 136–138° (13 mm), bp 146–147° (17 mm)]. Strong ir bands were at 1720 (ester C=O), and 1695 cm^{-1} (aldehyde C=O); a weak band at 1770 cm^{-1} (α,β-unsaturated γ-lactone) indicated a small degree of contamination by the pseudo ester, 3-methoxyphthalide.

2-(1-Amino-2-nitroethyl)benzolactam (6).—A mixture of **1** (0.75 g), nitromethane (0.75 ml), ammonium acetate (0.3 g), and glacial acetic acid (3 ml) was refluxed for 2 hr. The pale yellow liquid was cooled and poured onto crushed ice. The product was extracted with chloroform (25 ml) which was washed twice with water, dried (Na_2SO_4), and evaporated. By trituration of the semisolid residue with ethyl acetate (2 ml), crude **6** (102 mg) melting at 175–185° could be isolated. Recrystallization from ethyl acetate gave colorless needles (78 mg), mp 193°, ν_{max} 3225 (NH), 1720 (amide I),[14] and 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_9H_9N_2O_3$ (192.1): C, 56.25; H, 4.16; N, 14.57. Found: C, 56.22; H, 3.94; N, 14.82; OCH_3, 0.0.

Bis(3-phthalidyl)nitromethane (8). A. Catalysis by Sodium Acetate.—A mixture of **1** (0.75 g), nitromethane (0.75 ml), anhydrous sodium acetate (0.3 g), and glacial acetic acid (3 ml) was refluxed for 2 hr and then evaporated to dryness. The yellow residue was extracted with dry benzene and the extract concentrated to a small volume. Addition of a few drops of petroleum ether induced slow crystallization of colorless **8** (75 mg) that melted at 175–190° (at 226° after recrystallization from acetonitrile). Ir and uv spectra were identical with those of **8** described in section B.

B. By Catalysis with Trimethylamine.—A solution of **1** (4.92 g, 0.03 mol) and nitromethane (2.80 g, 0.046 mol) in methanol (50 ml) was chilled in an ice–water bath, and 5% methanolic trimethylamine (30 ml) was added dropwise, with stirring, in the course of 30 min. Stirring was continued for 5 hr at room temperature, and after renewed cooling to 0° the mixture was neutralized with cold 1 *N* HCl to about pH 4. Most of the methanol was then removed by evaporation, and the remaining, largely aqueous solution was extracted with ether (100 ml). The ethereal extract was washed twice with water, dried (Na_2SO_4), and evaporated to leave a yellow oil which was distilled at 20 Torr. A fraction collected at 150–151° weighed 3.6 g and was identified as starting ester **1** (recovery, 73%). The residue of distillation was treated with benzene (2 ml) and a few drops of petroleum ether, which caused colorless crystals (250 mg) of impure **8** (mp 175–185°) to be deposited within a few hours. Recrystallization from acetonitrile gave 125 mg of prisms: mp 230°, ν_{max} 1760 (C=O) and 1560 cm^{-1} (NO_2); λ_{max} 276 nm (ϵ 5300) and 283 (5200) in methanol.

Anal. Calcd for $C_{17}H_{11}NO_6$ (325.2): C, 62.77; H, 3.38; N, 4.30. Found: C, 62.88; H, 3.28; N, 4.41; mol wt, 325 (mass spectrum).

2-(1,3-Dinitro-2-propyl)benzoic Acid (9).—A solution of **1** (2.46 g, 0.015 mol) in nitromethane (12.5 g, 0.2 mol) was added dropwise (over a period of 2 hr) to a stirred and chilled (0 to −3°) solution of benzyltrimethylammonium hydroxide (6 ml, 40% in methanol, technical grade) in nitromethane (18.3 g, 0.3 mol). When the addition was complete the mixture was allowed to stand for another 15 min at 0° and was then neutralized with chilled 1 *N* HCl and extracted with ether (100 ml). The extract was washed twice with water, dried over Na_2SO_4, and evaporated to give a pale yellow, semisolid residue from which a crystalline material (2.15 g, mp 125–127°) could be isolated by trituration with benzene (5 ml). Two recrystallizations from benzene afforded colorless needles (1.0 g, plus 0.25 g from the mother liquors): mp 138–139°; ν_{max} 3300–3100 and 2700–2400 (OH), 1680 (C=O), and 1560 with shoulder at 1550 cm^{-1} (NO_2); nmr data (in acetone-d_6) τ 2.5–3.1 (m, 4 H, aromatic), 5.20 (m, 1 H, benzylic), 5.50 (d, 4 H, $2CH_2NO_2$). In the mass spectrum, the molecular ion peak expected at *m/e* 254 was not observed, but a fragment with *m/e* 208 was present (loss of NO_2).

Anal. Calcd for $C_{10}H_{10}N_2O_6$ (254.2): C, 47.22; H, 3.94; N, 11.03. Found: C, 47.44; H, 4.09; N, 10.82.

Methyl 2-(1,3-Dinitro-2-propyl)benzoate (10).—An ethereal solution of diazomethane was added in slight excess to the acid **9** (610 mg) in ether (50 ml). After 1 hr the solvent was evaporated and the residue was recrystallized from methanol to give colorless plates (462 mg, 72%) of **10**: mp 90°; ν_{max} 1720 (C=O) and 1570 with shoulder at 1560 cm^{-1} (NO_2); nmr data ($CDCl_3$) τ 1.9–2.6 (m, 4 H, aromatic), 4.78 (m, 1 H, benzylic), 5.08 (d, 4 H, 2 CH_2NO_2), 6.10 (s, 3 H, CO_2CH_3). In the mass spectrum, the molecular ion peak expected at *m/e* 268 was not observed, but a fragment with *m/e* 237 was present (loss of OCH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_6$ (268.2): C, 49.26; H, 4.51; N, 10.44. Found: C, 49.49; H, 4.70; N, 10.50.

Isochroman-1-one.—This compound was prepared[8] by selenium dioxide oxidation of commercial isochromane: nmr data (CCl_4) τ 2.05 (m, 1 H) and 2.65 (m, 3 H), aryl protons, 5.58 and 7.70, two sharp, symmetrical triplets (2 H each) with spacings of 6 Hz (A_2X_2 pattern of CH_2CH_2). No impurities were revealed. Characteristic ir bands (from liquid film) are given for comparison with **12**: 1720 s, 1610 m, 1460 m, 1427 w, 1390 m, 1293 s, 1240 s, 1121 s, 1103 m, 1090 s, 1063 m, 1035–1030 s, 992 w, 954 m, 805 m, 748 s, 716 w, 696 s, 640 m.

2-(2-Bromoethyl)benzoic Acid (11).—Commercial 30% hydrogen bromide in acetic acid was saturated by passing through dry hydrogen bromide gas at 0°. Isochromanone (10 g) was introduced into 40 ml of the reagent, and the mixture was heated in a sealed tube for 3 hr at 150°. After cooling to room temperature the tube was chilled in Dry Ice before opening. Removal of the reagent *in vacuo* led to a residue that crystallized from carbon tetrachloride. The yield of **11** was 11.7 g, mp 93° (lit.[8b] mp 93.5°): nmr data ($CDCl_3$) τ 1.75 (m, 1 H) and 2.45 (m, 3 H), aryl protons, 6.32 (narrow multiplet, 4 H), bromoethyl group. No trace of isochromanone was present.

Methyl 2-(2-Bromoethyl)benzoate (12).—The acid **11** (3.0 g) in ether (75 ml) was treated with a slight excess of ethereal diazomethane for 1 hr. Upon removal of the solvent **12** was obtained as pale yellow oil that was dried *in vacuo*: ir data (from liquid film) 1720 s, 1600 m, 1575 m, 1485 m, 1448 s, 1433 s, 1290 s, 1270 s, 1255 s, 1215 m, 1185 m, 1115 s, 1075 s, 1050 w, 1030 w, 965 m, 755 s, 715 s, 650 m; nmr data (CCl_4) τ 2.0 (m, 1 H) and 2.6 (m, 3 H), aryl protons, 6.11 (s, 3 H), CO_2CH_3, 6.45 (m, 4 H), bromoethyl group. No signals attributable to impurities were seen.

(11) All evaporations were performed *in vacuo* at about 40°. Melting points were taken in capillaries in an electric aluminum block apparatus. Infrared spectra were obtained, from Nujol mulls unless otherwise stated, with a Perkin-Elmer Infracord or a Beckman IR-8 instrument, and only the most characteristic bands are given. Nmr spectra (60 MHz) were recorded on a Varian HA-60 spectrometer and were internally standardized with tetramethylsilane.

(12) K. v. Auwers and A. Heinze, *Ber.*, **52**, 595 (1919), wherein few experimental details were recorded. Other methods of esterification of phthalaldehydic acid were stated to give 3-methoxyphthalide.

(13) E. L. Eliel and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **71**, 2251 (1949).

(14) In dilute solution in chloroform the carbonyl band was at 1710 cm^{-1}, close to that reported (1698 cm^{-1}) for phthalimidine; see A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 3809 (1956).

Anal. Calcd for $C_{10}H_{11}BrO_2$ (243.1): OCH_3, 12.75. Found: OCH_3, 12.50.

When a sample of **12** was distilled from a short-neck bulb at 0.3 Torr and 95–100° (bath temperature), the distillate gave unchanged ir and nmr spectra. Distillation of a larger quantity of **12** from an ordinary flask at 0.8 Torr and 108–110° (bath, 140–160°) caused the distillate to contain a considerable amount of isochromanone as revealed by spectroscopy. After three such distillations a sample was found to be nearly free from bromine (Found: Br, 0.42. Calcd for **12**: Br, 32.87.) and to give C and H values corresponding to isochromanone (Found: C, 73.34; H, 5.90. Calcd: C, 72.97; H, 5.40.).

Phenyl 2-(2-Bromoethyl)benzoate (13).—The acid **11** (508 mg) was refluxed with thionyl chloride (2 ml) for 1 hr. The excess of the reagent was then distilled off, and the reaction product was dissolved in pyridine (5 ml). Phenol (209 mg) was added, and the mixture was magnetically stirred for 2 hr at ambient temperature. The crystalline precipitate was discarded and the solution was evaporated to dryness. Crystallization of the residue from ethanol afforded colorless, hexagonal plates (400 mg) of the phenyl ester, mp 84°, ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}BrO_2$ (305.2): C, 59.00; H, 4.29; Br, 26.17. Found: C, 59.23; H, 4.16; Br, 26.06.

Methyl 2-(2-Nitroethyl)benzoate (4).—The bromo ester **12** (710 mg), sodium nitrite (350 mg), and phloroglucinol (166 mg) were stirred in dimethyl sulfoxide (3 ml) at room temperature for 8 hr. The mixture was then triturated with crushed ice, and the solid precipitate was collected and dried (375 mg, mp 45–48°). Recrystallization from methanol afforded **4** as colorless rods, mp 55–56°, ν_{max} 1720 (C=O) and 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{10}H_{11}NO_4$ (209.2): C, 57.41; H, 5.29; N, 6.69. Found: C, 57.20; H, 4.99; N, 6.35.

Use of sodium nitrite in *N,N*-dimethylformamide or of silver nitrite in ether failed to afford **4**.

Phenyl 2-(2-Nitroethyl)benzoate (14).—The bromo ester **13** (305 mg) and sodium nitrite (110 mg) were stirred in dimethyl sulfoxide (5 ml) at room temperature for 4 hr. The mixture was poured into ice water which was immediately extracted with three portions of ether. Thecom bined extracts were washed twice with water, dried (Na_2SO_4), and evaporated to give a colorless solid (155 mg). Recrystallization from ethanol furnished prisms, mp 71°, ν_{max} 1730 (C=O) and 1550 cm^{-1} (NO_2). This material showed two major spots in tlc on silica gel G with cyclohexane–chloroform (2:3, v/v). The nitrogen content (2.47%) was half of that expected, and the carbon content (63.35%) lay between the values calculated for **14** and **13**. Separation of the mixture by preparative tlc furnished unreacted **13** (77 mg) by chloroform extraction of the faster moving band, and pure **14** (60 mg, mp 81°) by extraction of the slow moving band.

Anal. Calcd for $C_{15}H_{13}NO_4$ (271.3): C, 66.40; H, 4.83; N, 5.16. Found: C, 66.20; H, 4.86; N, 5.33.

Extension of the reaction time to 24 hr yielded a product that was difficult to purify.

Registry No.—**4**, 25109-81-3; **6**, 25109-82-4; **8**, 25109-83-5; **9**, 25109-84-6; **10**, 25109-85-7; **12**, 25109-86-8; **13**, 25109-87-9; **14**, 25158-13-8.

Acknowledgment.—Support of this work by the National Research Council of Canada is gratefully acknowledged.

Synthesis of Bridgehead Functionalized Bicyclo[3.3.1]nonanes

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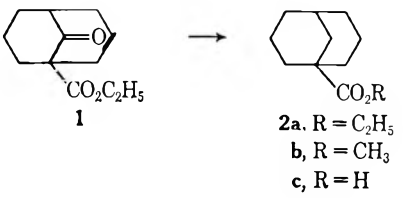
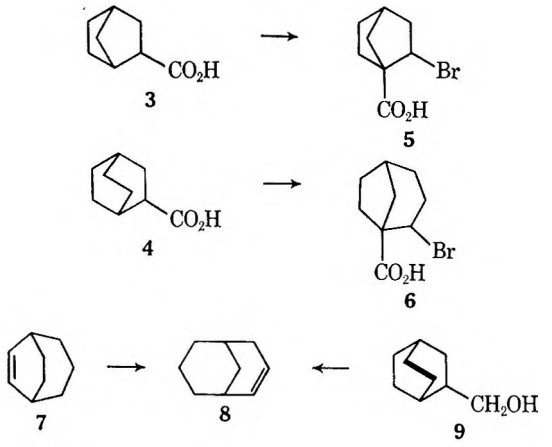
Received December 29, 1969

A wide variety of synthetic routes to the bicyclo[3.3.1]nonane ring system involves annelation of a three-membered bridge to the α positions of a cyclohexanone derivative.[1] Some of these methods[1c-f] have been applied to the synthesis of bicyclononanes functionalized at the bridgehead,[2] and our previous synthesis[3] of 1-ethoxycarbonylbicyclo[3.3.1]nonane (**2a**) is typical, being based on previous work. As we desired a compound functionalized only at the bridgehead, the ester **1** (prepared from acrolein and 2-ethoxycarbonylcyclohexanone[1c,d]) was converted to the ethylene dithioketal which was desulfurized with Raney nickel to give the ester **2a**. While the yields for this procedure are satisfactory, the desulfurization step is cumbersome and somewhat dangerous because of the quantities of Raney nickel which must be handled on large runs. Thus we have sought an alternative method for the synthesis of **2**.



Our alternative synthesis is based on the reports that bicyclo[2.2.1]heptane-2-carboxylic acid[4] (**3**) and bicyclo[2.2.2]octane-2-carboxylic acid[5] (**4**) rearrange when brominated under Hell–Volhard–Zelinsky conditions to give acids **5** and **6**, respectively. Hartmann[6] has shown



(1) For example, see (a) V. Prelog, P. Barman, and M. Zimmermann, *Helv. Chim. Acta*, **32**, 1284 (1949); (b) V. Prelog, P. Barman, and M. Zimmermann, *ibid.*, **33**, 356 (1950); (c) A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, **72**, 5228 (1950); (d) E. W. Colvin and W. Parker, *J. Chem. Soc.*, 5764 (1956); (e) R. P. Nelson and R. G. Lawton, *J. Org. Chem.*, **34**, 1225 (1969); (f) S. Danishevsky, G. Koppel, and R. Levine, *Tetrahedron Lett.*, 2257 (1968); (g) P. W. Hickmott and J. R. Hargraeves, *Tetrahedron*, **23**, 3151 (1967); (h) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5130 (1956); (i) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *ibid.*, **87**, 3130 (1965).

(2) For other routes to bridgehead-substituted bicyclononanes, see (a) W. G. Dauben and C. D. Poulter, *J. Org. Chem.*, **33**, 1237 (1968); (b) P. von R. Schleyer and P. R. Isele, *ibid.*, **33**, 1239 (1968); (c) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, **85**, 1325 (1963); (d) H. Meerwein and W. Schurmann, *Justus Liebigs Ann. Chem.*, **398**, 196 (1913); (e) R. Rabe and M. Jahr, *ibid.*, **360**, 276 (1908).

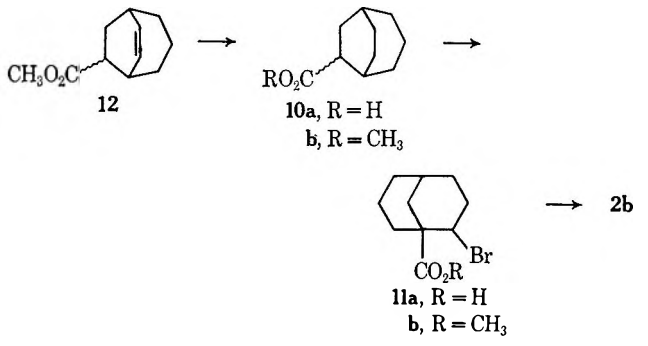
(3) (a) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 956 (1970); (b) J. R. Wiseman, *ibid.*, **89**, 5966 (1967).

(4) (a) W. R. Boehme, *ibid.*, **81**, 2762 (1959); (b) H. Kwart and G. Null, *ibid.*, **81**, 2765 (1959).

(5) A. W. Chow, D. R. Jakas, and J. R. E. Hoover, *Tetrahedron Lett.*, 5427 (1966).

(6) M. Hartmann, *Z. Chem.*, **7**, 101 (1967).

that bicyclo[3.2.2]non-6-ene (**7**) rearranges under acidic conditions to bicyclo[3.3.1]non-2-ene (**8**), and bicyclo[2.2.2]octane-2-methanol (**9**) has been converted to **8** by treatment with phosphoric acid.[7] On the basis of these results we felt that bromination of bicyclo[3.2.2]nonane-6-carboxylic acid (**10a**) would produce 2-bromobicyclo[3.3.1]nonane-1-carboxylic acid (**11a**) as the major product.



Reaction of cycloheptadiene with methyl acrylate[6] produced a 25:75 mixture of the *endo* and *exo* isomers of adduct **12**.[8] Esters **12** were hydrogenated to esters **10b**, which were saponified to acids **10a**. The mixture of acids **10a** melted sharply, but reaction of the purified acids **10a** with diazomethane produced a mixture of esters **10b** close to the original mixture produced by hydrogenation of **12**.

Bromination of acids **10a** in the presence of a catalytic amount of phosphorous tribromide, followed by esterification with methanol, produced the bromo ester **11b** in 58% yield. Debromination of **11b** with zinc in acetic acid produced ester **2b**, identical in all respects with the compound formed when acid **2c**[3] is treated with diazomethane. It is of interest that bromination of the acid chloride of **10a** gave a mixture of at least six products, presumably isomers of both unrearranged bromo esters, and probably including bromo esters with the [4.2.1] skeleton as well. This is similar to the findings of other workers[4a,b] and suggests that rearrangement is more rapid when the carboxylic acid is present. Apparently, slow rearrangement accompanies bromination of the acid chloride, but when the acid **10a** is brominated with a catalytic quantity of phosphorous tribromide, more rapid rearrangement allows equilibration of the bromo acids with formation of the thermodynamically favored bicyclo[3.3.1]nonanyl skeleton.

The sequence described above is comparable in yield to other methods of synthesis of bridgehead-functionalized bicyclo[3.3.1]nonanes, but is clearly superior in convenience and efficiency.

Experimental Section[9]

8-Methoxycarbonylbicyclo[3.2.2]non-6-ene (12).—A mixture of 1,3-cycloheptadiene (17.0 g, 0.185 mol) and methyl acrylate (20 g, 0.232 mol) was heated in a sealed tube at 170° for 150 hr. Distillation of the reaction mixture (62–65°, 0.75 mm) gave 18.6 g (57%) of a 75:25 mixture of the *exo* and *endo* isomers of the unsaturated ester: ir ν_{max} 1740, 1645, 3060, 2020 cm^{-1}; nmr τ 3.8–4.05 (complex, 2 H), 6.35, 6.43 (singlets, 3 H), 7.1–8.65 (complex, 11 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 8.99.

6-Methoxycarbonylbicyclo[3.2.2]nonane (10b).—An *exo*:*endo* (75:25) mixture of **12** (18 g, 0.10 mol) in 200 ml of methanol was hydrogenated on a Parr shaker apparatus using palladium-on-carbon catalyst. Distillation (67–68°, 0.70 mm) gave 17.5 g (96.4%) of saturated ester **10b**: ir ν_{max} 1740 cm^{-1}; nmr τ 6.38, 6.40 (singlets, 3 H), 7.90–8.60 (complex, 15 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.53; H, 9.92.

Bicyclo[3.2.2]nonane-6-carboxylic Acid (10a).—Compound **10b** (16.5 g, 0.091 mol) was stirred at reflux with 100 ml of 15% aqueous sodium hydroxide until complete solution was obtained (*ca.* 3 hr). The solution was cooled in an ice bath and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with ice water, and dried in a vacuum dessicator (25°, 20 mm) overnight to yield 15.3 g (100%) of acid. Compound **10a** sublimes (100°, 1 mm) to give white crystals: mp 63–64°; ir ν_{max} 1710, 3400–3000 (broad) cm^{-1}; nmr τ 7.1–8.8 (complex, 15 H), −1.7 (singlet, 1 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.58.

2-Bromo-1-methoxycarbonylbicyclo[3.3.1]nonane (11b).—Acid **10a** (5.0 g, 0.03 mol) was dissolved in bromine (10 g, 0.063 mol). Phosphorus tribromide (0.75 ml, 0.0079 mol) was then added slowly with stirring. The mixture was heated for 2 hr at 80°, and more bromine (5 g, 0.031 mol) was added. Heating was continued for 8 hr, then excess PBr_3 was added and heating was continued for 1 hr (ir showed complete conversion to acid halide). The cooled mixture was then poured into 65 ml of methanol. Some methanol was removed on the rotary evaporator, and the residue was taken up in ether, washed with 10% sodium bicarbonate (3 × 30 ml) and water (2 × 30 ml), and dried over sodium sulfate. Distillation (105–107°, 1.5 mm) gave 3.9 g (58%) of the bromo ester: ir ν_{max} 1740 cm^{-1}; nmr τ 5.25 (broad singlet, 1 H, width at half height 8 Hz), 6.36, 6.35 (singlets, 3 H), 7.5–9.0 (complex, 13 H).

Anal. Calcd for $C_{11}H_{17}O_2Br$: C, 50.58; H, 6.56; Br, 30.60. Found: C, 50.37; H, 6.37; Br, 30.41.

1-Methoxycarbonylbicyclo[3.3.1]nonane (2b).—Bromo ester **11b** (1.0 g, 0.0038 mol) was dissolved in 14 ml of glacial acetic acid. Zinc dust (2.4 g, 0.037 mol) was added slowly and stirred 1 hr. Water (25 ml) was then added and the mixture was let stand overnight. The suspension was extracted with ether (four 15-ml portions), washed with sodium bicarbonate (two 15-ml portions) and water (two 15-ml portions), and dried over sodium sulfate. The solvent was removed by a rotary evaporator and the product was distilled (66–68°, 0.50 mm) to give 0.51 g (74%) of ester **2b**: ir ν_{max} 1740 cm^{-1}; nmr τ 6.50 (singlet, 3 H), 7.7–8.65 (complex, 15 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.66; H, 9.96.

1-Methoxycarbonylbicyclo[3.3.1]nonane (2b).—Bicyclo[3.3.1]nonane-1-carboxylic acid (**2c**) (1.0 g, 0.006 mol) in 100 ml of ether was treated with an ether solution of diazomethane[10] until the yellow color persisted. The solvent was distilled and the product was isolated by vpc. This ester was identical (ir, nmr, vpc retention time) with the ester prepared by debromination of the bromo ester **11b** as described above.

Registry No.—**2b**, 24825-09-0; **10a**, 19574-12-0; **10b**, 24825-11-4; **11b**, 24825-12-5; *exo*-**12**, 23217-55-2; *endo*-**12**, 23217-53-0.

(7) J. P. Schaefer, L. S. Endres, and M. D. Moran, *J. Org. Chem.*, **32**, 3963 (1967).

(8) The *exo* isomer in the [3.2.2] ring system is the favored isomer by Alder's rule: K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

(9) Infrared spectra were determined in carbon tetrachloride with a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were obtained in carbon tetrachloride solution with TMS as standard with a Varian A-60 spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(10) F. Arndt, "Organic Synthesis," Coll. Vol. 2, Wiley, New York, N. Y., 1943, p 165.

Rearrangement of Allyl Phenyl Ethers

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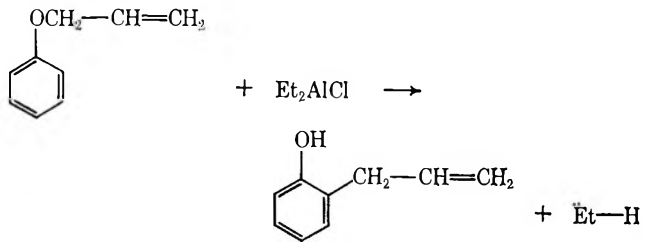
It has been found that allyl phenyl ethers undergo a facile rearrangement in the presence of alkylaluminum halides. Other workers have reported that Lewis acids such as boron trifluoride–acetic acid complex[1] or boron trichloride[2-4] cause an acid-catalyzed Claisen rearrangement. In addition when allyl phenyl ether was treated with aluminum bromide[5] in chlorobenzene, an adduct formed which was believed to have arisen from an intramolecular path in which allyl phenyl ether was first converted to *o*-allylphenol, then isomerized to the propenyl compound, which then adds to chlorobenzene.

Treatment of allyl phenyl ether in hexane with an excess of diethylaluminum chloride at room temperature resulted in the evolution of gas. Gas chromatographic analysis of the gas sample showed that at least 99% was ethane and the remainder ethylene. Decomposition of the reaction mixture with dilute acid afforded *o*-allylphenol in nearly quantitative yield. Gas chromatographic analysis of the isolated product showed that about 97% was *o*-allylphenol.



When ethylaluminum dichloride was substituted for diethylaluminum chloride, the rearrangement also occurred with the evolution of gas. However, a side product, 2-methylcoumaran, began to be formed in increasing amounts as shown in Table I. This additional product was not unexpected, as it had been reported[6] that treatment of *o*-allylphenol with acidic reagents resulted in the formation of 2-methylcoumaran. Treatment of *o*-allylphenol with the aforementioned aluminum alkyls leads to the formation of 2-methylcoumaran.

When the less acidic[7] triethylaluminum was substituted for diethylaluminum chloride, no rearrangement or gas evolution occurred. Use of triisobutylaluminum gave the same results as triethylaluminum, but use of the more acidic diisobutylaluminum chloride resulted in rearrangement without visual gas evolution.

TABLE I
REARRANGEMENT OF ALLYL PHENYL ETHER WITH ALUMINUM ALKYLS[a]

Aluminum alkyl	*o*-Allylphenol,[b] %	2-Methylcoumaran,[b] %
Diethylaluminum chloride	92.7	nil
Ethylaluminum sesquichloride	89.8	2.9
Ethylaluminum dichloride	68.1	18.2
Diisobutylaluminum chloride	95.8	nil

[a] Reaction was carried out as described in the general procedure. [b] Determined by vapor phase chromatographic analysis using a 10% polyphenyl ether (6 ft × 1/8 in.) column at 140–200° programmed at 8°/min.

In contrast to the boron trichloride catalyst,[4] the aluminum alkyl can be used to rearrange allyl aryl ethers bearing electron-withdrawing groups on the aromatic ring, as shown in Table II. Consequently, a detailed study of substituted allyl chlorophenyl ethers was undertaken. Allyl *o*-, *m*- and *p*-chlorophenyl ethers were found to rearrange to allylchlorophenols in nearly quantative yields with the allyl group being ortho to the phenolic group.

TABLE II
REARRANGEMENT OF ALLYL PHENYL ETHERS WITH DIETHYLALUMINUM CHLORIDE[a]

Starting material	Major product	Yield, %
Allyl phenyl ether	*o*-Allylphenol	93
Allyl *o*-chlorophenyl ether	2-Allyl-6-chlorophenol	94
Allyl *m*-chlorophenyl ether	2-Allyl-5-chlorophenol	92
Allyl *p*-chlorophenyl ether	2-Allyl-4-chlorophenol	89
Allyl 2,4-dichlorophenyl ether	2-Allyl-4,6-dichlorophenol	95
Allyl 2,4,5-trichlorophenyl ether	2-Allyl-3,4,6-trichlorophenol	96
2-Alloxypyridine	Starting material	
Allyl phenyl sulfide	Starting material	

[a] Reaction was carried out as described in the general procedure.

When the preferential ortho position for rearrangement is not blocked, as with allyl 2,4,5-trichlorophenyl ether, a normal "Claisen type" rearrangement occurs to form 2-allyl-3,4,6-trichlorophenol in nearly quantitative yield at room temperature when diethylaluminum chloride is used.

When the preferential ortho positions for rearrangement are blocked, as with allyl 2,6-dichlorophenyl ether, two major reactions occur in the presence of diethylaluminum chloride. The first is the rearrangement to form 4-allyl-2,6-dichlorophenol in 43% yield and 5% 2-allyl-4,6-dichlorophenol and the second reaction is cleavage of the allyl group to form 50% 2,6-dichlorophenol. In addition, gas chromatographic analysis showed 2% unreacted starting material.

(1) L. Y. Brynsova and M. L. Ioffe, *J. Gen. Chem. USSR*, **11**, 722 (1941).
(2) W. Gerrard, M. F. Lappert, and H. B. Silver, *Proc. Chem. Soc., London*, **19**, (1957).
(3) P. Fahrni, A. Habich, and H. Schmid, *Helv. Chim. Acta*, **43**, 448 (1960).
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(5) J. C. Petropoulos and D. S. Tarbell, *J. Amer. Chem. Soc.*, **74**, 1249 (1952).
(6) C. D. Hurd and W. A. Hoffman, *J. Org. Chem.*, **5**, 212 (1940).
(7) T. Takeshita and W. E. Frankle, *Tetrahedron Lett.*, **56**, 5913 (1968).

If the preferential positions for migration of the allyl group are blocked, as with allyl 2,4,6-trichlorophenyl ether, cleavage of the allyl group is the major reaction upon treatment with diethylaluminum chloride, to form 2,4,6-trichlorophenol in 96% yield. However, substitution of benzene for hexane as the solvent causes the formation of 35% allylbenzene and 13% 1,2-diphenylpropane as well as a 94% yield of 2,4,6-trichlorophenol. Treatment of allylbenzene in benzene with diethylaluminum chloride results in formation of 1,2-diphenylpropane as the major product.

Other compounds such as 2-alloxypyridine[8] or allyl phenyl sulfide[9] which are known to undergo the thermal Claisen rearrangement failed to rearrange when treated with diethylaluminum chloride at room temperature.

Experimental Section

The nmr spectra were obtained from a Varian HA-100 spectrometer with tetramethylsilane as internal standard. The infrared spectra were taken on a Perkin-Elmer Infracord. The gas chromatograph used for analyzing the composition of the off gases was F & M Model 5750, with a 5 ft × 1/4 in. column containing a 80–100 mesh Porapak S support. The same instrument was used for analyzing the composition of allyl phenyl ether reaction mixture using a 6 ft × 1/8 in. column containing 10% polyphenyl ether on 80–100 mesh Gas Chrom Q support. The allyl chlorophenyl ethers were analyzed with an F & M Model 720 using a 10 ft × 1/4 in. column containing 28.6% Apiezon L on a 60–80 mesh Gas Chrom Z support. The product ratios obtained by glc were derived from the peak area ratios.

The following compounds were prepared according to the procedure of Tarbell and Wilson:[10] allyl *o*-, *m*-, *p*-chlorophenyl ether; allyl 2,4-dichlorophenyl ether; allyl 2,6-dichlorophenyl ether; and allyl 2,4,5-trichlorophenyl ether. The following compounds were prepared by published procedures: allyl 2,4,6-trichlorophenyl ether;[11] 2-allyl-6-chlorophenol;[12] 2-alloxypyridine;[13] and allyl phenyl sulfide.[9] Yields and physical properties were in good agreement with literature values.

Organoaluminum compounds used in this work were purchased from Texas Alkyls. Solvents were purified and dried by conventional methods and distilled prior to use. Reactions involving the organoaluminum reagents were carried out under dry nitrogen with the usual precautions for the rigorous exclusion of moisture and air.

General Procedure.—In a typical procedure, to a solution of 0.01 mol of allyl phenyl ether in 50 ml of hexane was added 0.02 mol of diethylaluminum chloride in hexane. After stirring for 30 min, the reaction mixture was hydrolyzed below 5° with dilute hydrochloric acid. The upper layer was separated and concentrated on a rotary evaporator.

Reaction of Allyl 2,4,6-Trichlorophenyl Ether with Diethylaluminum Chloride. A. In Hexane.—To 23.7 g (0.10 mol) of allyl 2,4,6-trichlorophenyl ether in 500 ml of hexane was added 0.15 mol of diethylaluminum chloride in hexane. After stirring for 3 hr, the reaction mixture was worked up below 5° by hydrolysis with dilute hydrochloric acid. The upper layer was separated and treated with a solution of 10 g of sodium hydroxide in 300 ml of water. The aqueous phase was acidified with dilute hydrochloric acid. The solids were filtered and air dried. There was obtained 18.9 g (95.8%) of 2,4,6-trichlorophenol melting at 65-66° (lit.[11] mp 67°).

B. In Benzene.—The reaction was carried out in the same manner using 400 ml of benzene, except that in the work-up 18.5 g (93.5%) of 2,4,6-trichlorophenol was isolated from the aqueous phase. On distillation of the organic phase through a short fractionating column, there was obtained 4.1 g (34.8%) of liquid, bp 67–70° (20 mm), whose infrared spectrum was identical with that of allylbenzene, and 2.6 g (13.3%) of 1,2-diphenylpropane, bp 90–95° (0.5 mm), whose infrared spectrum was identical with that of an authentic sample, No. 2266 API Research Project 44.

Reaction of Allylbenzene with Diethylaluminum Chloride.—To a well-stirred solution of 11.9 g (0.10 mol) of allylbenzene in 300 ml of benzene was added 0.05 mol of diethylaluminum chloride in benzene. The mixture was kept at 60° for 30 min and stirred for an additional 30 min at room temperature. After hydrolysis below 10° with dilute hydrochloric acid, the upper layer was separated and concentrated on a rotary evaporator. Distillation gave 3.4 g (28.6%) of starting material, bp 60–62° (10 mm), and 3.9 g (39.8%) of 1,2-diphenylpropane, bp 121–125° (4 mm). *Anal.* Calcd for $C_{15}H_{16}$: C, 91.9; H, 8.1. Found: C, 92.0; H, 8.0. There remained behind 3.8 g of higher boiling material.

Registry No.—Allyl phenyl ether, 1746-13-0; diethylaluminum chloride, 96-10-6; ethylaluminum dichloride, 563-43-9; diisobutylaluminum chloride, 1779-25-5; allyl *o*-chlorophenyl ether, 20788-42-5; allyl-*m*-chlorophenyl ether, 24824-86-0; allyl *p*-chlorophenyl ether, 13997-70-1; allyl 2,4-dichlorophenyl ether, 5441-16-7; allyl 2,4,5-trichlorophenyl ether, 16516-83-9; 2-alloxypyridine, 5831-77-6; allyl phenyl sulfide, 5296-64-0; 1,2-diphenylpropane, 5814-85-7.

(8) B. I. Mikhant'ev, E. I. Fedorov, A. I. Kucherova, and V. P. Potapova, *J. Gen. Chem. USSR*, **29**, 1874 (1959).
(9) H. Kwart and C. M. Hackett, *J. Amer. Chem. Soc.*, **84**, 1754 (1962).
(10) D. S. Tarbell and J. W. Wilson, *J. Amer. Chem. Soc.*, **64**, 1070 (1942).
(11) L. C. Felton and C. B. McLaughlin, *J. Org. Chem.*, **12**, 298 (1947).
(12) B. Hoi, H. Ki-Wei and R. Royer. *Bull. Soc. Chim. Fr.*, **12**, 866 (1945).
(13) R. B. Moffett, *J. Org. Chem.*, **28**, 2885 (1963).

Oxidation of Carboxylic Acids and Anhydrides to Symmetrical Esters with Higher Valency Iodine

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Iodine in its higher valency forms can oxidize aliphatic acids or their anhydrides to symmetrical esters and carbon dioxide. The most efficient process involves the use of iodine triacylates and mercuric oxide and produces the corresponding esters in 70–90% yields for unbranched anhydrides. The synthesis is believed to involve a free-radical chain mechanism initiated by a homolytic thermolysis of an iodine–oxygen bond. Mercuric iodate and acid anhydrides also produce esters and, in the presence of olefins or ketones, produce olefinic or ketonic esters. Iodine triacylates are readily obtained by ozonation of solutions of iodine in aliphatic carboxylic acid anhydrides.

Recently, it was reported that tetravalent lead and iodine will oxidize carboxylic acids to symmetrical esters and carbon dioxide in substantial yields.[4] The synthesis was shown to proceed in three separate steps, only the last of which was established and was shown to be a displacement reaction between lead(II) carboxylates and alkyl iodides. The present work was undertaken in an effort to determine the natures of the first two steps in the synthesis and if possible to develop a better synthesis for symmetrical esters.

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(3) Commercial Solvents Corporation Research Assistant, 1966–1968.
(4) G. B. Bachman and J. W. Wittmann, *J. Org. Chem.*, **28**, 65 (1963).

A lead tetracarboxylate will decolorize 0.5 mol equiv of iodine at 60–70° without formation of ester or carbon dioxide, which accords with the following stoichiometry.

$$2Pb(O_2CR)_4 + I_2 \xrightarrow{60\text{–}70^\circ} [(RCO_2)_2PbI(O_2CR)_2]_2 \quad (1)$$

However, the reaction does not stop at this point, since after standing it was possible to isolate iodine triacylates, $(RCO_2)_3I$, from the mixture. Cooling the reaction mixture precipitated a white solid which was very sensitive to moisture and heat but which gave analyses for lead and iodine in a 1:1 atom ratio. Heating the mixture to 100° gave ester, alkyl iodide, carbon dioxide, and lead dicarboxylate in the ratios 1:2:3:2, respectively.

The above experiments suggested to us that the lead(IV) serves the purpose of oxidizing the iodine(0) to iodine(III), and the iodine(III), rather than the lead(IV), oxidizes the carboxyl group. This concept is in accord with the fact that lead(IV) carboxylates give very little ester when heated,[5] while iodine triacylates, $(RCO_2)_3I$, give ester, alkyl iodide, and carbon dioxide in the ratio 1:1:2.[6]

Iodine can be converted to iodine(III) by oxidizing agents other than lead(IV). Of particular interest to us was the report of Beger[7] that ozone reacts with iodine in acetic anhydride to yield a "solvated iodine trioxide complex" of the formula $3(CH_3CO)_2O \cdot I_2O_3$. We have found that the reaction of ozone with iodine in carboxylic acid anhydrides provides an excellent general synthesis for the preparation of iodine triacylates. The composition of iodine triacetate differs only slightly from the composition of Beger's compound.

Thermal decomposition of iodine triacylates prepared by the above method follows the stoichiometry given by Oldham and Ubbelohde,[6] which is shown in eq 2.

$$(RCO_2)_3I \xrightarrow{120^\circ} RCO_2R + RI + 2CO_2 \quad (2)$$

Thus 1.0 mol equiv of iodine ozonated in excess propionic anhydride and heated to 120° produced 1.54 mol equiv each of ethyl propionate and ethyl iodide (yields 77%) and 3.54 mol equiv of carbon dioxide (yield 88.5%).

In an attempt to prepare compounds of the complex type hypothesized in eq 1, various metal iodides were ozonated in acid anhydrides and the resulting mixtures heated to form ester and alkyl iodide. With the iodides of zinc, tin(IV), and lead(II) both ester and alkyl iodide were formed, but with mercury(II) iodide, only ester was formed, and mercuric iodide was regenerated quantitatively. In this case, analysis of the precipitate formed on ozonization showed it to be pure mercuric iodate.

Commercially available mercuric iodate reacts with acid anhydrides according to the following equation.

$$2(RCO)_2O + Hg(IO_3)_2 \xrightarrow{120^\circ} 2RCO_2R + HgI_2 + 2CO_2 + 2O_2 \quad (3)$$

Mercuric iodate (1 mol equiv) in excess propionic anhydride produced 1.88 mol equiv (94% yield) of ethyl propionate, while in excess octanoic anhydride it produced 0.92 mol equiv (46% yield) of heptyl octanoate and 0.60 mol equiv of heptane.

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(6) J. W. H. Oldham and A. R. Ubbelohde, *J. Chem. Soc.*, 368, 1941.
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Since mercuric iodate alone does not evolve oxygen at temperatures below about 175°, it is probable that the anhydride produces an intermediate species which is less stable to oxygen elimination that is mercuric iodate itself.

A series of experiments demonstrated the unique ability of iodine among the halogens to generate esters. Thus mercuric bromate or chlorate gives no esters with acid anhydrides unless mercuric iodide or iodate is also present. This may correlate with the fact that iodine alone among the halogens exhibits a +3 oxidation state in which there are ten electrons in the outer shell of the iodine atom.[8] On the other hand, iodine is not unique in its ability to oxidize carboxylic acids to alkyl halides. This is evident from the success of the Hunsdiecker reaction,[9] the Kochi reaction,[10] and the Cristol and Firth reaction[11] in the synthesis of alkyl halides. Simonini[12] has shown that the Hunsdiecker reaction may be adapted to the synthesis of esters if iodine is used

$$2RCO_2Ag + I_2 \longrightarrow RCO_2R + CO_2 + AgI \quad (4)$$

and we have shown that the Cristol and Firth reaction may also be adapted to the synthesis of esters if iodine and acid anhydride are used.

$$(RCO)_2O + HgO + I_2 \longrightarrow RCO_2R + CO_2 + HgI_2 \quad (5)$$

The yield of butyl valerate from valeric anhydride was 50% based upon iodine in the above equation.

It would appear that these two different types of decarboxylative oxidation reactions require two different oxidation states in the halogen atom, and that iodine alone is capable of generating esters.

Oxidation of acid anhydrides to esters with mercuric iodate suffers from certain disadvantages. In the first place, two-thirds of the available oxygen is lost as free oxygen, and in the second place the yields of ester decrease markedly among the higher anhydrides due to side oxidation reactions leading to the next lower aldehydes and acids. We have, therefore, developed a process of ester formation involving trivalent iodine for the decarboxylative oxidation and mercury for iodine scavenging.

When iodine dissolved in an acid anhydride (with or without added inert solvent) is ozonated, an equivalent amount of mercuric oxide added, and the mixture is heated to 120°, esters are formed in good yields even from the higher aliphatic acid anhydrides (Table I).

$$3(RCO)_2O + I_2 + 3O_3 \longrightarrow 2(RCO_2)_3I + 3O_2 \quad (6)$$

$$2(RCO_2)_3I + HgO \longrightarrow 3RCO_2R + 3CO_2 + {}^1/_2O_2 + HgI_2 \quad (7)$$

Branching at the α position sharply diminishes the yield of ester and the reaction fails with aromatic acid anhydrides. The high ratio of ester formed to mercury and iodine used (3:1) and the high yields of ester realized make this the method of choice for the synthesis of symmetrical esters among those studied.

Mechanistic Considerations.—Symmetrical ester formation in all of these processes is probably initiated by

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(9) C. Hunsdiecker and H. Hunsdiecker, *Chem. Ber.*, **75**, 291 (1942); see also R. Adams, *Org. React.*, **9**, 348 (1957).
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(11) S. J. Cristol and W. C. Firth, Jr., *ibid.*, **26**, 280 (1961).
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TABLE I
SYMMETRICAL ESTERS PRODUCED FROM THE REACTION OF ANHYDRIDES WITH IODINE AND OZONE, FOLLOWED BY THERMAL DECOMPOSITION IN THE PRESENCE OF MERCURIC OXIDE

Anhydride[a]	CO_2, mol equiv	Ester, mol equiv	Yield, %
Propionic	2.68	Ethyl propionate, (2.56)	85.5
Valeric[b]	2.98	Butyl valerate, (2.28)	76
Caproic	2.94	Amyl caproate, (2.72)	91
Octanoic[c]	2.76	Heptyl octanoate, (2.20)	73.5
Stearic[d]		Heptadecyl stearate, (2.06)	69
2-Methylbutyric[c]	2.36	*sec*-Butyl 2-methylbutyrate, (0.52)	17.3
Pivalic	2.00	*t*-Butyl pivalate, (0.46)	15.4
Benzoic[c]		Phenyl benzoate	Trace[e]

[a] The anhydride was present in tenfold molar excess except where otherwise noted; 1.0 mol equiv of iodine was present in each case. [b] 1,1,2,2-Tetrachloroethane as solvent. [c] Anhydride present in eightfold molar excess. [d] 3.0 mol equiv of anhydride present; 1,2,3-trichloropropane as solvent. [e] Iodobenzene (46%) obtained; yield based on iodine.

homolytic thermolysis of an oxygen–iodine bond. The following series of reactions is in accord with the known facts.

Initiation

$$(RCO_2)_3I \longrightarrow RCO_2\cdot + (RCO_2)_2I\cdot \quad (8)$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \quad (9)$$

Propagation

$$R\cdot + (RCO_2)_3I \longrightarrow RCO_2R + (RCO_2)_2I\cdot \quad (10)$$

$$(RCO_2)_2I\cdot \longrightarrow RCO_2\cdot + RCO_2I \quad (11)$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \quad (12)$$

$$RCO_2I \longrightarrow RCO_2\cdot + I\cdot \quad (13)$$

Termination

$$R\cdot + I\cdot \longrightarrow RI \quad (14)$$

$$HgO + 2I\cdot \longrightarrow HgI_2 + {}^1/_2O_2 \quad (15)$$

In an attempt to capture the proposed alkyl radical intermediates, iodine tricaproate was decomposed in the presence of an excess of nitrogen dioxide.

$$\underset{(1.0)}{(RCO_2)_3I} + \underset{(xs)}{NO_2} \longrightarrow \underset{(0.82)}{RI} + \underset{(0.50)}{RNO_2} + \underset{0.28)}{RCO_2R} + CO_2 \quad (16)$$

The mole equivalents of reactants and products (in parentheses) indicate that the amyl radicals converted to 1-nitropentane are derived primarily from those yielding amyl caproate rather than those leading to amyl iodide formation, since the yield of ester is diminished more than that of the alkyl iodide.

Mercuric Iodate as an Oxidizing Agent.—In addition to its action on acid anhydrides alone, mercuric iodate reacts with active methylene groups in the presence of acid anhydrides to form acyloxy derivatives. Thus cyclohexanone, propionic anhydride, and mercuric iodate react to produce α-propionoxycyclohexanone and propionic acid. Reaction of cyclohexene, propionic anhydride, and mercuric iodate affords 2-cyclohexenyl propionate, and 1-octene yields two isomeric esters, *trans*-2-octenyl propionate, and 1-octen-3-yl propionate. The mixture of esters obtained in the latter reaction indicates the formation of an octenyl species free enough to isomerize before uniting with a propionoxy group to produce the observed esters.

Experimental Section

Apparatus.—A Welsbach Style T-23 Oxonator was employed as the source of ozonized oxygen (110 V, 6.0 psi O_2, flow rate 0.005–0.020 ft³/min).

Analysis by Glpc.—Throughout this work many of the conversions and yields reported were calculated from vpc analyses using the common thermal conductivity correction factor method. An Aerograph Model A-350-B dual column temperature gas chromatograph and an F & M Model 720 dual column temperature programmed gas chromatograph, fitted with the appropriate columns, were employed. Butyl valerate and heptyl octanoate were analyzed on a 6.0-ft 10% FFAP liquid phase on Chromosorb W DMCS A/W column. All other esters were analyzed on either a 6.0-ft or a 9.0-ft 10% diisodecyl phthalate liquid phase on Chromosorb W DMSC A/W column. Products were identified by comparison of gas chromatographic retention times and infrared and nuclear magnetic resonance spectra with those of authentic samples. Where necesssary, mass spectral analyses were also obtained.

Materials.—All anhydrides employed were carefully distilled and exhibited not more than a 2° boiling point range. Mercuric iodate was obtained from the City Chemical Corporation of New York and dried over phosphorus pentoxide. This product gave poorer yields than ozonized mercuric iodide unless about 1% of iodine pentoxide was added to it.

Reaction of Lead Tetraacetate with Iodine.—Iodine (0.005 mol) was dissolved in warm (40–60°) trichloroethylene, lead tetraacetate (0.01 mol) was added with stirring, and the solution was allowed to stand overnight protected from atmospheric moisture. The white precipitate was separated by filtration and found to be extremely sensitive to moisture, turning brown in a few minutes when exposed to the air of the laboratory. Analyses showed an iodine:lead ratio of 1:1, but the results varied considerably with the details of preparation including the relative amounts of reactants and solvent. Heating of either the precipitate or the filtrate to 120° produced variable ratios of methyl acetate and methyl iodide. From a similar reaction of iodine and lead tetrastearate in carbon tetrachloride was isolated by concentration of the filtrate a small amount of iodine tristearate, mp 45–50°, CO_2 evolution at 100°, infrared absorption maxima at 7.25, 8.24, and 8.90 μ, similar constants to those reported previously.[6]

Preparation and Decomposition of Iodine Tripropionate.—In a flask equipped with a Dry Ice–acetone reflux condenser, an ozone inlet tube extending to the bottom of the flask, and a magnetic stirring bar, were placed 0.077 mol of propionic anhydride and 0.013 mol of iodine. Ozonized oxygen was passed through the stirred solution at 0°. The ozonation was deemed complete when the characteristic color of iodine had been discharged and replaced by yellow iodine tripropionate suspended in the solution. The ozone inlet tube was replaced by a ground-glass stopper. The small amount of yellow solid which adhered to the inlet tube turned dark brown and liberated iodine within 30 sec after exposure to the atmosphere. The Dry Ice–acetone reflux condenser was attached to a wet-test meter previously saturated with carbon dioxide. The stirred solution was then heated: a sudden and rather vigorous evolution of gas occurred at 120°. Gas evolution was completed within 5 min and a light wine-colored solution was obtained. Carbon dioxide, 0.046 mol (87.5% yield), was evolved. Vpc analysis revealed that 0.020 mol (77% yield) each of ethyl propionate and ethyl iodide were produced.

Ozonization of Metal Iodides in Acid Anhydrides and Thermal Decomposition of Products.—The metal iodide, 0.01 mol, was suspended in 20.0 g (excess) of the acid anhydride and ozonized with a 25% excess of the calculated amount of ozone. The re-

sulting mixture was heated at 120° under reflux until carbon dioxide evolution ceased, cooled, and filtered, and the filtrate was analyzed for ester and alkyl iodide. Using acetic anhydride, the following percentage yields were obtained per atom of iodine: ZnI_2, 16, 21; SnI_4, 87, 67; using butyric anhydride, PbI_2, 58, 24.

Mercuric iodide gave ester but very little or no alkyl iodide when employed in the above process. The precipitate formed upon ozonization of mercuric iodide in excess propionic anhydride was isolated by suction filtration, washed several times with carbon tetrachloride, and dried.

Anal. Calcd for $Hg(IO_3)_2$: Hg, 36.44; I, 46.12. Found: Hg, 36.28; I, 46.12.

Reaction of Propionic Anhydride with Mercuric Iodate.—In a flask equipped with a Dry Ice–acetone reflux condenser, a nitrogen inlet tube with a stopcock, and a magnetic stirring bar, were placed 0.050 mol of propionic anhydride and 0.0050 mol of mercuric iodate. A weighed Ascarite trap for carbon dioxide absorption was attached to the reflux condenser. A wet-test meter was attached to the Ascarite trap. Air was swept from the system by a stream of nitrogen. The stirred solution was heated until gas evolution ceased (0.0170 mol evolved), cooled to room temperature, and the wet-test meter was disconnected. The reaction flask was immersed in a Dry Ice–acetone bath, the nitrogen inlet tube stopcock was opened, and the residual gaseous product was swept through the Ascarite trap. Carbon dioxide, 0.0099 mol (99% yield), was found. The difference between total gas evolution, as measured by the wet-test meter, and carbon dioxide evolution, as measured by the Ascarite trap, was 0.0071 mol, a 72% yield of oxygen (identified by mass spectrometry). Quantitative vpc analysis of the liquid reaction mixture showed ethyl propionate, 0.0094 mol (yield 87% based on propionic anhydride), to be present. The reaction mixture was filtered and the filtrate was titrated to a phenolphthalein end point with standardized sodium hydroxide. Unreacted propionic anhydride, determined as propionic acid, 0.039 mol, was found. Air drying of the filtered solid yielded 0.0047 mol (94% yield) of mercuric iodide.

Reaction of Valeric Anhydride with Mercuric Oxide and Iodine.—In a flask equipped with a condenser, a pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar, were placed 15 ml of 1,2-dibromoethane, 0.050 mol of valeric anhydride, and 0.050 mol of red mercuric oxide. A solution of 0.050 mol of iodine dissolved in 71 ml of 1,2-dibromoethane was place in the dropping funnel. The slurry of valeric anhydride and mercuric oxide was heated with stirring, and the solution of iodine in 1,2-dibromoethane was slowly added. A temperature of 100° was required to decolorize the iodine. Gas evolution accompanied the decolorization. At the end of the iodine addition, gas evolution ceased and a clear solution containing red mercuric iodide was obtained. Vpc analysis revealed the presence of 0.025 mol of butyl valerate. Based upon iodine, the yield is 50%. Butyl iodide was not present.

Decomposition of Iodine Tricaproate in the Presence of Mercuric Oxide.—A mixture of 0.025 mol of caproic anhydride and 0.0025 mol of iodine was ozonized, red mercuric oxide, 0.0026 mol, was added, and the stirred solution was heated. At 120° a sudden and vigorous evolution of gas occurred, accompanied by the appearance of free iodine throughout the solution. Within 60 sec, gas evolution ceased and the free iodine color disappeared. Yellow mercuric iodide soon precipitated from the colorless solution; upon cooling, the red crystalline modification was formed. Carbon dioxide, 0.0074 mol, was evolved. Vpc analysis revealed the presence of 0.0068 mol (91% yield) of amyl caproate.

The above procedure, with only minor modification, was employed for all the liquid anhydrides studied. In the case of the solid stearic anhydride, stoichiometric amounts of anhydride and iodine were employed in the solvent 1,2,3-trichloropropane, and the mercuric iodide was separated from the heptadecyl stearate by thorough washing with aqueous KI.

When mercuric oxide was replaced by lead(II) oxide in the above reaction, alkyl iodide but no ester was formed. With red lead (Pb_3O_4), both ester (36% yield) and alkyl iodide were obtained.

Decomposition of Iodine Tricaproate in the Presence of Excess Nitrogen Dioxide.—A suspension of iodine tricaproate in caproic anhydride was prepared as described immediately above. The ozone inlet tube was replaced with a nitrogen dioxide inlet tube, and excess nitrogen dioxide was passed into the solution. The solution was heated with stirring and maintained at 130–135° for 30 min. The solution was cooled to room temperature and analyzed by vpc. Amyl iodide, 0.0041 mol (82% yield), amyl caproate, 0.0014 mol (28% yield), and 1-nitropentane, 0.0050 mol (25% yield), were obtained. Yields are based on the following equation.

$$(C_5H_{11}CO_2)_3I + NO_2 \longrightarrow \underbrace{C_5H_{11}I + C_5H_{11}CO_2C_5H_{11} + 2C_5H_{11}NO_2}_{1\text{ mol}} + 2CO_2$$

Reaction of Mercuric Iodate and Propionic Anhydride with Active Methylene Compounds.—A mixture of 0.010 mol each of propionic anhydride and cyclohexanone and 0.0035 mol of mercuric iodate was maintained at 135–140° under reflux for 12 hr. Upon cooling, a light wine-colored solution containing red mercuric iodide was obtained. Vpc analysis of the solution revealed ethyl propionate to be absent. The only major reaction products were α-propionoxycyclohexanone, 0.0022 mol (31% yield), and propionic acid.

Replacement of cyclohexanone with cyclohexene under the same reaction conditions afforded 0.0017 mol (24% yield) of 2-cyclohexenyl propionate and propionic acid as the only major reaction products.

Replacement of cyclohexanone with 1-octene produced 0.0015 mol (21% yield) of 1-octen-3-yl propionate, 0.0020 mol (29% yield) of *trans*-2-octenyl propionate, and propionic acid as the only major reaction products. These products were identified by ir, nmr, and mass spectra determined on samples isolated by vpc.

Registry No.—Ozone, 10028-15-6; propionic anhydride, 123-62-6; valeric anhydride, 2082-59-9; caproic anhydride, 2051-49-2; octanoic anhydride, 623-66-5; stearic anhydride, 638-08-4; 2-methylbutyric anhydride, 1519-23-9; pivalic anhydride, 1538-75-6; benzoic anhydride, 93-97-0; iodine tripropionate, 24824-83-7; mercuric iodate, 7783-32-6; mercuric oxide, 1344-45-2; iodine, 7553-56-2; iodine tricaproate, 24824-84-8.

Optically Active 1,2-Naphthalene Oxide

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Valence tautomerism in unsaturated medium ring systems is an area of considerable current interest.[2] Certain arene oxides (benzene oxide,[3] 3,4-toluene oxide[4]) exist as equilibrium mixtures of oxide and oxepin forms, while others appear to exist solely in either the oxide (8,9-indan and 9,10-tetralin oxide)[5] or the oxepin form (1,2-dimethyl-1,2-benzene oxide[6]). Spectroscopic studies on 1,2-naphthalene oxide (1) suggest that it exists solely in the oxide form but do not exclude the possibility of an equilibrium between 1 and 2 which greatly favors 1. If such an equilibrium does not exist or if it exists and the interconversion rate is slow, 1

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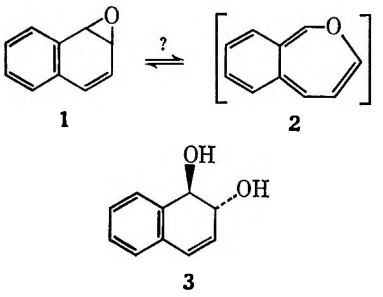
should be isolable in optically active forms. Discrete optical enantiomers of **1** were indeed inferred from the microsomal metabolism of **1** and naphthalene. Monooxygenases oxidize napthalene to **1** which is rapidly converted to (−)-*trans*-1,2-dihydroxy-1,2-dihydronaphthalene (**3**) by a stereospecific epoxide hydrase.[7−9]

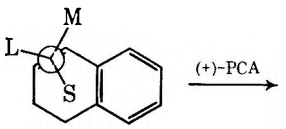


1 **2**

3

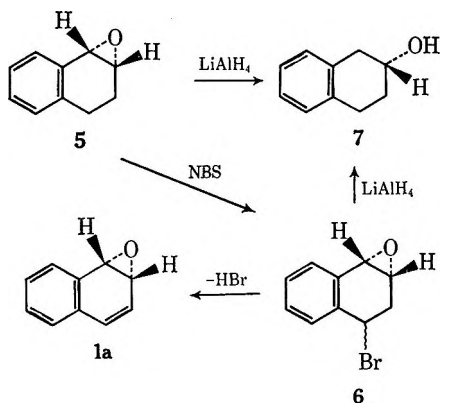
The optical activity associated with **3** is ~10% lower when racemic **1** is employed in place of enzymatically generated **1** from naphthalene as the substrate for the epoxide hydrase. This suggests an asymmetric synthesis of an arene oxide by microsomal monooxygenases. Testing this hypothesis directly is not practical since enzymatically synthesized **1** is not accessible in sufficient quantity.[9]

The route to optically active **1** followed the original synthesis of racemic material[10] with the exception that optically active 1,2-dihydronaphthalene oxide (**5**) was used. The latter was prepared by (+)-peroxycamphoric acid (PCA) oxidation of 1,2-dihydronaphthalene (**4**). Bromination with N-bromosuccinimide (NBS)



4

L, M, S refer to groups in (+)-PCA of decreasing size



5 **7** **1a** **6**

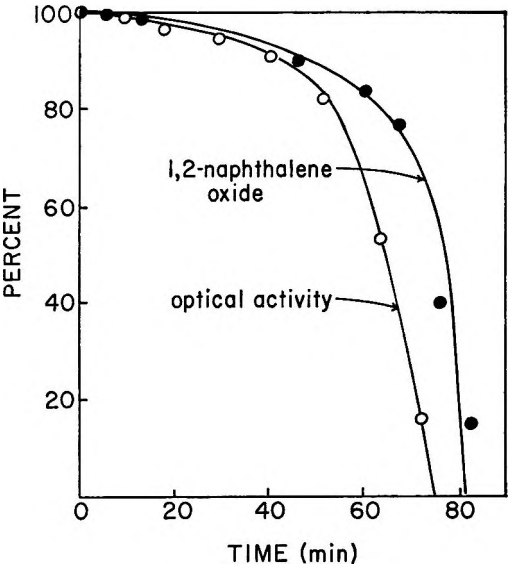


Figure 1.—Per cent remaining optical activity (○) and 1,2-naphthalene oxide (●) with time in the presence of acetic acid.

yielded (−)-1-bromo-1,2-dihydronaphthalene-3,4-oxide (**6**). Reduction of **5** and **6** with $LiAlH_4$ provided (+)-(2*S*)-2-tetralol (**7**)[11] of 5 and 10% optical purity, respectively. The increased optical purity of **6** relative to **5** was the result of fractional crystallization. The major optical antipode produced in the (+)-PCA oxidation is consistent with that predicted from consideration of the lowest energy transition state for the reaction[12] (see **4**). Dehydrohalogenation[9] of **6** produces optically active **1a** in high yield (85%). The optical purity of **1a** was assumed to be ~10%. Optical rotatory dispersion on **1a** and **5** show simple negative plain curves above 285 and 240 mμ, respectively.

Measuring the optical stability of **1a** is complicated by the chemical instability of the compound. Naphthalene oxide readily isomerizes to naphthol in the presence of heat or weak acids such as naphthol. Thermal isomerization such as that studied for carbocyclic systems[13] could not be attempted because of the rapid isomerization of **1a** to naphthol in methanol at 50°. However, **1a** is both optically and chemically stable at −80°. Initial experiments showed complete chemical and optical stability for 24 hr in $CHCl_3$ and 8 hr in CH_3OH at 20°. Addition of a trace of acetic acid to methanolic solution of **1a** caused complete loss of optical activity within 1.5 hr (Figure 1) along with a parallel formation of naphthol. The data (Figure 1) suggest that loss of optical activity proceeds at a slightly greater rate than naphthol formation. This is particularly true during the naphthol-catalyzed portion of the reaction and thus may indicate some racemization. Addition of a small amount of methanolic KOH to a CH_3OH solution of **1a** causes racemization without isomerization to naphthol or formation of other products (see Experimental Section). Methanolic acetamide caused neither racemization nor isomerization over a period of several hours, which was surprising, since benzene

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oxide and 8,9-indane oxide rapidly rearrange to phenols in aqueous acetamide.[14,15]

The results presented here demonstrate that **1** can be prepared optically active. In addition, the absolute stereochemistry has been related to the sign of rotation for compounds **1**, **5**, and **6**. Preliminary studies with epoxide hydrase demonstrate that optical activity in **1a** is reflected in the optical activity of **3** obtained by enzymatic hydration, thus providing further evidence that the microsomal formation of **1** from naphthalene[7-9] is, in fact, an asymmetric synthesis, which forms (+)-(1*R*,2*S*)-1,2-naphthalene oxide of less than 10% optical purity.

Experimental Section

General.—All compounds synthesized were judged pure by nmr spectra and chromatographic properties as compared to those of the known, optically inactive materials. Glassware used in connection with **1a** was soaked in Na_2CO_3 solutions, washed repeatedly with distilled water, and dried to prevent acid-catalyzed isomerizations. Rotations were measured at 20° with a Perkin-Elmer 141 Polarimeter using a 10-cm cell holding 2 ml of solvent. During studies on racemization of **1a**, small aliquots (5–10 μl) were removed at intervals to measure the ratio of **1a** to naphthol by uv spectroscopy. For the acid-catalyzed reaction, the cell contained 24.2 mg of **1a** and 10 μl of HOAc in 2.0 ml of CH_3OH (data in Figure 1). For the base-catalyzed racemization, the cell contained 12.1 mg of **1a** and 10 mg of KOH in 2.0 ml of CH_3OH. In the later experiment, the rotation decreased 25% in a linear fashion during a 20-hr period.

(−)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene (5).—A cold solution (0°) of (+)-peroxycamphoric acid (30.0 g, 0.148 mol) in 200 ml of $CHCl_3$ was added dropwise (0.5 hr) to stirred suspension of anhydrous sodium carbonate (8.0 g) and 1,2-dihydronaphthalene (13.6 g, 0.10 mol) in 100 ml $CHCl_3$ at −28°. The resulting mixture was stored at −20° for 4 weeks, filtered to remove solids, washed with sodium sulfite and sodium carbonate solutions, dried (Na_2SO_4), and concentrated to a small volume. Distillation [bp 55–62° (0.3–0.4 mm)] provided 7.2 g (49%) of **5** with $[\alpha]_{589}$ −6.1°, $[\alpha]_{365}$ −20.1° (*c* 9, $CHCl_3$). Lithium aluminum hydride reduction of **5** followed by distillation [67–70° (0.2 mm)] of the product after hydrolysis gave (+)-(2*S*)-2-tetralol[11] with $[\alpha]_{589}$ +3.3°, $[\alpha]_{365}$ +11.5° (*c* 10, $CHCl_3$), 5% optical purity. Thus, **5** is (−)-(1*S*,2*R*)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene with 5% optical purity.

(−)-4-Bromo-1,2-epoxy-1,2,3,4-tetrahydronaphthalene (6).—N-Bromosuccinimide halogenation of **5** was conducted as previously described (47% yield, mp 94–95°, lit.[10] racemate 94–95°). The resulting product, **6**, was fractionally crystallized from ethyl acetate. The first crop had $[\alpha]_{589}$ −19.0°, $[\alpha]_{436}$ −50.5° (*c* 10, $CHCl_3$). Later fractions with lower rotations were discarded. Lithium aluminum hydride reduction of **6** followed by distillation [bp 70° (0.2–0.3 mm)] of the product after hydrolysis gave (+)-(2*S*)-2-tetralol with $[\alpha]_{589}$ +6.7°, $[\alpha]_{365}$ +24.0° (*c* 10, $CHCl_3$), 10% optical purity. Thus **6** is (−)-(1*S*,2*R*)-1,2-epoxy-4-bromo-1,2,3,4-tetrahydronaphthalene with 10% optical purity.

(−)-1,2-Naphthalene Oxide (1a).—Dehydrohalogenation of **6** was conducted as previously described[10] (75–85% yield), producing **1a** with $[\alpha]_{589}$ −11.7°, $[\alpha]_{368}$ −73.2° (*c* 2, $CHCl_3$). Racemization did not occur under the conditions of this reaction, since extending the time for dehydrohalogenation did not decrease the optical activity of the product. The absolute stereochemistry (1*S*,2*R*) and optical purity (10%) are based on **5**. Samples were stored at −80°.

Registry No.—**1a**, 24825-00-1; **5**, 24825-01-2; **6**, 24825-02-3.

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Bridged Polycyclic Compounds. LXIII. Reductive Ring Opening of 3,6-Dibenzotricyclo[3.3.0.0^{2,8}]octadiene[1]

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Although the initial report of the formation of a radical anion from cyclopropane[3] seems to have been incorrect,[4,5] considerable interest in substituted cyclopropane radical anions has been generated. Walborsky and Pierce[6] proposed a cyclopropane radical anion as a transient intermediate in the ring cleavage of 1-methyl-2,2-diphenylcyclopropane by sodium in liquid ammonia. Since they were unable to observe an esr signal, they proposed that the radical anion initially formed suffered rapid ring cleavage and electron-transfer reactions. Miller and Jacoby[7] found that very rapid cyclopropane ring opening occurred in the reduction of dibenzonorcaradiene with alkali metal in 1,2-dimethoxyethane (DME). Winstein and coworkers[8] and Katz and Talcott[9] concluded (from esr data) that the cyclopropane ring was partially broken in the radical anion derived from *cis*-bicyclo[6.1.0]nonatriene; however, there was no evidence for ring opening in the radical anion derived from *trans*-bicyclo[6.1.0]condiene.[10] Papa[11] has reported the esr spectrum of the radical anion of 1,2,3-tricyano-1,2,3-tricarboethoxycyclopropane. A series of cyclopropyl-substituted aromatic radical anions[12,13] and semidiones[14] have been reported, but extensive delocalization of π spin density onto the cyclopropane ring was not observed.

Treatment of a 0.1 *M* solution of 3,6-dibenzotricyclo[3.3.0.0^{2,8}]octadiene (**1**)[15] in dry, deoxygenated DME with freshly cut sodium or potassium metal at 0° yielded a dark red solution within a short time. A similar solution was produced instantaneously when a solution of **1** in DME was treated with a solution of sodium biphenyl or sodium naphthalene radical anion.

It was demonstrated by esr spectroscopy that the red solution was not paramagnetic. Only with concentrated solutions of **1** (>0.1 *M*) in the presence of an excess of sodium–potassium alloy (DME, −40°) was an esr signal detected. The esr signal was very weak

(1) Previous paper in series: S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, **92**, 4013 (1970).
(2) National Institutes of Health Postdoctoral Fellow, 1969–1970.
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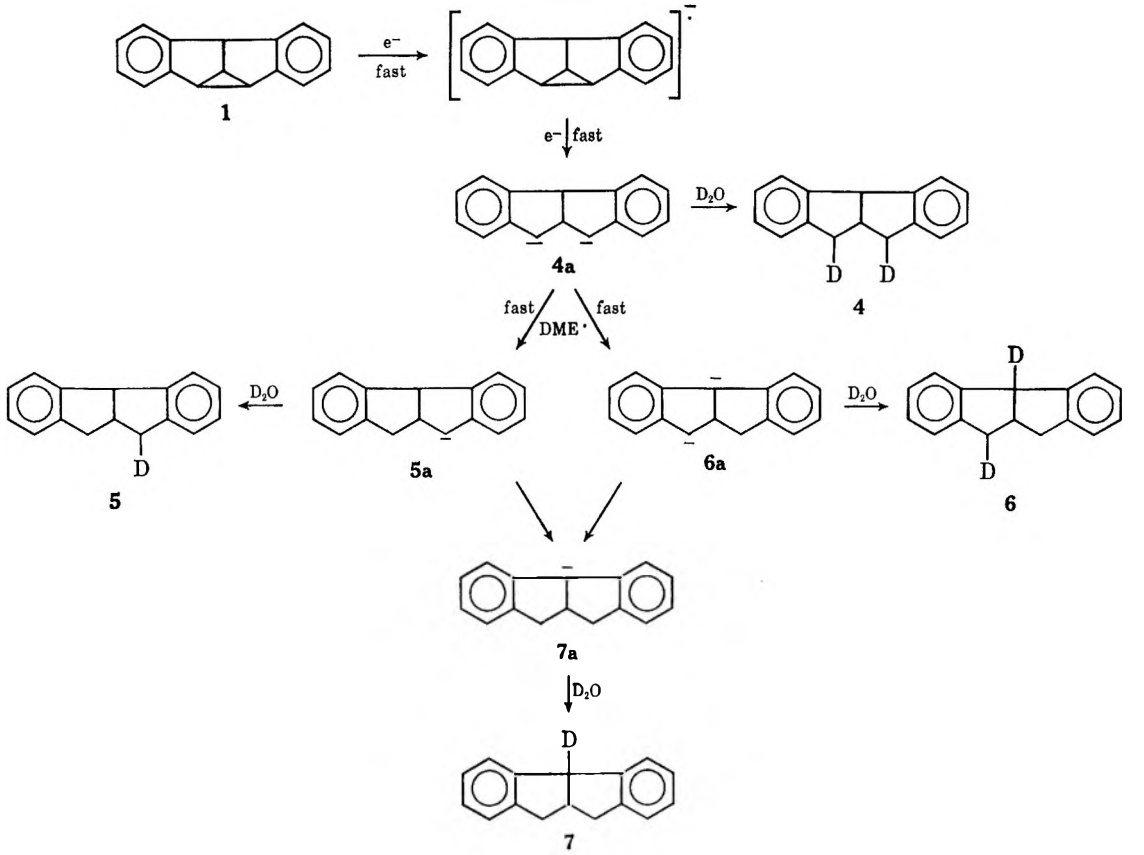
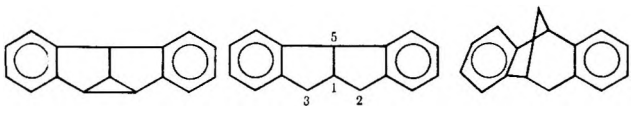
SCHEME I



and could be only partially resolved (total spectrum width was about 23 G), presumably due to line broadening by rapid electron exchange in the concentrated solutions. Numerous attempts to generate the radical anion of **1** by reaction of a solution of **1** with a sodium or potassium mirror in DME or tetrahydrofuran (THF) at −78° (standard high-vacuum techniques)[16] led only to the diamagnetic red solution. When a solution of sodium biphenyl was treated with a fourfold excess of **1** in DME at −78°, only the biphenyl radical anion could be detected by esr. When this latter solution was warmed above −40°, the red diamagnetic solution was produced.

When **1** was treated with sodium biphenyl in DME at 0° and the resulting red solution was quenched with water, the only volatile products were biphenyl, 3,6-dibenzobicyclo[3.3.0]octadiene (**2**),[17,18] and **1**. No dibenzobicyclo[3.2.1]octadiene (**3**) was detected. The



1 **2** **3**

ratio of 2:1 was dependent upon the initial ratio of sodium biphenyl to **1**. When the molar ratio of sodium biphenyl to **1** was 2:1 or greater, only **2** and biphenyl were observed (*i.e.*, 2 mol of sodium biphenyl convert 1 mol of **1** to 1 mol of **2**).

When deuterium oxide was used to quench the reactions of **1** with sodium biphenyl, deuterium was incorporated at C-2, C-8, and C-5 of **2** (no deuterium was detected in the recovered **1**). Typical deuterium incorporation data are shown in Table I. The reductive

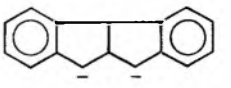
TABLE I

DEUTERIUM INCORPORATION IN DIBENZOBICYCLO[3.3.0]OCTADIENE[a]

Reaction time	Observed ratio, 2:1	Deuterium incorporation in 2[b] C-5	C-2 + C-8
10 sec	0.63	0.1	1.4
30 sec	0.71	0.1	1.4
10 min	0.83	0.2	1.0
2 hr	0.83	1.0	0.0

[a] Formed by reaction of equimolar amounts (~0.1 *M* solutions) of **1** and sodium biphenyl in DME at 0°; quenching with deuterium oxide. [b] Deuterium analysis by pmr integration (relative to eight aromatic hydrogens).

ring opening of **1** appears to involve the dianion **4a**



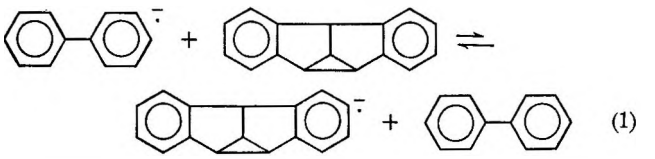
4a

since quenching with deuterium oxide after very short reaction times gave a large fraction of **2** with two deuterium atoms at C-2 and C-8. When the reactions were quenched with deuterium oxide after longer reaction times, lesser deuterium incorporation was observed at C-2 and C-8, but very significant deuterium incorporation was observed at C-5 (after a 2-hr reaction period, quenching with deuterium oxide gave **2** with no deuterium atoms at C-2 and C-8, but with 1.0 deuterium atom at C-5).

An analysis of the described results leads us to postulate the mechanistic scheme in Scheme I. At 0°, ring

(16) D. Casson and B. J. Tabner, *J. Chem. Soc. B*, 887 (1969).
(17) W. Baker, J. F. W. McOmie, S. D. Parfitt, and D. A. M. Watkins, *ibid.*, 4026 (1957).
(18) S. J. Cristol and B. B. Jarvis, *J. Amer. Chem. Soc.*, **89**, 401 (1967).

opening and further reduction (or *vice versa*) of the transient radical anion to the dianion **4a** must be extremely facile and irreversible. Thus, in the reaction of sodium biphenyl with **1**, the reaction (eq 1) is driven from left to right by the formation of **4a**. Jagur-

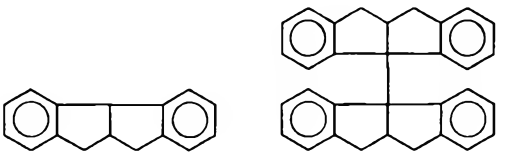


(1)

Grodzinski and Szwarc[19] have recently shown in related systems that equilibria, such as eq 1, greatly favor the radical anion of the hydrocarbon with the higher electron affinity. If biphenyl has a significantly higher electron affinity than **1**, the equilibrium (eq 1) should greatly favor biphenyl radical anion and no overall reaction would be observed in the absence of secondary processes (*e.g.*, formation of **4a**). At −78°, the ring opening must be extremely slow and overall electron transfer from sodium biphenyl to **1** cannot be detected. When an alkali metal mirror was used as the reductant, ring opening occurred even at −78° and must have taken place on the metal surface.

The dianion **4a** is very unstable (significant amounts of **4** were formed only if the reaction was quenched after very short reaction times), possibly because of the close proximity of the two negatively charged centers, and reacts very rapidly, either by proton abstraction from the solvent to give **5a** or by rearrangement to **6a**. Both **5a** and **6a** appear to be converted to **7a**, since quenching with deuterium oxide after long reaction times led to **7** as the only dibenzobicyclo[3.3.0]octadiene isolated. That **7a** is not only more stable than **5a**, but also more accessible kinetically, was demonstrated by the reaction of **2** with potassium *t*-butoxide in hexadeuteriodimethyl sulfoxide (DMSO-d_6), which gave **7** exclusively.

Oxidation of a solution of **7a** with iodine or molecular oxygen gave **2** and the symmetrical dimer **8**. The



7b **8**

dimer must arise by dimerization of the radical **7b**, a one-electron oxidation product of **7a**.

Experimental Section

General.—3,6-Dibenzotricyclo[3.3.0.0^{2,8}]octadiene (**1**) and 3,6 dibenzobicyclo[3.3.0]octadiene (**2**) were prepared by the method of Ciganek.[16] 1,2-Dimethoxyethane (DME) was distilled from sodium–potassium alloy and then from sodium benzophenone ketyl directly into the reaction flask. Sodium biphenyl radical anion was prepared by the method of Liggett.[20] Gas–liquid partition chromatographic (glpc) analyses and separations were accomplished with 15% diethylene glycol succinate (DEGS) on Chromosorb W columns.

Reduction of 1 with Sodium Biphenyl.—Dry, prepurified N_2 was bubbled through a solution of 204 mg (1.0 mmol) of **1** in 10 ml of DME in a 25-ml round-bottom flask sealed with a rubber serum stopper for 2 hr at 0°. The desired volume of a 0.3 *M* solution of sodium biphenyl in DME was added *via* a syringe. The solution was stirred at 0° for the desired period of time and then 0.3 ml of water (or D_2O) was added *via* a syringe. The solution was added to 100 ml of ether and the ethereal solution was extracted with 30-ml portions of saturated $NaHCO_3$ and NaCl solutions, dried ($MgSO_4$), and concentrated *in vacuo*. The pure components, **1** and **2**, were isolated by preparative glpc (7 ft × $^3/_8$ in. column packed with 15% DEGS on Chromosorb W, 175°, helium flow of about 600 cm^3/min) and identified by comparison of their retention volumes (10,800 and 16,200 cm^3, respectively), pmr spectra,[21] and melting points[17,18] with those of the authentic compounds; pmr of **2** (CCl_4) δ 2.6–3.5 (m, 5), 4.6 (d, 1, J = 7 Hz), 7.0–7.5 (m, 8).

Base-Catalyzed Hydrogen–Deuterium Exchange of 2.—To a deoxygenated solution of 103 mg (0.50 mmol) of **2** in 2 ml of DMSO-d_6 was added 66 mg (0.59 mmol) of freshly sublimed potassium *t*-butoxide. The solution was stirred at 25° for 4 hr and then 1.0 ml of D_2O was added. The mixture was extracted with 100 ml of ether. The ethereal solution was washed several times with water, dried ($MgSO_4$), and concentrated *in vacuo*. The pure dibenzobicyclo[3.3.0]octadiene was isolated by preparative glpc (same conditions as above). A pmr spectrum of the pure compound showed the complete disappearance of the hydrogen located at δ 4.6 (the hydrogen at C-5 in **2**). No deuterium incorporation at C-2 and C-8 could be detected by pmr.

Oxidation of 7a.—To a solution of **7a** (prepared from 278 mg (1.36 mmol) of **1** and 2.80 mmol of sodium biphenyl) in 15 ml of DME was added 169 mg (0.67 mmol) of iodine in 5 ml of DME. The solution was stirred at 0° for 20 min and then added to 100 ml of ether. The ethereal solution was extracted with saturated $NaHCO_3$, 10% NaS_2O_3, and saturated NaCl solutions, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product mixture was passed over 40 g of Merck 71707 alumina. Elution with petroleum ether (bp 60–70°) yielded a mixture of **2**, biphenyl, and **8**. Recrystallization of this mixture from methanol gave 84 mg (0.21 mmol, 31%) of **8**: mp 233–235°; pmr ($CDCl_3$) δ 2.3–3.3 (m, 10), 6.8–7.4 (m, 16); mass spectrum *m/e* 205 was the major peak (one-half of that expected for the molecular ion).

Anal. Calcd for $C_{32}H_{26}$: C, 93.66; H, 6.34. Found: C, 93.50; H, 6.45.

Registry No.—**1**, 2199-28-2; **8**, 25244-21-7.

Acknowledgment.—The authors are indebted to Dr. Melvin Hanna of this department for use of his esr equipment.

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(20) L. M. Liggett, *Anal. Chem.*, **26**, 748 (1954).

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Condensation between Homophthalic Acid and o-Chlorobenzaldehydes

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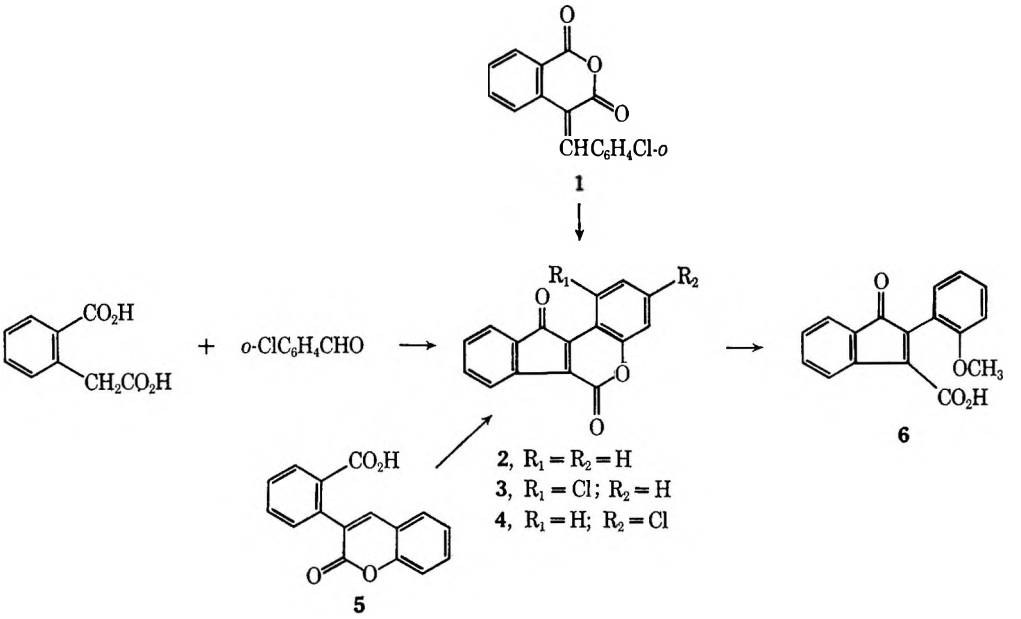
The reaction between homophthalic acid and aromatic aldehydes in the presence of an organic base leads to 4-arylidenehomophthalic anhydrides.[1] During studies of this reaction in these laboratories homophthalic acid and *o*-chlorobenzaldehyde (at 240–250°) in the presence of piperdine unexpectedly gave 2-(2-hydroxyphenyl)indenone-3-carboxylic acid lactone (**2**). Similarly, 2,6-dichlorobenzaldehyde and 2,4-dichlorobenzaldehyde gave **3** and **4**, respectively. Compounds **2**, **3**, and **4** are red crystalline substances subliming at 250–300° (1 atm).

(1) M. Buu-Hoi, *C. R. Acad. Sci.*, **211**, 330 (1940).

SCHEME I



Treatment of 2 with alcoholic potassium hydroxide followed by addition of dimethyl sulfate yielded 2-(2-methoxyphenyl)indenone-3-carboxylic acid (6). The ultraviolet spectra for 2, 3, 4, and 6 were very similar to that of 2-(2-methoxyphenyl)-1,3-indandione.[2] Mass spectral studies of 2 gave a parent peak at m/e 248.0471 and a peak at 163.0552 probably arising from destruction of 2 analogous to loss of CO from phenols and carbonyl compounds.[3]

Compound 2 also was formed when 1 or 3-(2-carboxyphenyl)coumarin (5)[4] was heated in the presence of piperidine (Scheme I).

Experimental Section[5]

2-(2-Hydroxyphenyl)indenone-3-carboxylic Acid Lactone (2).—A mixture of *o*-chlorobenzaldehyde (16.8 ml, 0.150 mol), homophthalic acid (18.0 g, 0.100 mol, freshly crystallized, mp 175–177°), and piperidine (4 drops) was heated for 15 min at 180° (internal temperature) and 3 hr at 250°. When the mixture had cooled to 70°, acetone was carefully added until the total volume was about 175 ml. When this mixture had cooled to room temperature, red needles of 2 were collected (12.4 g, 50%, mp 283–285°). The analyzed sample (from 2-methoxyethanol) melted at 286° (with sublimation): ir 1720 (cyclic ketone), 1732 (lactone), 1610 cm^{-1} (conjugated double bond); uv max 470 (ϵ 3100), 348 (2400), 280 (35,000), 263 (24,200, sh), 210 mμ (50,000); mass spectrum m/e 248.0471 (theoretical parent peak for $C_{16}H_8O_3$ 248.0473) and 163.0552 (theoretical for $C_{13}H_7$ 163.0548).

Anal. Calcd for $C_{16}H_8O_3$: C, 77.41; H, 3.25. Found: C, 77.59; H, 3.28.

The oxime, red crystals (from 2-methoxyethanol), had mp 276–277°.

Anal. Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.86; H, 3.75; N, 5.59.

Nitration of 2 (0.50 g, 0.0020 mol) at 0–10° in sulfuric acid (10 ml) was carried out by adding a solution of 0.6 g of potassium nitrate in 5 ml of sulfuric acid during 15 min. The mixture was poured over 25 g of ice and the red-orange precipitate collected. Crystallization from *o*-dichlorobenzene yielded 0.50 g, mp 289–291°.

Anal. Calcd for $C_{16}H_6N_2O_7$: C, 56.81; H, 1.79; N, 8.28. Found: C, 57.07; H, 2.10; N, 8.29.

Compound 2 from 4-(2-Chlorobenzylidene)homophthalic Anhydride and 3-(2-Carboxyphenyl)coumarin (5).—In a typical experiment piperidine (1 drop) and 0.10 g of 1 were heated at 170–180° for 6 hr, yielding 0.06 g (87%) of 2, mp 285° (from 2-methoxyethanol). Mixture melting point with authentic 2 was not depressed.

Methylation of 2 Using Dimethyl Sulfate.—A mixture of 4.96 g (0.200 mol) of 2, 6.48 g (0.120 mol) of potassium hydroxide, and 50 ml of methanol was heated under reflux for 10 min to effect complete opening of the lactone ring, followed by removal of methanol *in vacuo*. The red-orange residue was dissolved in 50 ml of water and cooled to 0–10°; 14 ml of dimethyl sulfate was added over 2 hr in 2-ml portions. After stirring overnight at room temperature, 11.2 g (0.200 mol) of potassium hydroxide was added; the mixture was heated under reflux until the orange oil which separated on standing overnight had disappeared (15 min). Fifty grams of ice and 50 ml of hydrochloric acid were added to the solution and the precipitate containing 6 was collected. Unreacted 2 was separated from 6 by stirring the precipitate with 100 ml of 20% sodium carbonate and acidifying. Crystallization from methanol furnished magenta crystals of 6 (2.1 g, 38%): mp 204–205°; ir 1722 (cyclic ketone), 2500–3300 (carboxylic acid), 1605 cm^{-1} (conjugated carbonyl); uv max 450 (ϵ 1800), 320 (2000, sh), 275 (16,000), 252 mμ (22,000).

Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32; O, 22.84. Found: C, 72.90; H, 4.35; O, 22.63.

2-(2-Hydroxy-4-chlorophenyl)indenone-3-carboxylic Acid Lactone (4).—This compound was prepared as described for 2: 25.9 g (91.8%); mp 252–253° (2-methoxyethanol); ir 1730, 1715, 1600 cm^{-1}; uv 460 (ϵ 4400), 287 (41,000), 212 mμ (53,000).

Anal. Calcd for $C_{16}H_7ClO_3$: C, 67.98; H, 2.50; Cl, 12.54. Found: C, 67.96; H, 2.46; Cl, 12.58.

The oxime, red crystals (from *o*-dichlorobenzene), had mp 263–265°.

Anal. Calcd for $C_{16}H_8ClNO_3$: C, 64.55; H, 2.71; Cl, 11.91, N, 4.71. Found: C, 64.58; H, 2.78: Cl, 12.23, N, 4.77.

2-(2-Hydroxy-6-chlorophenyl)indenone-3-carboxylic Acid Lactone (3).—This compound was prepared as described for 2: 14.4 g (51.1%); mp 226–228° (2-methoxyethanol); ir 1725 (broad), 1595 cm^{-1}; uv 428 (ϵ 1150), 334 (2100), 277 (6400), 245 (29,400), 208 mμ (30,000).

Anal. Calcd for $C_{16}H_7ClO_3$: C, 67.98; H, 2.50; Cl, 12.54. Found: C, 68.21; H, 2.65; Cl, 12.50.

Registry No.—Homophthalic acid, 89-51-0; 2, 7703-04-0; 2 oxime, 25109-93-7; 2 nitrate, 25109-94-8;

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(5) All melting points are corrected and were determined with a Hershberg melting point apparatus. Ultraviolet spectra were measured in methanol using a Model 202 Perkin-Elmer spectrophotometer, ir spectra were measured as potassium bromide pellets on a Model 21 Perkin-Elmer spectrophotometer, and mass spectra were obtained with a AEI, MS-9 mass spectrometer utilizing a direct probe with source temperature 200°.

3, 25109-95-9; **4**, 25109-96-0; **4** oxime, 25158-23-0; **6**, 25109-97-1.

Acknowledgment.—The author is indebted to Dr. Ralph Dougherty for assistance in obtaining the mass spectrum and to Miss Florence Kraft and Mr. Marvin Pflaumer for technical assistance.

Synthesis of *cis,cis*-2,6-Dimethyl-*cis*-9-oxabicyclo[5.3.0]decane. A Novel Stereospecific Synthetic Route to Bicyclic Systems Containing *cis*-1,4-Dimethylcycloheptane Rings

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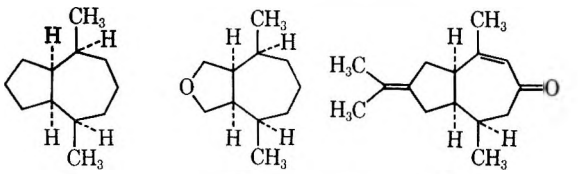
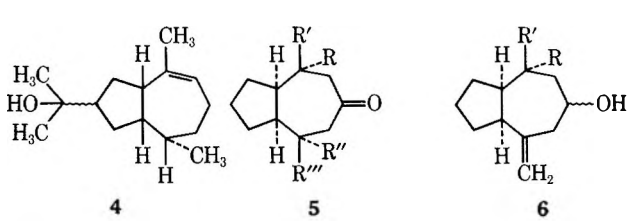
Received January 8, 1970

In a projected synthetic sequence leading to bicyclo[5.3.0]decane systems possessing methyl substituents as formulated in **1**, we wish to report a stereospecific synthesis of **2**, a model heterocyclic analog of **1**.[2]



1 **2** **3**

At the inception of this research synthetic routes to methyl-substituted bicyclo[5.3.0]decane systems of the type **1** were sought in order to develop a total synthesis of β-vetivone and hinesol. The sesquiterpene β-vetivone had been formulated as **3** in 1941.[3] Hinesol had been converted into the enantiomer of β-vetivone and it was therefore assigned structure **4**.[4]

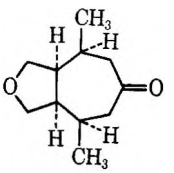


4 **5** **6**

a, R = R″ = CH_3; R′ = R‴ = H **a**, R = CH_3; R′ = H
b, R = R‴ = CH_3; R′ = R″ = H **b**, R = H; R′ = CH_3
c, R′ = R‴ = CH_3; R = R″ = H

(1) (a) Abstracted in part from a thesis presented to the Graduate College of the University of Vermont, Aug 1969, in partial fulfillment of the requirements for the Ph.D. degree; (b) National Aeronautics and Space Administration Predoctoral Traineeship, 1965–1968.

(2) A keto analog **2a** has been prepared by A. P. Krapcho and B. P. Mundy, *J. Org. Chem.*, **32**, 2041 (1967).

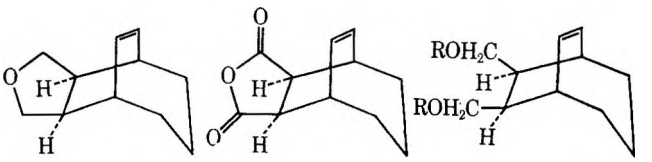


2a

The recent investigations of Marshall and coworkers have necessitated a structural revision of **3** and **4** to spiro[4.5]decane skeletons.[5] The total synthesis of β-vetivone[6] and hinesol[7] has unambiguously supported this structural revision.

Marshall and coworkers have reported a *stereoselective* route to bicyclo[5.3.0]decanes of type **5**.[5] This synthetic sequence leads to methyl isomers. Catalytic hydrogenation of **6a** followed by chromic acid oxidation led to the ketones **5a** and **5b** and a similar reaction sequence on **6b** led to **5b** and **5c**.

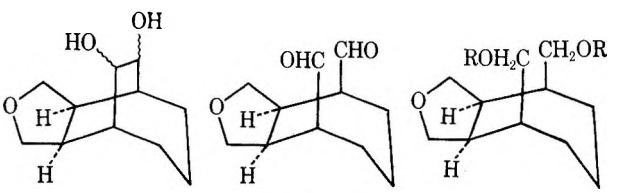
The accessibility of compounds such as **7** led us to investigate the stereospecific conversion of the carbon atoms of the double bond into methyl groups to lead to **2**. A route of this type had obvious potential for systems with carbocyclic skeletons.



7 **8** **9**

Results and Discussion

The reaction of cycloheptadiene with maleic anhydride led to the adduct **8** in an excellent yield.[8] This adduct **8** was reduced to the diol **9** (R = H) using lithium aluminum hydride in refluxing 1,2-dimethoxyethane. If the reduction was performed in ether, the formation of the lactone occurred along with the diol **9** (R = H).[9] The diol **9** (R = H) was converted into the cyclic ether **7** by addition of *p*-toluenesulfonyl chloride to a refluxing pyridine solution of the diol.[10] The ether **7** was treated with osmium tetroxide in pyridine to form the osmate ester which was cleaved by (1) a basic mannitol solution or (2) reaction with lithium aluminum hydride to yield a *cis*-diol **10** of undetermined stereochemistry.[11] This *cis*-diol **10** was cleaved to the dialdehyde **11** by reaction with sodium metaperiodate in an aqueous solution.[2,12] Compound **11** was not obtained analytically pure, but the alde-



10 **11** **12**

(3) (a) Y. R. Naves and E. Perrottet, *Helv. Chim. Acta*, **24**, 3 (1941); (b) for a summary of the experimental data, see J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol III, Cambridge University Press, London, 1952, pp 224–232.

(4) I. Yosioka and T. Kimura, *Chem. Pharm. Bull.*, **13**, 1430 (1965).

(5) (a) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967); *J. Org. Chem.*, **35**, 186 (1970); (b) J. A. Marshall and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2750 (1967); *J. Org. Chem.*, **35**, 192 (1970).

(6) J. A. Marshall and P. C. Johnson, *Chem. Commun.*, 391 (1968).

(7) J. A. Marshall and S. F. Brady, *Tetrahedron Lett.*, 1387 (1969).

(8) K. Alder and H. H. Molls, *Chem. Ber.*, **89**, 1960 (1956).

(9) B. E. Cross and J. C. Stewart, *Tetrahedron Lett.*, 3589 (1968).

(10) A. P. Krapcho and B. P. Mundy, *J. Heterocycl. Chem.*, **2**, 355 (1965).

(11) F. D. Gunstone, *Advan. Org. Chem.*, **1**, 103 (1960).

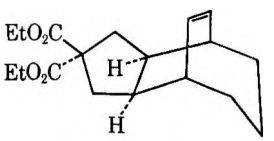
(12) C. A. Bunton, "Oxidations in Organic Chemistry, Part A," K. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter 6.

hydic protons exhibited a singlet at δ 9.15 in the nmr spectrum indicating that coupling with the adjacent α proton had not occurred. One might attribute this lack of splitting to a hindered rotation of the aldehyde groups and the adoption of a conformation for minimal like dipole–dipole repulsions of the >C=O of the aldehyde groups in which the dihedral angle between the aldehydic proton and the adjacent α proton is about 90°.

A more direct method for the preparation of the dialdehyde **11** was ozonolysis of **7**.[13] A solution of **7** in methylene chloride was treated with ozone at a temperature of −78°. Decomposition of the reaction mixture with dimethyl sulfide led to crude **11**.

The dialdehyde **11** was reduced with lithium aluminum hydride to a crude diol (**12**, R = H),[2,14] which was then converted to the ditosylate **12** (R = Ts).[2] The tosylate groups were displaced by hydride in the reaction of **12** (R = Ts) with lithium aluminum hydride in 1,2-dimethoxyethane to yield **2**.[14] Compound **2** exhibited only one doublet in the nmr for the C-2 and C-6 methyl groups (δ 0.93; J = 6.5 Hz). This supports the *all-cis* stereochemistry of the protons at C-1, C-2, C-6, and C-7.

During the course of this work the ditosylate **9** (R = Ts) was prepared by reaction of the diol **9** (R = H) with *p*-toluenesulfonyl chloride in pyridine at 0°. The reaction of this ditosylate with the anion of diethyl malonate in refluxing 1,2-dimethoxyethane led to the carbocyclic geminal diester **13**. Intermediate **13** was of possible utility for the synthesis of systems of type **1** possessing a functional group at C-9. Research on the development of the carbon atoms of the double bond of **13** into methyl groups was terminated when the carbocyclic skeletones of β-vetivone and hinesol were revised.



13

Experimental Section

Cycloheptadiene–Maleic Anhydride Adduct 8.—Cycloheptadiene (22.8 g, 0.25 mol) and maleic anhydride (23.8 g, 0.24 mol) in 100 ml of dry *m*-xylene were refluxed for 24 hr. At the end of this reflux period the uv spectrum of an aliquot of the reaction mixture indicated the absence of unreacted diene. The solvent was removed by distillation under reduced pressure of the water aspirator. The crude solid which remained was recrystallized from carbon tetrachloride to yield 39.0 g (81%) of **8**, mp 110–111° (lit.[8] mp 114°).

Reduction of 8 to 9 (R = H).—The adduct **8** (15.0 g, 0.078 mol) was dissolved in 20 ml of dry 1,2-dimethoxyethane, placed in an addition funnel, and added dropwise to lithium aluminum hydride (4.0 g, 0.105 mol) in 200 ml of dry 1,2-dimethoxyethane. On completion of the addition the mixture was refluxed for 36 hr. At the end of this period, water was slowly added until the mixture turned white, and the salts were filtered. The solvent was removed with the rotary evaporator and the residual oil solidified on standing to give 10.1 g (71%) of **9** (R = H): ir (KBr) 3200 (O—H), 3030 (=C—H), and 1023 cm^{-1} (C—O); nmr ($CDCl_3$) δ 6.02 (m, 2, H—C=C—H), 4.80 (s, broad, 2, -OH) and 3.64 (m, 4, $-CH_2-O-H$). The analytical sample was prepared by three crystallizations from ether–pentane, mp 70.5–72.0°.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.51; H, 9.96. Found: C, 72.48; H, 10.11.

Preparation of Ether 7.—The diol **9** (R = H) (8.9 g, 0.049 mol) was dissolved in 60 ml of dry pyridine and the solution was placed under a nitrogen atmosphere. The solution was heated to 80° and a solution of *p*-toluenesulfonyl chloride (9.4 g, 0.049 mol) in 40 ml of dry pyridine was added dropwise over a 2-hr period. On completion of the addition heating was continued for 1 hr. The reaction mixture was cooled to room temperature and then poured over a sulfuric acid–ice mixture (100 g/100 g) and extracted with four 100-ml portions of methylene chloride. The methylene chloride extract was washed with a saturated sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The tricyclic ether was distilled to yield 7.3 g (91%): bp 46–47° (0.1 mm); ir (neat) 3045 (=C—H) and 1098 cm^{-1} (C—O—C); nmr (CCl_4) δ 6.05 (m, 2 H, vinyl), 3.92 and 3.21 (each a multiplet similar to a triplet for 2 H, $-CH_2-O-CH_2-$), 2.65 (m, 2), 2.22 (m, 2), and 1.55 (m, 6). The analytical sample was obtained by redistillation and taking a center cut, bp 46–47° (0.1 mm).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.43; H, 9.82. Found: C, 80.66; H, 9.84.

Preparation of *cis*-Diol 10.—The ether **7** (0.20 g, 0.0012 mol), dry pyridine (0.25 g, 0.0032 mol), and osmium tetroxide (0.31 g, 0.0012 mol) were added to 6 ml of anhydrous ether. The flask was fitted with a calcium chloride drying tube and the mixture was stirred for 1 hr. The brown solid was filtered and two procedures were employed for working up the osmate ester.

A.—The osmate ester was transferred to a 50-ml erlenmeyer flask containing 20 ml of a 10% potassium hydroxide solution and 1.0 g of mannitol. This mixture was allowed to stir for 12 hr. The aqueous hydroxide solution was extracted with three 20-ml portions of methylene chloride. The methylene chloride extracts were combined, washed with water, and dried over anhydrous sodium sulfate. The organic material was concentrated and the oil crystallized to give 160 mg (70%) of the diol, mp 116–119°.

B.—To a 250-ml two-necked round bottom flask was added 0.7 g (excess) of lithium aluminum hydride and 25 ml of dry 1,2-dimethoxyethane. To this mixture the osmate ester (1.25 g, 0.003 mol), dissolved in 150 ml of dry 1,2-dimethoxyethane, was added dropwise. The salts were filtered and the organic layer was dried over anhydrous sodium sulfate. The material on concentration gave 440 mg (75%) of dark brown crystals. One crystallization from ether gave slightly colored crystals: mp 118–120°; ir (KBr) 3445, 3365, 3245, and 3180 cm^{-1}; nmr ($CDCl_3$) δ 4.17 (m, 2, -O—C<H), 3.78 (m, 4, $-CH_2-O-CH_2-$), 3.42 (s, 2, -OH), and 2.65–1.2 (m, 10).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15. Found: C, 66.57; H, 9.29.

Preparation of 11.—To a 10-ml round-bottom flask were added sodium metaperiodate (0.1 g, 0.0040 mol), 3 ml of water, and *cis*-diol **9** (0.077 g, 0.0035 mol). The mixture was stirred at room temperature for 1 hr. At this time, the reaction mixture was extracted with three 7-ml portions of methylene chloride. The organic layers were combined, washed with water, then dried over anhydrous sodium sulfate. The methylene chloride was removed with the rotary evaporator yielding 0.07 g (92%) of a crude oil (this material was not distilled): ir (neat) 2720 (-CHO) and 1720 cm^{-1} (HC=O); nmr (CCl_4) δ 9.51 (s, 2, -CHO) and 3.50 (m, 4, $-CH_2-O-CH_2-$).

Preparation of 12 (R = H).—To a 50-ml flask was added 10 ml of dry 1,2-dimethoxyethane and lithium aluminum hydride (0.03 g, 0.0007 mol). To this was added dropwise **11** (0.15 g, 0.00077 mol) dissolved in 10 ml of dry 1,2-dimethoxyethane. The mixture was allowed to reflux for 20 hr. At this time, water was added to the mixture until the mixture turned white. The salts were filtered by suction and washed with small portions of methylene chloride. The organic phase was concentrated to give 0.125 g (82%) of an oil: ir (neat) 3280 cm^{-1} (O—H); nmr ($CDCl_3$) δ 3.68 (d, 4, J = 6 Hz), 3.33 (d, 4, J = 7 Hz), 2.93 (s, 2, -OH), 2.63 (m, 2), and 2.07–1.0 (m, 8).

Ozonolysis of 7 to the Dialdehyde 11.—The ozone generator was a commercial Welsbach apparatus. The ether **7** was dissolved in methylene chloride. The solution was cooled to −78° and then the ozone–oxygen mixture was bubbled through the solution for the appropriate period of time. The system and reaction mixture were then purged with oxygen for about 15 min.

(13) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(14) N. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956.

The methylene chloride solution was drained from the reaction buret and the ozonide was decomposed with dimethyl sulfide. The organic layer was concentrated to give a nearly quantitative yield of the crude dialdehyde.

Preparation of 12 (R = Ts).—To a 10-ml flask, *p*-toluenesulfonyl chloride (0.4 g, 0.0021 mol) was added and to this was added dropwise a solution of **12** (R = H) (0.1 g, 0.0005 mol) dissolved in 3 ml of dry pyridine. The mixture was cooled by means of an ice water bath. After addition was complete, the mixture was placed in the refrigerator for 18 hr. The mixture was then poured over ice water and the aqueous mixture was extracted three times with 20-ml portions of methylene chloride. The organic layers were combined and washed with 10% HCl, saturated $NaHCO_3$, and water, respectively. The extract was dried with sodium sulfate and concentrated to give 0.1 g (39%) of the ditosylate **12** (R = Ts) after one recrystallization from methylene chloride–petroleum ether (30–60°). The analytical sample was obtained after five recrystallizations: mp 147–149°; ir (KBr) 1600 (aromatic C=C), 1170 (S—O), and 956 cm^{-1} (C—O); nmr ($CDCl_3$) δ 7.60 (A_2B_2 centrosymmetric quartet, 8, J = 8 Hz, aromatic protons), 3.80 (d, 4, J = 7 Hz, $-CH_2-$OTs), 3.54 (m, 4, $-CH_2-O-CH_2-$), 2.47 (s, 6, $-CH_3$), and a pattern spread over 2.6 to 1.1 for 10 H for the ring envelope hydrogens.

Anal. Calcd for $C_{25}H_{32}O_7S_2$: C, 59.04; H, 6.34. Found: C, 58.71; H, 6.57.

Preparation of 2.—To a 10-ml flask was added lithium aluminum hydride (0.05 g, 0.0014 mol), 1 ml of dry 1,2-dimethoxyethane, and **12** (R = Ts) (0.1 g, 0.0002 mol) dissolved in 4 ml of dry 1,2-dimethoxyethane. The reaction mixture was refluxed for 20 hr and then cooled. Water was added to destroy the excess lithium aluminum hydride. The salts were filtered by suction and washed with methylene chloride. The organic material was concentrated to give 0.021 g (60%) of an oil. The analytical sample was obtained after this material had been chromatographed on alumina (activity I) and eluted with petroleum ether–benzene (1:1), then distilled: bp 70–75° (0.5 mm); nmr ($CDCl_3$) δ 3.60 (m, 4, $-CH_2-O-CH_2-$), 2.4–1.1 (m, 10, ring hydrogens), and 0.93 (d, 6, J = 6.5 Hz, $-CH_3$).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.63; H, 11.79.

Preparation of Ditosylate 9 (R = Ts).—The *p*-toluenesulfonyl chloride (10.5 g, 0.055 mol) was dissolved in 5 ml of dry pyridine and the solution was cooled in an ice bath. A solution of **9** (R = H) (5.0 g, 0.027 mol) in 25 ml of dry pyridine was added dropwise to the cold toluenesulfonyl chloride solution. After the addition was complete, the mixture was placed in the freezer for 24 hr. The reaction mixture was poured over ice water and allowed to stir for 20 min to insure the hydrolysis of any excess *p*-toluenesulfonyl chloride. The heterogeneous mixture was extracted with three 30-ml portions of methylene chloride. The organic layers were combined and washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water, respectively. The organic phase was dried overnight with anhydrous sodium sulfate. The organic phase was concentrated with the rotary evaporator to give 9.4 g (85%): ir (KBr) 1600 (aromatic C=C), 1180 (S—O), and 952 cm^{-1} (C—O); nmr ($CDCl_3$) δ 7.63 (centrosymmetric A_2B_2 quartet, 8, J = 8 Hz, aromatic protons), 5.87 (m, 2, H—C=C—H), 3.92 (m, 4, $-CH_2OTs$), 2.47 (s, 6, aromatic CH_3), 2.35 (m, 4, tertiary protons), and 1.45 (m, 6, $-CH_2-$ of ring). The analytical sample was obtained after four recrystallizations from ether, mp 93–94°.

Anal. Calcd for $C_{26}H_{30}O_6S_2$: C, 61.20; H, 6.16. Found: C, 61.59; H, 6.35.

Preparation of 13.—To a 100-ml three-neck round-bottom flask was added 1.0 g (0.024 mol; 58.6% mineral oil dispersion) of sodium hydride. This was washed with four 10-ml portions of dry 1,2-dimethoxyethane. After washing, 15 ml of dry 1,2-dimethoxyethane was added and the system placed under nitrogen. To this mixture diethylmalonate (3.8 g, 0.024 mol) was added. After the hydrogen evolution had ceased, **9** (R = Ts) (3.6 g, 0.0074 mol) dissolved in 30 ml of dry 1,2-dimethoxyethane was added dropwise. After the addition was complete, the mixture was refluxed for 72 hr with stirring. The reaction mixture was allowed to cool and most of the salt was filtered by suction. The residue was washed with two 30-ml portions of hot 1,2-dimethoxyethane. The organic phase was concentrated with the rotary evaporator. To this residue, 20 ml of water was added and the mixture extracted with four 20-ml portions of methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 0.78 g (33%): bp 135–140° (0.5 mm); nmr (CCl_4) δ 4.07 and 4.16 (2 q, 4, J = 7 Hz, $-O-CH_2-$), 1.18 and 1.22 (2 t, 6, J = 7 Hz, $-CH_3$), 6.12 (m, 2, H—C=C—H), and 2.4–1.5 (several peaks, 14). The analytical sample was obtained after a portion of this material had been chromatographed on an alumina column (activity III). The *gem* diester was eluted from the column with an ether–benzene mixture (1:9). The material was then redistilled, bp 135–140° (0.5 mm).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.83; H, 8.72.

Registry No.—**2**, 25090-89-5; **7**, 25090-90-8; **9** (R = H), 25090-91-9; **9**, (R = Ts), 25090-92-0; *cis*-**10**, 25090-93-1; **12** (R = Ts), 25090-94-2; **13**, 25090-95-3.

Acknowledgment.—This research was generously supported by Research Grant GM-08241 from the U. S. Public Health Service.

Conformational Analysis. LXVII. The Effect of Solvent on the Conformational Energy of the Carbethoxy Group[1,2]

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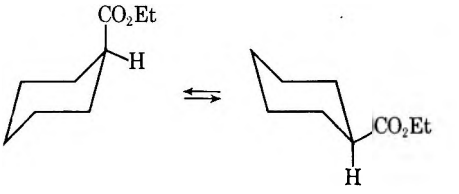
In recent years, conformational equilibria of the type



have been the subject to many investigations.[4] These investigations have resulted in the determination of numerous $-\Delta G°$ values (termed "conformational energies,"[5] "G values,"[5] or "A values"[6]) for a large variety of substituents.[7] These values are often thought of as constants related to the steric "size" of the particular substituent, and in a recently compiled table of conformational energies,[7] only two substituents (hydroxyl and amino) were listed as having more than one "best value." In these two cases, it is well known that hy-

(1) Paper LXVI: N. L. Allinger, I. Lillien, C. L. Neumann, H. Sugiyama, and N. A. Pamphilis, *J. Org. Chem.*, **35**, 1255 (1970).

(2) This Research was supported by Grants GP 6763 and GP 15263 from the National Science Foundation and is abstracted from a Ph.D. dissertation presented to Wayne State University by R. A. F., June 1968.

(3) (a) Catholic University; (b) University of Georgia.

(4) Comprehensive reviews include (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1965; (c) M. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965; (d) J. McKenna, "Conformational Analysis of Organic Compounds," The Royal Institute of Chemistry Lecture Series, No. 1, London, 1966.

(5) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **4**, 761 (1965).

(6) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(7) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1967.

drogen bonding with the solvent can cause large increases in conformational energies.[8] Other solvent effects, however, have for the most part been ignored.

Although no definite evidence has been offered to support the idea, it would be very surprising if hydrogen bonding did not affect the conformational energies of groups other than amino and hydroxyl.[9] It would also be surprising if solvent effects other than hydrogen bonding were not important. In spite of this, a close look through the literature reveals that only very limited studies of solvent effects on conformation have been made.[8-10] In the present work, it was shown that not only can hydrogen bonding substantially change the conformational energy of the carbethoxy (CO_2Et) group, but even in cases where hydrogen bonding is not possible, solvent can have an appreciable effect.

In checking the various reported G values for the ester groups,[11] an interesting observation was made. Eliel and Gianni's[11c] value of 1.1 kcal/mol for CO_2Et, obtained by what seemed to be the best method,[12] was lower than all but one[8b] of the others, including those for the carbomethoxy group. This is particularly surprising considering the reported values range from 1.05 to 1.7 kcal/mol. Examination of the conditions of these determinations revealed one unique characteristic of the Eliel and Gianni work. Their value was obtained using carbon tetrachloride as a solvent, while all other values were determined using either ethanol or methanol as a solvent. This was our first clue that hydrogen bonding might increase the G value of the ester group. With this in mind, a systematic study of the effect of solvent on the conformational energy of the carbethoxy group was undertaken.

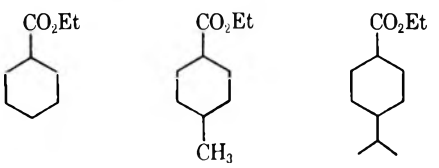
Method.—Of the various methods that have been used to determine conformational equilibria, the nmr method[5,13] seemed to be the most straightforward. In particular, the method of Eliel[12] seemed to lend itself very well to the systems of interest and has been used for this purpose previously.[11c] This method involves the determination of the time-averaged chemical shift (ν) of the proton α to the functional group which with the chemical shift of the axial and equatorial protons (ν_a and ν_e) yields the equilibrium constant K (eq 1).[14]

$$K = (\nu_a - \nu)/(\nu - \nu_e) \quad (1)$$

Determination of ν_a and ν_e could be made from the spectra of the conformationally biased *cis*- and *trans*-4-*t*-butylcyclohexyl derivatives, respectively. This method, however, has been the subject of recent controversy.[15] The criticism has been made[15] that the 4-*t*-butyl group has an effect on the chemical shift of the α hydrogen. This effect might arise from either the magnetic anisotropy of the *t*-butyl group or the ring distortion forced by this group. Molecular mechanics calculations have indicated that the latter is probably negligible.[16]

Whatever the *t*-butyl effect may be due to, one should be able to reduce this effect by making measurements on hydrogens further from it than the α hydrogen, if such hydrogens are available in which the chemical shift differs between the axial and equatorial conformations. In the case of the carbethoxy function, the methylene hydrogens of the ethyl group satisfy these requirements. It was found that this difference is about 3 Hz at 60 MHz in carbon tetrachloride. While this is quite small, very careful measurements utilizing the sideband calibration technique[17] would be expected to yield meaningful results. That this is indeed the case is evidenced by the very low standard deviations obtained in repeated measurements by this method (Table I), and by the excellent agreement between determinations in similar but different solvents.

TABLE I



	I	II	III
Solvent	*G* value	*G* value	*G* value
Isooctane	1.07 ± 0.04 1.04 ± 0.04[a]	1.11 ± 0.03	1.18 ± 0.03
CCl_4	1.05 ± 0.02	1.08 ± 0.04	1.24 ± 0.03
Acetone	1.08 ± 0.02	1.25 ± 0.04	1.27 ± 0.06
Acetonitrile	0.93 ± 0.03 0.92 ± 0.03[a]	1.14 ± 0.04	1.26 ± 0.06
$CHCl_3$	1.20 ± 0.01 1.18 + 0.03[b]	1.29 ± 0.03 1.31 + 0.02[b]	1.42 ± 0.03 1.37 + 0.04[b]
HOAc	1.27 ± 0.04		1.28 ± 0.04

[a] Repeats at the same concentration. [b] Repeats at lower concentration.

To check the validity of this method, a determination was made in carbon tetrachloride to compare with the earlier G value of 1.1 kcal/mol obtained by Eliel and Gianni[11c] in this solvent using the α-hydrogen chemical

(8) (a) E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Lett.*, 831 (1963); (b) E. L. Eliel and S. H. Shroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965); (c) J. Sieher, J. Jonas, and M. Tichy, *Tetrahedron Lett.*, 825 (1963).

(9) Some evidence has been presented for an increase in the G values of the halogens in hydrogen bonding solvents, but this evidence is far from definitive: E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 689 (1968).

(10) (a) G. Chiurdoglu and W. Masschelein, *Bull. Soc. Chim. Belg.*, **69**, 154 (1960); (b) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962); (c) J. Reisse, J. C. Celotti, and G. Chiurdoglu, *Tetrahedron Lett.*, 397 (1965); (d) J. C. Celotti, J. Reisse, and G. Chiurdoglu, *ibid.*, 2249 (1966); (e) E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 689 (1968).

(11) (a) N. L. Allinger and R. J. Curby, *J. Org. Chem.*, **26**, 933 (1961); (b) E. L. Eliel, H. Haubenstock, and R. V. Aeharya, *J. Amer. Chem. Soc.*, **83**, 2351 (1961); (c) E. L. Eliel and M. H. Gianni, *Tetrahedron Lett.*, 97 (1962); (d) G. J. Fonken and S. Shiengthong, *J. Org. Chem.*, **28**, 3435 (1963); (e) E. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 744 (1964); (f) R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964); (g) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **31**, 587 (1966); (h) N. L. Allinger and L. A. Freiberg, *ibid.*, **31**, 894 (1966); (i) M. Tichy, F. Sipos, and J. Sicher, *Collect. Czech. Chem. Commun.*, **31**, 2889 (1966); (j) E. L. Eliel and M. C. Reese, *J. Amer. Chem. Soc.*, **90**, 1560 (1968).

(12) This method compares the nmr chemical shift of the hydrogen α to the substituent with that of the analogous hydrogen in the *cis* and *trans* 4-*t*-butyl derivatives which are used as models for the pure equatorial and axial conformations: E. L. Eliel, *Chem. Ind. (London)*, 568 (1959).

(13) Reviews of the use of nmr in conformational analysis include: (a) H. Feltkamp and N. L. Franklin, *Angew. Chem., Int. Ed. Engl.*, **4**, 774 (1965); (b) *Justus Liebigs Ann. Chem.*, **683**, 55 (1964); (c) ref 1b, pp 152–156.

(14) H. S. Gutowski and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).

(15) (a) E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968); (b) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 3251 (1968); (c) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *ibid.*, **91**, 344 (1969).

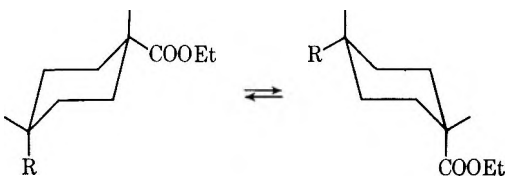
(16) (a) N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967); (b) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *ibid.*, **90**, 1199 (1968).

(17) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 74.

shift method. The value obtained, 1.05 ± 0.02 kcal/mol, is in very close agreement. This indicates the validity of both methods and suggests the effect of the *t*-butyl in both cases is negligible to within experimental error. This conclusion is also supported by the observation that the signal for the methoxy protons in 1,1-dimethoxycyclohexane appears exactly halfway between the two signals for the methoxy protons in 4-*t*-butyl-1,1-dimethoxycyclohexane.[10e]

Discussion

Table I contains the values obtained for the conformational energy of the carbethoxy group in different solvents, and from different compounds using the "methylene chemical shift method." In the case of the *cis*-4-methyl- and *cis*-4-isopropyl-substituted compounds, correction for the *G* value of the alkyl substituents was made, based on the usual assumption that the *G* values of the substituents are additive. Since the measurements were carried out on the *cis* isomers, the actual equilibrium studied in the substituted cases was



and the *difference* in the *G* values was in fact determined. The *G* value for the methyl group is fairly well known and is 1.70 kcal/mol.[7] The corresponding value for the isopropyl group is less well known and was taken to be 2.15 kcal/mol.[7]

The data obtained for the *cis*-4-methylcarbethoxycyclohexane in isooctane and in carbon tetrachloride are in almost exact agreement with the data for the unsubstituted compound in the same solvents. This is strong support for the reported 1.70 kcal/mol value for the methyl group. On the other hand, the data for the *cis*-4-isopropyl-substituted compound are slightly higher than those for either the unsubstituted or the *cis*-4-methyl compound. This indicates that the 2.15-kcal/mol value for the isopropyl group is a little high. A value of 2.05 would give much better agreement. The greater variation between the values for the unsubstituted and the substituted compounds in other solvents could be due to some unusual solvation effects, since all of these solvents would be expected to interact with the ester group much more specifically than can either isooctane or carbon tetrachloride.

In this investigation three types of solvents were used: nonpolar solvents incapable of forming hydrogen bonds (carbon tetrachloride and isooctane), polar solvents incapable of forming hydrogen bonds to the carbethoxyl (acetone and acetonitrile), and hydrogen bonding solvents (chloroform and acetic acid). It was hoped that within any of these pairs, similar effects would be noticed. As already noted, this was certainly true for the nonpolar solvents.

It is interesting to note the effects of chloroform and acetic acid. Both of these solvents are certainly capable of hydrogen bonding to the ester group. If analogy is drawn with the amine group and the hydroxyl group, both of which are known to be strongly affected by hydrogen bonding solvents,[8] it would be expected that hydrogen bonding would increase the conformational energy of the ester group. The data in Table I show that this in indeed the case. If previous determinations of the *G* value of the ester group[11] (all in alcohol solvent, also capable of forming hydrogen bonds) are considered, the average value of about 1.2 kcal/mol fits very nicely into Table I. This effect of hydrogen bonding might be rationalized using either entropy or enthalpy effects.[11i] However, the fact that acetic acid (presumably capable of forming stronger hydrogen bonds) only increases the conformational energy by about the same amount as chloroform (relatively weak hydrogen bonds) would lead one to think that entropy effects are probably the more important in these cases.

The effect of aprotic polar solvents is not nearly as clear-cut. About the only statement that can safely be made is that the more polar the solvent, the larger the discrepancy between values obtained with I and those obtained with II and III. Our interpretation of this fact is as follows. When the ester group is in the axial position, a *cis*-alkyl substituent is equatorial. The latter position offers more opportunity for an interaction with the solvent, but a polar substituent will interact more favorably with a polar solvent. The effect of an equatorial methyl, since it disrupts the solvent–solvent interactions, is unfavorable, which therefore causes this conformation to be less favorable than in a nonpolar solvent. This in turn causes an apparent increase in the *G* value of the ester group, if the *G* value of the alkyl group is assumed to be constant. When the ester group is in the axial position, the *cis*-alkyl substituents are in the equatorial position and thus, presumably, interacting more with the solvent. If this is an unfavorable interaction, then the energy of this isomer will increase, causing an apparent increase in the *G* value of the ester group, as is observed. It is not too presumptive to expect the interaction of the alkyl group to be stronger with the more polar solvents than with the nonpolar ones.

These ideas can alternatively be expressed in terms of the "internal pressure" of the solvent.[18] This internal pressure effect is a result of the intermolecular attractive forces among molecules of the solvent, and it requires an increase in the energy of the system if a cavity is created in the solvent.[19] Such a cavity can be created by dissolving a molecule in the solvent, and the larger the solute molecule, the more energy required. (This, of course, assumes the solute molecules to have attractive interactions with the solvent which are less than the attractive interactions of the solvent molecules for one another.) Thus, if two conformations of the molecule are possible, this internal pressure effect ought to shift the equilibrium towards the smaller conformation.

In the case of substituted cyclohexanes, it is reasonable to think that the axial conformation will be smaller than the equatorial. This is known to be true in many cases, and is the basis of the "conformational

(18) J. H. Hildebrand, "International Critical Tables," Vol. IV, McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p 19.

(19) H. Russ, H. L. Frisch, E. Helfand, and J. L. Lebowitz, *J. Chem. Phys.*, **32**, 119 (1960).

rule,"[20] and is typified by the experimental fact that *cis*-1,4-dimethylcyclohexane (axial–equatorial) has a higher density than *trans*-1,4-dimethylcyclohexane (equatorial–equatorial),[21] for example. The internal pressure of a solvent, therefore, would be expected to shift the equilibrium between the axial and equatorial conformations of substituted cyclohexanes toward the axial conformation. This is exactly what is observed in the great majority of cases where conformational free energies have been determined in both the gas phase and in solution.[7]

It is thus to be expected that the more polar the solvent, the higher the internal pressure, and therefore the larger the shift in equilibrium towards the axial isomer. This is certainly consistent with the value of 0.93 ± 0.03 kcal/mol determined for the unsubstituted carboethoxycyclohexane in acetonitrile. Unfortunately the data for this compound in the less polar acetone do not reveal this effect.

In conclusion, it can be said that there is definite evidence for an increase in the conformational energy of the carbethoxy group when hydrogen bonding to the solvent is possible. While an explanation of the effect of polar solvents is more complicated, there is no doubt that this effect is quite significant. Perhaps the most important point to be made is that the conformational energy of a group is not a constant but is quite dependent on solvent, as is evidenced by the variation of about 0.5 kcal/mol observed in this limited study.

Experimental Section

Spectra.—All nmr spectra for this work were run on a Varian A-60 spectrometer using two Hewlett-Packard wide-range oscillators, Model 200 CDR, for the side-band calibration. The frequency of the osillation was determined using a Hewlett-Packard electronic counter, Model 523 CR. This frequency was counted as the reciprocal to gain more accuracy, and the reading taken was the average of three ten-period averages displayed. The spectra were all run at a sweep time of 250 sec with a sweep width of 50 Hz, filter bandwidth of 4 Hz, and a radiofrequency field of 0.01 mG. In order to minimize machine error (nonlinear sweep, magnetic field shift, etc.), at least four spectra were run, each at different offset settings, and then each peak position was measured twice. In order to minimize other sources of error, several precautions were taken. All samples for a particular determination were made up to equal mole per cent concentration. This concentration was picked so as to make as dilute a solution as possible and still get a useful nmr signal. In one solvent (chloroform), determinations were made at two concentrations and the results indicated that the measurements were insensitive to concentration in the range used.

Preparation of Samples.—All samples were made up to a standard mole per cent concentration. The concentrations follow: carbon tetrachloride, 0.8 mmol/g; chloroform, 0.8 and 0.5 mmol/g; acetonitrile, acetone, isooctane, and acetic acid, 10 mmol/g. All samples had a standard amount of TMS measured by volume (20 μl).

The samples were then vacuum degassed using the standard method of freeze–vacuum–thaw cycles, freezing with liquid nitrogen.

Preparation of Compounds.—All compounds were synthesized as reported.[8d] The separation of the *cis* and *trans* isomers was by gas chromatography using a 6 ft × 3/8 in. glass column packed with 22% E-20,000 on Chromsorb W. The column temperature ranged from 105° for the 4-methyl derivative to 135° for the 4-*t*-butyl derivative. All compounds gave infrared spectra identical with those obtained before and the nmr spectra were all consistent with the structure assigned.

Purification of Solvents.—All solvents were obtained as reagent grade and then (with the exception of acetic acid which was used as is) dried over sodium sulfate overnight. The solvent was then decanted and distilled through a Vigreux column under nitrogen. All refractive indices checked within experimental error with those reported.[21]

Calculation of Data.—Since the determinations were made using the methylene hydrogens of the ester, any of four peak positions could have been used. Owing to some second-order broadening, all four peak positions were not equally well defined. In all cases the lowest field peak seemed to be the most distinctive, and it was this peak that was used in the reported data. Use of any of the other three peaks gave essentially the same results. Using the chemical shifts of the *cis*- and *trans*-4-*t*-butylcarbethoxycyclohexanes as the standard, the unknown equilibrium constants were calculated using eq 1.

The eight values obtained for each compound in each solvent were then used to calculate eight free energy differences using eq 2. These eight values were then used to calculate the mean free energy and the standard deviations by the standard method.

$$-\Delta G^\circ = RT \ln K \qquad (2)$$

Registry No.—I, 3289-28-9; *cis*-II, 25244-23-9; *cis*-III, 25244-24-0.

(20) N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Amer. Chem. Soc.*, **81**, 4074 (1959).

(21) C. D. Hodgman, Ed., "Handbook of Chemistry and Physics," 40th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958–1959.

Dehalogenation of Vicinal Dibromoalkanes with Triethyl Phosphite[1]

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In the most common example of the Michaelis–Arbuzov reaction,[2] a phosphonate ester is formed from an alkyl halide and a trialkyl phosphite (eq 1). When

$$RX + P(OR')_3 \longrightarrow RP(O)(OR')_2 + R'X \qquad (1)$$

1,2-dibromoethane is the alkyl halide, the reaction is normal, *i.e.*, the major products are the phosphonate esters **1** and **2** (eq 2).[3–6] However, for vicinal dihalides

$$BrCH_2CH_2Br + P(OEt)_3 \longrightarrow \underset{\mathbf{1}}{BrCH_2CH_2P(O)(OEt)_2} + \underset{\mathbf{2}}{(EtO)_2P(O)CH_2CH_2P(O)(OEt)_2} + EtBr \qquad (2)$$

with electron-withdrawing groups adjacent to both halogen atoms, dehalogenation is the principal reaction (eq 3). A number of electronegative substituents (G

$$G-\underset{X}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-G' + P(OR)_3 \longrightarrow G-\overset{|}{C}=\overset{|}{C}-G' + (RO)_2P(O)X + RX \qquad (3)$$

(1) Supported by National Science Foundation Undergraduate Research Participation Grant No. GY-5830.

(2) R. G. Harvey and E. R. De Sombre, "Topics in Phosphorus Chemistry," Vol. I, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1964, p 57.

(3) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **66**, 109 (1944); **70**, 1971 (1948).

(4) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(5) A. N. Pudovik and M. G. Imaev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 916 (1952).

(6) A. Y. Garner, E. C. Chapin, and P. M. Scanlon, *J. Org. Chem.*, **24**, 532 (1959).

and G′) have been shown to be effective: halogen,[7-11] carbonyl (including acyl, carboxyl, carbalkoxyl, and carbamyl),[12-14] aryl,[12,13,15] and perchloro-1,3-butadienylene.[16] An interesting related reaction is the dechlorination of 1,4-bis(trichloromethyl)benzene, a vinylog of hexachloroethane, by triethyl phosphite.[17]

There have been conflicting results as to the course of the reaction when only one electron-withdrawing substituent is present. 1-Alkoxy-1,2-dibromoethanes[18-19] and the methyl esters[20-22] and nitriles[20] of 2,3-dichloro- and 2,3-dibromopropionic acid were found to give phosphonate esters as the major products. However, Abramov and Il'ina[20] reported that a small amount of methyl acrylate is also formed from methyl 2,3-dibromopropionate, and one of us[23] found that the acrylate is the main product of this reaction. Arbuzov and Lugovkin[24] obtained styrene from 1,2-dibromo-1-phenylethane.

These contradictory observations prompted the present investigation. The objective was to broaden and clarify knowledge as to the effects of substituents (and, particularly, single substituents) on the reaction. The experimental method was to heat an equimolar mixture of a vicinal dibromoalkane and triethyl phosphite to 180–185° over a period of 5–6 hr with concurrent distillation of the more volatile products and then to distill the residue at reduced pressure. We confirmed the formation of styrene from 1,2-dibromo-1-phenylethane[24] and of methyl acrylate from methyl 2,3-dibromopropionate.[23] Debromination was also found to be the main reaction of 2,3-dibromopropionitrile. The last two results are in disagreement with those reported in ref 20–22. Turning to previously untried dibromides, we found that 3,4-dibromo-2-butanone and 2,3-dibromobutyronitrile behave similarly. In these reactions, about 2 mol of ethyl bromide per mole of substituted alkene and a viscous residue with the properties of ethyl metaphosphate[25] were obtained, suggesting the sequence shown in eq 4 and 5.

$$RCHBrCHBrR' + P(OEt)_3 \longrightarrow RCH{=}CHR' + EtBr + (EtO)_2P(O)Br \quad (4)$$

$$(EtO)_2P(O)Br \longrightarrow EtOPO_2 + EtBr \quad (5)$$

Equation 4 is the usual representation of the dehalogenation reaction,[2,9] and the diethyl phosphohalidate has, in fact, been isolated when the halogen is chlorine[7,10,16,17] or fluorine.[10,11] Under our experimental conditions, the diethyl phosphobromidate appears to pyrolyze (eq 5) in the manner described by Balarew[26] for the chloro compound.

3,4-Dibromobutyronitrile gave a 90% yield of ethyl bromide based on eq 4 and 5 but no alkene and a large amount of tar. We also repeated the reaction of 1,2-dibromopropane, which had been studied by Ford-Moore and Williams,[4] and confirmed their finding that it is strikingly unreactive. Most of the dibromide was recovered and no propene was formed. Finally, we dehalogenated stilbene dibromide which, surprisingly, had not been investigated before in this reaction.

In some of the runs, diethyl ethylphosphonate was a by-product. This is readily accounted for by the Michaelis–Arbuzov reaction of ethyl bromide with triethyl phosphite (eq 1, R = R′ = Et). In some instances small amounts of high-boiling liquids were obtained which were assumed to be normal Michaelis–Arbuzov products from the dibromide.

In Table I, the dibromides that were examined are listed in order of apparent reactivity toward debromination, using the ethyl bromide yield as the criterion. The first two compounds gave no alkene and a large amount of undistillable residue by the regular procedure. Under milder conditions, 3,4-dibromo-2-butanone produced 3-buten-2-one, indicating that the latter, a highly reactive vinyl monomer,[27] had polymerized completely in the earlier experiment. This explanation is not satisfactory for 3,4-dibromobutyronitrile, however, since the corresponding alkene polymerizes much less readily and none was isolated under milder conditions. It is also puzzling that this dibromide is apparently more reactive than 2,3-dibromoproprionitrile in which the cyano group is nearer the reaction site. Almost certainly a different process is involved here[28]

Table I
Effect of Substituents on the Debromination of RCHBrCHBrR′ with Triethyl Phosphite

R	R′	Registry no.	C_2H_5Br, % yield[a]	RCH=CHR′, % yield[a]	% conversion of dibromide
H	$COCH_3$	25109-57-3	95	0	100
			88[b]	49[b]	95[b]
H	CH_2CN	25109-74-4	90	0	100
H	CN	4554-16-9	80	83	c
CH_3	CN	25109-76-6	75	85	100
H	$COOCH_3$	1729-67-5	70	70	83
C_6H_5	C_6H_5	5789-30-0	50	58	58
H	C_6H_5	93-52-7	35	29	42
H	CH_3	78-75-1	8	0	14

[a] Based on eq 4 and 5. [b] Reaction run under milder conditions. [c] Not determined.

(7) H. R. Davis (to M. W. Kellogg Co.), U. S. Patent 2,742,510 (1956).
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(28) A possible alternative is

$$BrCH_2CHBrCH_2CN \longrightarrow BrCH_2CH{=}CHCN + HBr$$

$$HBr + (EtO)_3P \longrightarrow HOP(OEt)_2 + EtBr$$

$$BrCH_2CH{=}CHCN + HOP(OEt)_2 \longrightarrow HO(EtO)P(O)CH_2CH{=}CHCN + EtBr$$

This also yields 2 mol of ethyl bromide/mol of dibromide and a high-boiling compound (a phosphonic acid) as the other product.

TABLE II
REACTION OF *vic*-DIBROMOALKANES, RCHBrCHBrR′, WITH TRIETHYL PHOSPHITE

		Products, mol/mol of dibromide				
R	R′	Unreacted dibromide	EtBr	RCH=CHR′	Nonvolatile residue[a]	Other
H	$COOCH_3$	0.17	1.4	0.70	0.99	*b*
H	CN	*c*	1.6	0.83[d]	*c*	*c*
CH_3	CN		1.5	0.85	1.24[e]	
H	$COCH_3$	0.05	1.75	0.49	1.15	*f*, *g*
H	C_6H_5	0.58	0.69	0.29	0.77[h]	*i*
C_6H_5	C_6H_5	0.42	1.0	0.58	*c*, *j*	
H	CH_2CN		1.8		1.48	*k*
H	CH_3	1.0			0.18[e]	*l*
		0.86	0.16		0.14	*m*, *n*

[a] Assumed to be $EtOPO_2$ for calculation of yield. [b] Diethyl ethylphosphonate and an unidentified liquid, bp 63° (1.5 mm) in low yields. [c] Not determined. [d] Hydrolysis with 90% H_2SO_4 gave acrylamide, mp 81–83° (lit.[33] mp 84.5°). [e] High yield probably due to incomplete distillation. A higher pressure (30 mm) was used. [f] Diethyl ethylphosphonate, 0.14. [g] Reaction run at 30-mm pressure and volatile products collected in a cold trap. [h] Soluble in both $CHCl_3$ and ether, d^{25}_4 1.421, $n^{28}D$ 1.469. [i] Diethyl ethylphosphonate, 0.18, three unidentified high-boiling liquids in low yields. [j] Principally unreacted dibromide and stilbene. [k] Liquid (lachrymator) bp 49° (2 mm), $n^{30}D$ 1.4542, d^{25}_4 1.252, 2.1 g from 0.10 mol run. [l] Unreacted triethyl phosphite 0.70, liquid bp 92–94° (29 mm), 1.7 g from 0.10 mol run. [m] Unreacted triethyl phosphite, 0.54, diethyl ethylphosphonate, 0.03, three unidentified high-boiling liquids, 4.4 g from 0.10 mol run. [n] Reaction mixture refluxed (bath temperature 180°) for 5 hr.

and, therefore, it does not seem valid to compare this reaction with the others.

For the remaining dibromides, there is a good correlation between the yields of ethyl bromide and alkene by the stoichiometry of eq 4 and 5 except for 1,2-dibromopropane which gave no alkene. Again with this exception, a comparison of alkene yield with per cent dibromide conversion shows that debromination was the principal reaction.

In general, the reactivity order is consistent with the expected activating effects of the substituents ($COCH_3$, CN, $COOCH_3 > 2C_6H_5 > C_6H_5 > CH_3$), but in consideration of the marked deactivating effect of the electron-releasing methyl group in 1,2-dibromopropane, it is somewhat surprising that there is no significant difference in reactivity between 2,3-dibromopropionitrile and its 3-methyl homolog.

The most significant conclusion to be drawn from the results is that, in the reaction of equimolar amounts of a vicinal dibromoalkane and triethyl phosphite, a single electron-withdrawing substituent on one of the bromine-bearing carbon atoms is sufficient to make dehalogenation the principal reaction path, a situation which was by no means clear before.[2] In fact, the dehalogenation is a high-yield reaction when the substituent is strongly electron withdrawing. This is not to say that the products cannot be altered by varying the conditions. *E.g.*, it has been shown[9,13] that the dihalide–trialkyl phosphite ratio makes a difference when two activating groups are present. Formation of phosphonate esters is encouraged by excess phosphite, dehalogenation by excess dihalide. The same effect would undoubtedly be observed with only one activating substituent. Also, halo groups other than bromo might behave differently, although this seems unlikely.

Experimental Section

Materials.—The chemicals were commercial products with the exception of four of the dibromo compounds which were prepared by bromination of the appropriate substituted alkenes. These are listed with their boiling points and the bromination conditions (solvent and temperature): 2,3-dibromopropionitrile, bp 99–100° (25 mm) [lit.[29] bp 106–107° (22 mm)], CCl_4, 0–5°; 2,3-dibromobutyronitrile, bp 102–108° (17 mm) [lit.[30] bp 106–110° (18 mm)], CCl_4, 0–5°; 3,4-dibromobutyronitrile, bp 100–105° (3 mm) [lit.[31] bp 125–127° (10 mm)], CCl_4, 0–5°; 3,4-dibromo-2-butanone, isolated as a residue product in quantitative yield, pentane, −15°.[32]

Reaction of *vic*-Dibromides with Triethyl Phosphite.—The following procedure is typical. To 24.6 g (0.100 mol) of methyl 2,3-dibromopropionate in a 50-ml pear-shaped flask, 16.6 g (0.100 mol) of triethyl phosphite was added gradually with ice cooling and stirring. A few crystals of hydroquinone were placed in the reaction flask and in each of the receivers as a polymerization inhibitor. The flask was connected to a distillation apparatus (Vigreux column, condenser, ice-cooled receiver), and the mixture was heated to 185° over a period of 6 hr. Two fractions, bp 38–41° and 48–72°, were collected during this time. The residue was distilled at reduced pressure to yield two more fractions, bp 55–63° (1.5 mm) and 63° (1.5 mm).

The boiling points, densities, refractive indices, and ir spectra of fractions 1 and 2 indicated that they were mixtures of ethyl bromide and methyl acrylate. This was confirmed and the compositions determined by glpc (Carbowax 20M on Chromosorb-W column) using authentic samples of these compounds as standards. Fraction 3 was unreacted methyl 2,3-dibromopropionate (glpc and ir spectrum). Fraction 4 was shown by glpc to contain additional unreacted dibromide, diethylethylphosphonate, and a third component which was not identified.

The residue from the distillation (10.7 g) was a viscous liquid. From its properties and yield, it appeared to be crude ethyl metaphosphate. This is reported[25] to be an undistillable syrup, soluble in halogenated solvents, insoluble in ether, d^{25}_4 *ca.* 1.42, $n^{25}D$ *ca.* 1.438. Our product was soluble in $CHCl_3$ but partly soluble in ether (ether-insoluble fraction, d^{25}_4 1.45, $n^{29}D$ 1.450), ether-soluble fraction, d^{25}_4 1.33, $n^{29}D$ 1.438.

Differences in the stabilities and physical properties of the products necessitated some variations in the method. Using the procedure described above, 3,4-dibromo-2-butanone gave a 95% yield of ethyl bromide but no other distillable material. However, by mixing the reactants at Dry Ice temperature and conducting the reaction at 30-mm pressure with flash distillation of the volatile products into a cold trap as formed, a 49% yield of 3-buten-2-one was obtained. 3,4-Dibromobutyronitrile also gave a high yield (90%) of ethyl bromide and little other distillable material by the standard procedure. Accordingly, the same modification was tried here but without success. Apparently, this dibromide is much less reactive than 3,4-dibromo-2-butanone, because the distillate was mainly unreacted triethyl phosphite.

For the stilbene dibromide reaction, the residue after distillation proved to be largely unreacted dibromide. This was purified by washing with water and then methanol. Stilbene was obtained from the methanol extract, but the aqueous washings

(29) C. Moureu and R. L. Brown, *Bull. Soc. Chim. Fr.*, **27**, 901 (1920).

(30) P. Bruylants, *Bull Soc. Chim. Belg.*, **31**, 175 (1922).

(31) L. Leclercq and A. Bruylants, *ibid.*, **58**, 5 (1949).

(32) E. R. Buchman and H. Sargent, *J. Amer. Chem. Soc.*, **67**, 400 (1945).

left only a small residue on evaporation, suggesting that most of the ethyl metaphosphate decomposed during the distillation.

All of the 1,2-dibromopropane was recovered using the standard procedure. Even when the reaction mixture was refluxed for 5 hr, 86% of the dibromide survived. In both runs, provision was made to collect evolved propene over water, but none was produced. The experimental data are summarized in Table II.

Registry No.—Triethyl phosphite, 122-52-1.

(33) E L. Carpenter and H. S. Davis, *J. Appl. Chem.* **7**, 671 (1957).

Formation of α,β-Diphenyl-γ-butyrolactone from Styrene Oxide by the Action of Organo Transition Metal Complexes

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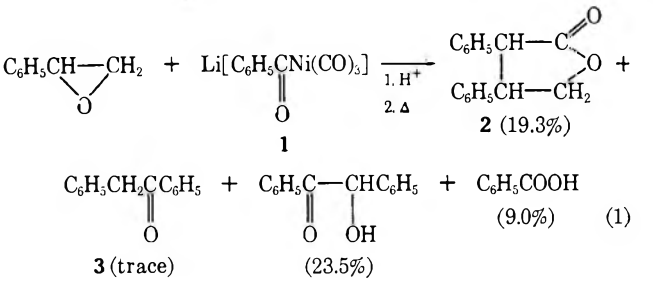
It has been known that epoxides are transformed to the corresponding ketones by the action of cobalt tetracarbonyl anion or dicobalt octacarbonyl.[1] In the presence of carbon monoxide, carbon monoxide insertion reactions occur to give β-hydroxy carboxylic acid esters in alcohol solution[2] and α,β-unsaturated acids in benzene solution.[3] Furthermore, under the oxo conditions, α,β-unsaturated aldehydes are produced.[4] Although the interesting reaction behaviors of σ-organometallic compounds toward olefins, acetylenes, ketones, or aldehydes have been evealed during these 10 years, the reactivity of alkyl or acyl transition metal complexes toward epoxides has not yet been defined. However, the facility with which π-methallylnickel bromide reacts with styrene oxide to give 2-methyl-4-phenyl-5-hydroxypentene-1[5] suggests that the analogous reactions of alkyl or acyl transition metal complexes might be important in organic synthesis.

Lithium acylmetal carbonylates, prepared by the reaction between organolithium compounds and metal carbonyls, are efficient nucleophilic acylating agents, and many useful organic reactions using these reagents, such as syntheses of aldehydes,[6] acyloins,[7] α-diketones,[7] unsymmetrical ketones,[7] and 1,4-dicarbonyl compounds[8] have been reported. The reaction of lithium aroylnickel carbonylate with styrene oxide was carried out and it was found that the product is not the expected aroylphenylethyl alcohol but α,β-diphenyl-γ-butyrolactone, which seemed to be produced by dimerization and hydrogen abstraction of styrene oxide. In this paper, we report the formation of α,β-diphenyl-γ-butyrolactone from styrene oxide by the action of lithium aroylnickel carbonylate or dibenzyliron tetracarbonyl, which is a new type of transformation of olefin oxide and would promise a unique synthetic route to lactones from olefin oxides.

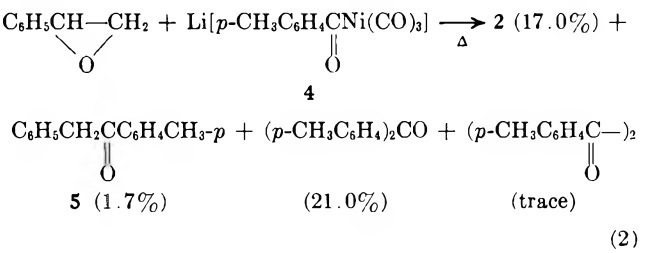
Results and Discussion

Styrene oxide undergoes reaction with lithium benzoylnickel carbonylate (**1**) to give *trans*-α,β-diphenyl-γ-butyrolactone (**2**, 19.3%), benzyl phenyl ketone (**3**, trace), benzoin (23.5%), and benzoic acid (9.0%). The latter two compounds are produced by the hydrolysis of **1**,[7] and the former two seem to be the products derived from the reaction between styrene oxide and **1**.



(1)

The formation of **2** was not explained by the combination of benzoyl group in **1** with styrene oxide; so, in order to clarify whether the phenyl groups in **2** came from styrene oxide or **1**, an analogous reaction was carried out using lithium *p*-toluoylnickel carbonylate (**4**) instead of **1**.



(2)

After the reaction was complete, the ether was evaporated and the benzene-soluble part was distilled under reduced pressure. Then, **2** was obtained in a similar yield to that from reaction 1, and the formation of benzyl *p*-tolyl ketone **5** corresponded to the formation of **3**. Di-*p*-tolyl ketone and *p,p'*-bitolyl are the products formed by thermal decomposition of **4**.[7] The fact that **2** was obtained in both reactions 1 and 2 in similar yields shows that the aroyl group in **1** or **4** is not incorporated into the structure of **2**, and so 2 mol of styrene oxide is transformed to 1 mol of **2** with the aid of the aroylnickel carbonylate complex. As the reaction mixture before distillation (bath temp 200–250°) under reduced pressure does not show a peak due to the carbonyl group of the γ-lactone at 1780 cm^{-1}, heating is necessary for the formation of **2** in addition to the aroylnickel carbonylate complex. By column chromatographic separation of the residual oil after removal of the solvent, the crude material, which had a peak at 3600–3200 cm^{-1} and no peaks in the carbonyl region (2100–1630 cm^{-1}), was obtained from the methanol eluate, and this material, which could not be purified by recrystallization, was transformed to **2** by heating above 200°. This suggests that an alcoholic compound is

(1) J. L. Eisenmann, *J. Org. Chem.*, **27**, 2706 (1962).

(2) (a) J. L. Eisenmann, R. L. Yamartino, and J. F. Howard, Jr., *ibid.*, **26**, 2102 (1961); (b) A. Rosenthal and J. N. C. Whyte, *Can. J. Chem.*, **46**, 2239 (1968).

(3) W. A. McRae and J. L. Eisenmann, U. S. Patent 3,024,275 (1962).

(4) W. D. Niederhauser, U. S. Patent 3,054,813 (1962).

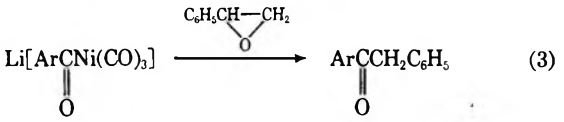
(5) E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, **89**, 2755 (1967).

(6) M. Ryang, I. Rhee, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **37**, 341 (1964).

(7) M. Ryang, Song K-M, Y. Sawa, and S. Tsutsumi, *J. Organometal. Chem.*, **5**, 305 (1966).

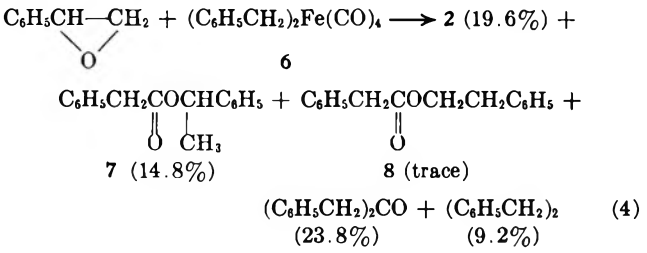
(8) (a) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2159 (1968); (b) E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969).

formed prior to the formation of 2 and heating of the compound results in the formation of 2. The formation of 3 in reaction 1 and 5 in reaction 2 is important in spite of the low yields, for they are the sole products, respectively, formed by the addition of the aryl group in the nickel complex to styrene oxide, but the mechanism is still open to question.



(3)

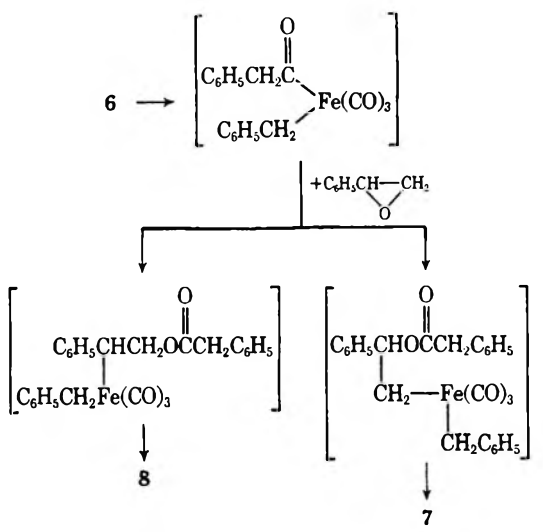
Further, to establish the formation of γ-lactone from styrene oxide by the action of metal complexes, the reactions of styrene oxide with dibenzyliron tetracarbonyl, nickel carbonyl, iron tetracarbonylate anion, and palladium dichloride were carried out. Styrene oxide gives 2 and α- and β-phenylethyl phenylacetate (7 and 8) by the reaction with dibenzyliron tetracarbonyl



(4)

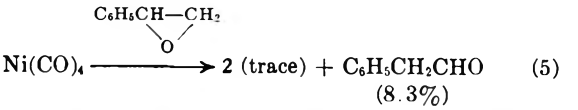
6 (reaction 4). In the formation of the esters 7 and 8, the sequences shown in Scheme I seem to be probable.

SCHEME I



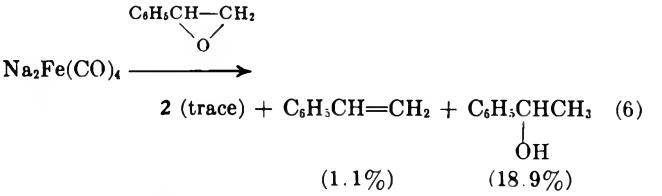
When propylene oxide was used instead of styrene oxide, isopropyl phenylacetate, and *n*-propyl phenylacetate were produced. The formation of the γ-lactone 2 was not explained in terms of the attack of the benzyl or the phenylacetyl group to styrene oxide, for in the analogous reaction using *p*-methylbenzyl bromide instead of benzyl halide as a partner in the reaction with iron tetracarbonylate anion, 2 was also produced in a similar yield (14.9%). Styrene oxide (2 mol) is transformed to 2 as well as in the case of reaction 1 or 2.

On the other hand, in the case of nickel carbonyl, styrene oxide was transformed to 2 (trace amount) and phenylacetaldehyde (8.3%) but not to acetophenone.



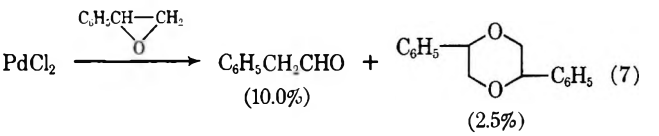
(5)

From the reaction of styrene oxide with disodium iron tetracarbonylate, 2 (trace amount), styrene (1.1%), and α-phenylethyl alcohol (18.9%) were obtained (reaction 6). Therefore, nickel carbonyl or disodium iron



(6)

tetracarbonylate is not effective for the transformation of styrene oxide to 2. As the formation of 2 from styrene oxide seems to involve the dimerization and the hydrogen abstraction processes, it is expected that palladium dichloride which causes easy hydrogen transfer may cause the analogous reaction behavior to occur, but the formation of 2 was not observed and the isolated products were phenylacetaldehyde (10.0%) and *trans*-2,5-diphenyl-1,4-dioxane (2.5%, reaction 7).[9]



(7)

It is interesting to note that styrene oxide is transformed to *trans*-α,β-diphenyl-γ-butyrolactone by the action of lithium aroylnickel carbonylate or dibenzyliron tetracarbonyl in contrast to the reaction of styrene oxide with π-methallylnickel bromide,[5] in which case the epoxide ring was cleaved as a result of the addition of the methallyl group to form 2-methyl-4-phenyl-5-hydroxypentene-1. A study of the mechanism of the γ-lactone formation reaction, which remained unexplored because of the lack of structure determination of the precursor to the γ-lactone, and further studies of the reaction between σ-organometallic compounds and olefin oxides are continuing and will be reported in the near future.

Experimental Section

All reactions were carried out under nitrogen. Yields of **2**, **3**, **5**, **7**, and **8** and the products obtained in parts F, G, and H were calculated based on the used styrene oxide, and those of the other products were calculated based on the used organic halide. Gas–liquid partition chromatographic analyses were performed on a Yanagimoto GCG-5DH instrument using 2.5 m × 3 mm columns packed with 5% SE-30 (column temperature 160–280°, 4° min^{-1}, carrier gas He, 15 cc min^{-1}) or on a Hitachi K53 instrument using 2.4 m × 3 mm columns packed with Polyester DS (column temperature 160°, carrier gas He, 25 cc min^{-1}).

A. Reaction of Styrene Oxide with Lithium Benzoylnickel Carbonylate.—The ether solution (50 ml) of nickel carbonyl (17.1 g, 0.1 mol) was added dropwise to the ether solution of phenyllithium prepared from bromobenzene (15.7 g, 0.1 mol) and lithium metal (1.5 g, 0.22 g-atom) at −70 to −60°, and the mixture was stirred for 2 hr at that temperature.[7] Then styrene

(9) This compound was known to be produced by the action of tetrachlorotin on styrene oxide: R. K. Summerbell and M. J. Kland-English, *J. Amer. Chem. Soc.*, **77**, 5095 (1955).

oxide (15 g, 0.13 mol) was added to this lithium benzoylnickel carbonylate solution and the mixture was stirred for 5 hr from −60° to room temperature. Benzene (100 ml) was added to this solution and the mixture was stirred for 5 hr at 50–60°. After hydrolysis with 4 *N* hydrochloric acid (50 ml), the reaction mixture was extracted with ether, and this ether solution was separated by extraction with 5% aqueous sodium hydroxide to an acidic part and a neutral part. From the acidic part, benzoic acid (1.1 g, 9.0%) was obtained. The neutral part was distilled under reduced pressure after removal of the solvents to give the following fractions: 1, bp 50–100° (5 mm), 1.6 g; 2, bp 100–180° (5 mm), 9.4 g; 3, bp 180–200° (5 mm), 6.6 g; and 4, bp 200–210° (2 mm), 2.4 g. Most of fraction 1 consisted of the recovered styrene oxide. Recrystallization of fractions 2 and 3 from petroleum ether (bp 30–60°)–benzene gave *trans*-α,β-diphenyl-γ-butyrolactone (**2**) [mp 96–96.5°; white crystals; *m/e* 238, 193, 179, 116; $\nu_{C=O}$ 1780 cm^{-1}; nmr ($CDCl_3$) τ 6.05 (2 H), 5.1–5.8 (2 H), 2.75 (10 H) (*Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92; mol wt, 238. Found: C, 81.00; H, 5.90); 3 g, 19.3%] and benzoin (2.5 g, 23.5%). Benzyl phenyl ketone (**3**, trace) was identified by glpc of fractions 2 and 3. Alkali hydrolysis (KOH–ethylene glycol) of **2** gave α,β-diphenyl-γ-hydroxybutyric acid: mp 147–148°; white crystals; *m/e* 256, 238, 179, 137; $\nu_{C=O}$ 1690 cm^{-1}; ν_{O-H} 3600–3300 cm^{-1}. Reduction of **2** with lithium aluminum hydride gave 2,3-diphenyl-1,4-butanediol: mp 102–102.5°; white crystals; *m/e* 242, 212, 194, 180, 165; ν_{O-H} 3400 cm^{-1}; nmr ($CDCl_3$) τ 7.25 (2 H), 6.60 (2 H), 6.10 (4 H), 3.00 (10 H). As fraction 4 had no peaks at the carbonyl region of the lactone, more purification was not carried out.

B. Reaction of Styrene Oxide with Lithium *p*-Toluoylnickel Carbonylate.—In place of bromobenzene, *p*-bromotoluene (17.1 g, 0.1 mol) was used, and an analogous reaction was carried out under the same conditions as those of reaction A. After the reaction was over, the reaction mixture was extracted with hot benzene and the benzene-soluble part was distilled under reduced pressure to give **2** (3.0 g, 17.0%), benzyl *p*-tolyl ketone **5** (0.5 g, 1.7%), di-*p*-tolyl ketone (4.4 g, 21.0%), and *p,p'*-bitolyl (trace). The identification and the calculation of yields of the products were carried out by glpc analysis. Instead of distillation under reduced pressure, the reaction mixture was separated by alumina column chromatography, and **5**, di-*p*-tolyl ketone, and *p,p'*-bitolyl were also obtained from a benzene or ether eluate. From the methanol eluate, a yellow solid (16.4 g) was obtained, and it showed a peak at 3600–3200 cm^{-1} but no peaks at the carbonyl region. Attempts to purify this yellow solid were unsuccessful but it was transformed to **2** (2 g) by distillation under reduced pressure above 200°.

C. Reaction of Styrene Oxide with Dibenzyliron Tetracarbonylate.—To the tetrahydrofuran solution (150 ml) of disodium iron tetracarbonylate prepared from sodium dispersion (1.4 g, 0.06 g-atom) and triiron dodecacarbonyl (5 g, 0.01 mol), styrene oxide (15.5 g, 0.13 mol) was added at −40 to −30°. After stirring for 1–2 hr at that temperature, benzyl bromide (10.3 g, 0.06 mol) was added and the reaction mixture was stirred for 2 hr from −30° to room temperature and then for 4 hr under refluxing tetrahydrofuran. The solvent was removed by distillation and then the residue was extracted with hot benzene. The benzene-soluble part was distilled under reduced pressure after removal of benzene to give the following fractions: 1, bp 80–140° (0.4 mm), 2.0 g; 2, bp 140–200° (1 mm), 6.0 g. A glpc analysis of these fractions showed that fraction 1 consisted of dibenzyl ketone (1.5 g, 23.8%) and bibenzyl (0.5 g, 9.2%), and fraction 2 consisted of **2** (2.8 g, 19.6%), α-phenylethyl phenylacetate **7** (2.2 g, 14.8%), and β-phenylethyl phenylacetate **8** (trace). An analogous reaction using benzyl iodide (13.1 g, 0.06 mol) gave the same products: dibenzyl ketone (1.4 g, 22.2%), bibenzyl (1.9 g, 35.0%), **2** (2.3 g, 16.1%), **7** (0.2 g, 1.4%), and **8** (trace).

D. Reaction of Styrene Oxide with Di-(*p*-methylbenzyl)iron Tetracarbonyl.—In place of benzyl halide, *p*-methylbenzyl bromide (11.1 g, 0.06 mol) was used and an analogous reaction was carried out under the same conditions as that in part C. Products were α-phenylethyl alcohol (0.8 g, 11.1%), *p,p'*-dimethylbibenzyl (0.8 g, 13.2%), di-(*p*-methylbenzyl) ketone (1.9 g, 27.9%), and **2** (1.0 g, 14.9%), which were identified by glpc analysis.

E. Reaction of Propyrene Oxide with Dibenzyliron Tetracarbonyl.—Propyrene oxide (14.0 g, 0.24 mol) and benzyl iodide (13.1 g, 0.06 mol) were used and an analogous reaction was carried out under the same conditions as in reaction C, and isopropyl phenylacetate (0.18 g, 1.7%), *n*-propyl phenylacetate (0.14 g, 1.3%), dibenzyl ketone (1.5 g, 23.8%), and bibenzyl (2.5 g, 45.6%) were identified by glpc analysis.

F. Reaction of Styrene Oxide with Nickel Carbonyl.—A mixture of styrene oxide (2.4 g, 0.02 mol) and nickel carbonyl (3.5 g, 0.02 mol) in ether (10 ml) and benzene (10 ml) was stirred for 3 hr at 10° and then for 5 hr at 50°. After removal of the solvents and the remaining nickel carbonyl, the residual oil was distilled under reduced pressure to give phenylacetaldehyde (0.2 g, 8.3%) and **2** (trace), which were identified by glpc analysis. Phenylacetaldehyde was also confirmed by its infrared (2750, 1730 cm^{-1}) and nmr (τ 0.55) spectra. No acetophenone was detected by glpc.

G. Reaction of Styrene Oxide with Disodium Iron Tetracarbonylate.—Styrene oxide (1.56 g, 0.013 mol) was added to the tetrahydrofuran solution of disodium iron tetracarbonylate, prepared from triiron dodecacarbonyl (1.7 g, 0.0034 mol) and sodium dispersion (0.7 g, 0.03 g-atom), and the mixture was stirred for 9 hr under refluxing tetrahydrofuran. After removal of the solvent, the residue was filtered and the filtrate was distilled under reduced pressure to give styrene (0.015 g, 1.1%), α-phenylethyl alcohol (0.3 g, 18.9%), and **2** (trace), which were identified by glpc analysis.

H. Reaction of Styrene Oxide with Palladium Dichloride.—Styrene oxide (4.8 g, 0.04 mol) was added to a suspension of palladium dichloride in benzene (50 ml); the mixture was stirred for 27 hr under reflux of benzene. The mixture was filtered and the filtrate was distilled under reduced pressure after removal of benzene to give the following fractions: 1, bp 60–82° (12 mm), 0.62 g; 2, bp 100–134° (1.5 mm), 0.89 g; 3, bp 150–210° (1 mm), 1.0 g. A glpc analysis of fractions 1 and 2 showed that the recovered styrene oxide (0.5 g, 10.4%) and phenylacetaldehyde (0.48 g, 10.0%) were contained in these fractions. Recrystallization of fraction 2 from petroleum ether gave *trans*-2,5-diphenyl-1,4-dioxane: mp 180–180.5° (lit.[9] 174–175°); white plates; *m/e* 240, 149, 120, 104, 91. *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71; mol wt, 240. Found: C, 80.69; H, 6.93. As fraction 3 had no peaks at the carbonyl region of the lactone, more purification was not carried out.

Registry No.—**1**, 25154-62-5; **2**, 25109-89-1; **4**, 25154-63-6; **6**, 25154-64-7; styrene oxide, 96-09-3; di-(*p*-methylbenzyl)iron tetracarbonyl, 25154-65-8; α,β-diphenyl-γ-hydroxybutyric acid, 25109-09-4; 2,3-diphenyl-1,4-butanediol, 6583-62-6.

Acknowledgment.—The authors gratefully acknowledge the assistance of Mr. Kazumasa Kinugasa and Mr. Masaki Iwafuzi for the experimental work.

Synthesis and Some Properties of 2,2,6,6-Tetramethyl-1,4,8-trioxaspiro[2.5]octane, an Epoxy Ketene Ketal[1]

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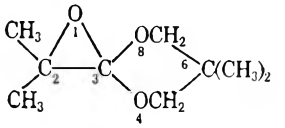
The synthesis of compounds such as the title compound **I** was undertaken because of their possible use as valuable reagents for the synthesis of a variety of α-substituted acids desired for testing for biological activity. In addition, the novel functionality, epoxide and ortho ester, would make a study of their chemical reactivity of interest.

(1) This work was supported by Grant No. GM 12379 from the National Institutes of Health.

The synthesis of I (20–25% yield) was best accomplished by treatment of 2,2-dimethyl-3-hydroxypropyl α-bromoisobutyrate (II) with sodium hydride in 1,2-dimethoxyethane (glyme). The ester II was prepared by ester interchange between ethyl α-bromoisobutyrate and neopentyl glycol,[2] or, preferably, by reaction of α-bromoisobutyroyl bromide with neopentyl glycol.

$$(CH_3)_2CBrCOOCH_2C(CH_3)_2CH_2OH \xrightarrow{NaH}$$

II



I

In spite of many attempts to synthesize I in which the bases used were sodium hydride, sodium methoxide, sodium amide, metallic sodium, and potassium *t*-butoxide and the solvents were ether, glyme, benzene, dimethyl sulfoxide, hexamethylphosphoramide, and *t*-butyl alcohol, the best yield of I was in the 20–25% region (NaH in glyme). Several attempts to make analogs of I in which corresponding esters of α-bromopropionic and α-bromoacetic acids were used (β-hydroxyethyl esters were also tried) failed. When the chloro analog of II was used, the yield of I was slightly worse than in the case of II.

The epoxy ketene ketal I proved to be very inert to basic reagents as it was recovered in high yield after heating with several strongly basic reagents (see Experimental Section). After treatment with methyllithium in ether for 2 hr at reflux, or with sodium methoxide in methanol at room temperature, I was surprisingly converted in high yield into 2,2-dimethyl-3-hydroxypropyl α-hydroxyisobutyrate (III).

On the other hand, I was readily converted in high yield into III on treatment with aqueous acid. On treatment of a solution of I in benzene (or anisole) at room temperature with 1 equiv of aluminum chloride, a 65% yield of 3-chloro-2,2-dimethylpropyl α-hydroxyisobutyrate (IV) was obtained. When boron trifluoride etherate was used instead of aluminum chloride, a 70% yield of III was obtained. No products resulting from alkylation or acylation of the aromatic nuclei were obtained.

Experimental Section[3]

2,2-Dimethyl-3-hydroxypropyl α-Bromoisobutyrate (II).—To a well-stirred suspension of 76 g of sodium bicarbonate in 416 g of neopentyl glycol dissolved in 500 ml of dry glyme was added, during 10 min, 205 g of α-bromoisobutyryl bromide.[4] After stirring for 15 min following the bromide addition, the solid was removed by filtration, and the filtrate was concentrated under reduced pressure to remove most of the solvent. A solution of the residue in ether was washed several times with water to remove neopentyl glycol. After the usual work-up, distillation in a spinning-band column afforded 155 g (69%) of II as a colorless liquid: bp 76° (0.1 mm); ir bands at 3400 (2.94, broad) and 1720 cm^{-1} (5.81 μ); nmr bands ($CDCl_3$) at τ 6.0 (s, 2 H, OCH_2), 6.70 (s, 2 H, CH_2OH), 7.1 (s, 1 H, OH), 8.1 [s, 6 H, $(CH_3)_2$-CBr] and 9.05 [s, 6 H, $(CH_3)_2C$].

Anal. Calcd for $C_9H_{17}BrO_3$: C, 42.7; H, 6.8. Found: C, 42.5; H, 6.4.

The ester II can also be prepared by ester interchange of ethyl α-bromoisobutyrate with neopentyl glycol but the yield (50%) is less, and the product is less pure (90–95%) by glpc, (XE-60 column).

Other Halogenated Hydroxyalkyl Esters.—In a similar way 2,2-dimethyl-3-hydroxypropyl α-bromopropionate was prepared from α-bromopropionyl bromide as a liquid: bp 95–100° (0.6 mm); nmr bands (CCl_4) at τ 5.52 (q, 1 H, $CHBrCH_3$), 5.97 (s, 2 H, OCH_2), 6.63 (s, 2 H, CH_2OH), 6.72 (s, 1 H, OH), 8.17 (d, 3 H, CH_3CHBr), and 9.05 (s, 6 H, $(CH_3)_2C$), in 73% yield.

Anal. Calcd for $C_8H_{15}BrO_3$: C, 40.2; H, 6.3. Found: C, 40.0; H, 6.1.

Similarly, 2,2-dimethyl-3-hydroxypropyl α-bromoacetate was obtained from α-bromoacetyl bromide as a colorless liquid: bp 105–110° (0.6 mm); nmr bands (CCl_4) at τ 6.03 (s, 2 H, $BrCH_2$), 6.15 (s, 2 H, OCH_2), 6.70 (s, 2 H, CH_2OH), 6.85 (s, 1 H, OH), and 9.07 [s, 6 H, $(CH_3)_2C$] in 86% yield.

Anal. Calcd for $C_7H_{13}BrO_3$: C, 37.4; H, 5.8. Found: C, 37.1; H, 5.7.

When α-chloroisobutyroyl chloride was reacted with neopentyl glycol as above, the reaction mixture had to be warmed to 60–70° for 1 hr for reaction to be complete. 2,2-Dimethyl-3-hydroxypropyl α-chloroisobutyrate was isolated as a colorless liquid: bp 82–85° (0.5 mm); nmr bands (CCl_4) at τ 5.83 (s, 2 H, OCH_2), 6.53 (s, 2 H, CH_2OH), 6.75 (s, 1 H, OH), 8.15 [s, 6 H, $(CH_3)_2$-CCl], and 9.03 [s, 6 H, $(CH_3)_2C$] in 77% yield.

Anal. Calcd for $C_9H_{17}ClO_3$: C, 51.8; H, 8.2. Found: C, 51.8; H, 8.3.

When α-bromoisobutyryl bromide and α-bromopropionyl bromide were treated with ethylene glycol in glyme as above, the purification of the 2-hydroxyethyl esters was difficult. Analytical samples of 2-hydroxyethyl α-bromopropionate were not obtained, as glpc analyses showed (XE-60 column) that the esters were only about 80% pure. Because no trace of epoxy ketene ketals (similar to I) were obtained by treating these esters with basic reagents (see below), no further attempts at purification were made.

2,2,6,6-Tetramethyl-1,4,8-trioxaspiro[2.5]octane (I).—In a typical experiment the washed solid from 5 g of a 54% suspension of sodium hydride in mineral oil was added all at once to a solution of 29.4 g (0.11 mol) of II in 200 ml of dry glyme. The evolution of hydrogen was rapid. After 15 min the sodium bromide, collected by filtration and washed with solvent, weighed 11.3 g (about theoretical). Removal of solvent from the filtrate on a rotary evaporator afforded a viscous oil which partly solidified. Filtration with the aid of hexane yielded 4.3 g (23%) of I, mp 157–159°, which did not melt higher after several recrystallizations from hexane, from which it separated as colorless elongated prisms which could be sublimed at 80–100° (0.5 mm). No hydroxyl or carbonyl bands appeared in the ir; nmr bands ($CDCl_3$) at τ 6.45 (m, 4 H, OCH_2), singlets at 8.72, 8.87, 9.00, and 9.25 (12 H, 4 CH_3).

Anal. Calcd for $C_9N_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.4; H, 9.7.

The viscous oil obtained by removal of solvent from the hexane mother liquor decomposed on attempted vacuum distillation (0.1–0.3 mm). The oil before heating showed a broad hydroxyl band and a carbonyl peak in the ir at 1725 cm^{-1}.

Reactions of I.—On treatment of a suspension of 3.0 g of I in 100 ml of water with a few milliliters of concentrated hydrochloric acid, the solid slowly dissolved. After 40 min ether extraction afforded 3.1 g (91%) of 2,2-dimethyl-3-hydroxypropyl α-hydroxyisobutyric acid (III): bp 118–120° (10 mm); ir bands (neat) at 3570 (broad) and 1740 cm^{-1}; nmr ($CDCl_3$) τ 5.93 (s, 2 H, $COCH_2$), 6.57 (s, 2 H, OH), 6.62 (s, 2 H, CH_2OH), 8.55 [s, 6 H, $COHC(CH_3)_2$], and 9.05 [s, 6 H, $(CH_3)_2CCH_2$].

Anal. Calcd for $C_9H_{18}O_4$: C, 56.2; H, 9.5. Found: C, 56.5; H, 9.5.

To a stirred solution of 1.0 g of I in 100 ml of dry ether was added 8 ml of freshly prepared 0.74 *M* methyllithium in ether. After 2 hr at reflux the mixture was cooled and treated with

(2) We thank the Tennessee Eastman Co. for a generous sample of neopentyl glycol.

(3) All temperatures are uncorrected. Microanalyses by nmr spectra were taken on a Varian A-60 instrument. The term "worked up in the usual way" means that an ether or ether–benzene solution of the products was washed with aqueous alkali and saturated salt solutions, dried by filtration through anhydrous magnesium sulfate, and heated under reduced pressure on a rotary evaporator. Glpc analyses were done on 2% XE-60 (nitrile–silicone gum rubber), SE-30 (silicone gum rubber–methyl), and QF-1 (fluorinated silicone gum rubber), on chromosorb W columns. Nmr reported in τ relative to TMS, 10.

(4) C. W. Smith and D. G. Norton, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 348.

water, and the ether layer was dried over magnesium sulfate. Removal of the ether left 0.94 g (82%) of oil which, by preparative glpc on an Aerograph autoprep Model A-700 using a 10-ft 20% FFAP (free fatty acid phase) on Chromosorb W at 180°, was shown to consist almost entirely of III plus a small amount of neopentyl glycol. The sample of III was shown to be identical with that described above.

When 1.0 g of I was dissolved in the solution made by adding 0.14 g of sodium to 100 ml of pure methanol and the product isolated after 1 hr, there was obtained 0.97 g (85%) of a mixture similar to that described above, *i.e.*, mostly III and a small amount of neopentyl glycol.

Attempts to react the epoxy ketene ketal I with sodium and potassium *t*-butoxide in refluxing *t*-butyl alcohol, with piperidine or di-*n*-butylamine, with sodium amide (in ammonia or glyme), and with the sodium enolate of cyclohexanone failed. In all cases recovery of I was almost quantitative.

To a stirred solution of 1.0 g of I in 20 ml of dry benzene was added 0.80 g of anhydrous aluminum chloride in one portion. Two layers were formed but soon the mixture was homogeneous. After 1 hr at room temperature 15% hydrochloric acid was added. After a conventional work-up, removal of the benzene left an oily residue which on distillation yielded 0.79 g (65%) of 3-chloro-2,2-dimethylpropyl α-hydroxyisobutyrate (IV): bp 98–100° (10 mm); ir (neat) bands at 3625 and 1740 cm^{-1}; nmr bands ($CDCl_3$) at τ 5.98 (s, 2 H, CH_2Cl), 6.58 (s, 2 H, CH_2O), 6.66 (s, 1 H, OH), 8.58 [s, 6 H, $COHC(CH_3)_2$], and 8.97 [s, 6 H, $(CH_3)_2CCl$]. The analytical sample was obtained by preparative glpc on a 5-ft QF-1 on chromosorb W column at 120°.

Anal. Calcd for $C_9H_{17}ClO_3$: C, 51.8; H, 8.2. Found: C, 51.7; H, 8.3.

When a similar experiment was performed with anisole instead of benzene, the yield of IV (isolated) was 70%. In a similar experiment in anisole with boron fluoride etherate replacing the aluminum chloride, an aqueous work-up followed by extraction with ether afforded III in 70% yield. Treatment of I with anhydrous hydrogen fluoride (followed by an aqueous work-up) for 1 hr, benzoic acid in glyme for 1 day at 25°, and *p*-chlorophenol in glyme for 2 hr at reflux afforded III in 82–89% yields.

Registry No.—I, 25109-69-7; II, 25109-70-0; III, 25109-71-1; IV, 25109-72-2; 2,2-dimethyl-3-hydroxypropyl α-bromopropionate, 25109-73-3; 2,2-dimethyl-3-hydroxypropyl α-bromoacetate, 25109-56-2; 2,2-dimethyl-3-hydroxypropyl α-chloroisobutyrate, 25109-55-1.

Fluoronitroaliphatics. V. Carbonyl Additions of Fluorodinitromethane

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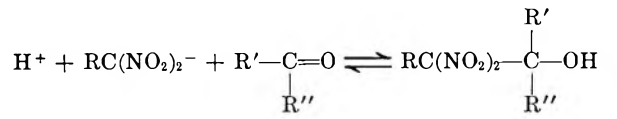
The addition of 1,1-dinitroalkanes and trinitromethane to carbonyl groups (Henry reaction) has been successful primarily with formaldehyde as the acceptor.[1] Far fewer additions to other carbonyl compounds giving isolable and stable product have been reported,[2] and some of these must, in the absence of a rigorous proof of structure, be regarded as unconfirmed in view of the ability of trinitromethane and probably other polynitroalkanes to form isolable complexes with some carbonyl compounds.[3]

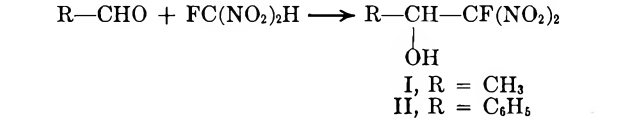
This frequent lack of stability or existence of adducts of polynitroalkanes to higher aldehydes and ketones is due to the reversibility of the Henry reaction and the fact that the equilibrium in these cases does not lie predominantly on the product side. A number of such



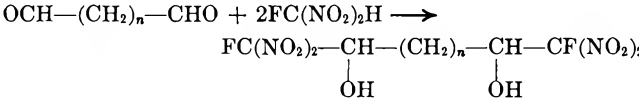
equilibria have been studied by Rondestvedt and coworkers[4] and by Hall[5] who clearly demonstrated the dependence of the Henry equilibrium on the stability of the carbanion, $RC(NO_2)_2^-$ and on the degree of substitution at the carbinol carbon atom.

We wish now to report on a number of carbonyl additions of fluorodinitromethane, a new dinitroalkane whose preparation has been reported only recently.[6] Fluorodinitromethane was found to be the weakest acid[7] among all known 1,1-dinitroalkanes despite the presence of an additional strongly electron-withdrawing substituent. Its carbanion is the least stable known dinitrocarbanion.

Based on these and the above considerations, fluorodinitromethane should therefore form particularly stable carbonyl adducts. Qualitative observations demonstrating the unusual stability of 2-fluoro-2,2-dinitroethanol toward dissociation into formaldehyde and fluorodinitromethane in alkaline medium[6] are in agreement with this expectation. Regarding the addition to higher aldehydes, we find that fluorodinitromethane in buffered aqueous solution (pH 6.5–7.5) readily reacts with acetaldehyde, glyoxal, malondialdehyde, succindialdehyde, glutardialdehyed, and benzaldehyde to give isolable 1-fluoro-1,1-dinitro-2-alkanols I–VI in 50–80% yield.[8] Only one diastereomer of III



I, R = CH_3
II, R = C_6H_5



III, n = 0
IV, n = 1
V, n = 2; a, mp 86–87°
b, mp 90–92 and 102–104° (polymorphs)
VI, n = 3; a, mp 86–88°
b, mp 99–101 and 106.5–108° (polymorphs)

(1) P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **64**, 19 (1964); G. A. Shevkhgeimer, N. F. Pyatakov, and S. S. Novikov, *Usp. Khim.*, **28**, 48 (1958).

(2) P. Duden and G. Ponndorf, *Ber.*, **38**, 2031 (1905); N. Maraus and R. Zelinski, *J. Amer. Chem. Soc.*, **72**, 5329 (1950); H. Plaut, U. S. Patent 2,544,103 (1951); R. Schenk, Swedish Patent 135,832 (1952).

(3) For example, a 2:1 complex of trinitromethane and 2,2,4,4-tetramethyl-1,3-cyclobutanedione has been isolated as colorless crystals devoid of OH absorption in the infrared (private communication, L. A. Kaplan, this laboratory), and we have obtained strong indication of complex formation between fluorodinitromethane and acetone.

(4) C. S. Rondestvedt, Jr., M. Stiles, and A. L. Krieger, *Tetrahedron*, **19**, 197 (1963).

(5) T. N. Hall, *ibid.*, *Suppl.*, **No. 1**, 115 (1963); *J. Org. Chem.*, **29**, 3587 (1964); **30**, 3157 (1965).

(6) H. G. Adolph and M. J. Kamlet, *ibid.*, **34**, 45 (1969).

(7) V. I. Slovetskii, L. V. Okhobystina, A. A. Feinzil'berg, A. I. Ivanov, L. J. Birynkova, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2063 (1965); H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966).

(8) After completion of this manuscript our attention was directed to the work of Eremenko, *et al.*, who prepared III by the same method in *ca.* 5% yield, and I by the aqueous fluorination of potassium 1,1-dinitropropanol-2: L. T. Eremenko and G. V. Oreshko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 380, 1765 (1969).

TABLE I
PMR SPECTRA OF $FC(NO_2)_2CH(OH)R$[a]

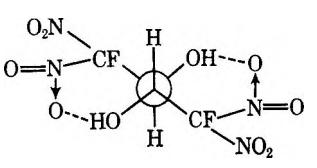
Compound	Solvent	>CH–	–OH	–R
I	$CDCl_3$	5.13 m, on irradiating OH, pair of q J_{HF} = 17 cps $J_{HH(CH_3)}$ = 6.5 cps	2.83 d, $J_{HH(OH)}$ = 6 cps	CH_3, 1.47 two d J_{HF} = 1.2 cps
	CD_3CN + ~10% D_2O	5.13 two q J_{HF} = 20.5 cps $J_{HH(CH_3)}$ = 6.5 cps	3.30 s	CH_3, 1.38 two d J_{HF} = 1.0 cps
II	$CDCl_3$	6.10 d J_{HF} = 19 cps	2.04 s	C_6H_5, 7.37 s
III (single diastereomer)	CD_3NO_2	5.72 m (14 lines or more)	5.13 d (unresolved substructure) J_{HH} = 8 cps	...
IV (mixture of diastereomers)	CD_3NO_2	5.4 broad m	4.41 and 4.46	CH_2, 2.00 and 2.05
Va[b]	CD_3NO_2	5.16 broad m	4.15 s	CH_2, ~1.95 m
Vb				
VIa[b]	CD_3NO_2	5.07 two t; on irradiating CH_2 region, d J_{HF} = 19 cps	3.95 s	CH_2, ~1.7 m
VIb				

[a] Obtained on a Varian HA-100 spectrometer; chemical shifts in ppm relative to TMS (δ = 0.00) as internal standard. [b] Although the chemical shifts were essentially the same for the diastereomers a and b, the structure of the multiplets, particularly in the CH_2 region, was distinctly different.

was produced, but mixtures of diastereomers were obtained of the adducts IV–VI.

The stability of these alcohols is demonstrated by the fact that the diols V and VI are separable into their diastereomers by fractional recrystallization from chloroform. Thus, at least in this solvent no dissociation to fluorodinitromethane and aldehyde occurs. Thermally, I–VI dissociate with varying ease on heating to temperatures above 100°. The benzaldehyde adduct II is the least stable. It was, in fact, not obtained completely pure since it contains detectable (by nmr and ir) equilibrium concentrations of both fluorodinitromethane and benzaldehyde even at room temperature. All fluorodinitroalkanols I–VI are completely dissociated in 0.01 *N* aqueous hydroxide solutions and exhibit the characteristic uv absorption of fluorodinitromethane anion (λ_{max} 382 nm, ϵ 19,400).

The ir spectra of the alcohols I–VI show the expected nitro absorption at 1300 ± 20 and 1600 ± 20 cm^{-1} and generally two or more OH bands between 3300 and 3550 cm^{-1}. III in the crystal (spectrum obtained in a fluorolube mull) exhibits only one fairly sharp OH band at 3450 cm^{-1} which may indicate the presence of a highly symmetrical structure such as the *trans*-decalin type conformation of *meso*-III.



Also notable are the large differences in OH absorption, again in the crystal, between the diastereomers of V and VI: Va, three bands, 3200 (strong, broad), 3360 (medium, sharp), 3505 (medium, sharp) cm^{-1}; Vb (mp 102–104°), two bands, 3460 (medium, sharp), 3505 (medium, sharp) cm^{-1}; VIa, two bands, 3400 (strong, sharp), 3480 (medium, sharp) cm^{-1}; VIb (mp 106.5–108°); two bands, *ca.* 3350 (strong, broad), 3470 (medium, sharp) cm^{-1}. These and particularly the following additional differences in the ir spectra of the diastereomers are useful for monitoring the extent of their separation by fractional crystallization: Va has a band of medium intensity of 908 cm^{-1} which is absent in Vb (Nujol mull); VIa has a moderately strong band at 1090 cm^{-1}, absent in VIb (Nujol mull).

The pmr spectra of the alcohols I–VI are recorded in Table I. Some of the compounds exhibit H–OH coupling, even in $CDCl_3$ (I), while others show no coupling even in CD_3NO_2 where such coupling has been shown to be induced in methanol.[9] Compound I exhibits long-range fluorine coupling to the methyl protons with a coupling constant of about 1 cps.

Experimental Section

General (Caution).—Fluorodinitromethane was prepared from 2-fluoro-2,2-dinitroethanol;[6] it is a skin irritant as well as an explosive and should be handled with *care*. Most of its derivatives also exhibit moderate to considerable sensitivity to initiation by impact, shock, friction, and other means.

Microanalyses and molecular weight determinations were by Professor Mary H. Aldridge, American University, Washington, D. C., and by Mr. D. J. Glover of this laboratory. The ir spectra were obtained on a Beckman IR 4 spectrometer with NaCl prisms. Melting points and boiling points are uncorrected.

1-Fluoro-1,1-dinitropropanol-2 (I).—A 38% aqueous solution of acetaldehyde, 5.2 g, was added to a well-stirred and cooled mixture of 3.7 g of fluorodinitromethane and 5 ml of water. A few drops of saturated sodium bicarbonate solution was added and the mixture stirred with continued cooling for 1 hr. It was then acidified with dilute sulfuric acid, the product extracted into methylene chloride, and the extract dried and distilled. Obtained was 4 g (79%), bp 40–42° (0.5 mm).

(9) N. F. Hepfinger and P. A. Clarke, *J. Org. Chem.*, **34**, 2572 (1969).

Anal. Calcd for $C_3H_5FN_2O_5$ (168.09): C, 21.43; H, 3.00; F, 11.30; N, 16.67. Found: C, 21.1; H, 3.1; F, 11.4; N, 16.4.

2-Fluoro-2,2-dinitro-1-phenylethanol (II).—To 50 ml of a $NaOH-KH_2PO_4$ buffer of pH 7[10] was added 2.1 g of freshly distilled benzaldehyde; the mixture was stirred and cooled in an ice bath, 5 g of fluorodinitromethane was added, and stirring and cooling were continued for 1 hr. Methylene chloride, 25 ml, was then added to the mixture, the phases were separated, and the organic phase was dried ($MgSO_4$) and freed from solvent *in vacuo* at ambient temperature. The residual pale yellow oil was shown by nmr (Table I) to be mainly II. However, small amounts (<10%) of benzaldehyde and fluorodinitromethane were also detected in the nmr spectrum and a carbonyl band (benzaldehyde) was present in the ir spectrum.

1,4-Difluoro-1,1,4,4-tetranitrobutane-2,3-diol (III).—Fifty milliliters of a $NaOH-KH_2PO_4$ buffer solution of pH 7[10] was cooled in an ice bath, and 17.7 g of a 30% aqueous solution of glyoxal was added with stirring, followed by 25 g of fluorodinitromethane. The mixture was stirred for 0.5 hr at 0–5°, then acidified with dilute sulfuric acid, saturated with NaCl, and extracted with four 25-ml portions of ether. The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was triturated with a small amount of methylene chloride; the mixture was chilled in the freezer and filtered to give 21.5 g of crude III, mp 175–180°. One recrystallization from methylene chloride or benzene gave 20.6 g (67%), mp 178–180° dec; ϵ in 0.01 *N* aqueous KOH (382 nm) 38,200.

Anal. Calcd for $C_4H_4F_2N_4O_{10}$ (306.10): C, 15.69; H, 1.31; F, 12.42; N, 18.31. Found: C, 15.8; H, 1.6; F, 12.1; N, 18.1

1,5-Difluoro-1,1,5,5-tetranitropentane-2,4-diol (IV).—A solution of 5.5 g of sodium malonaldehyde[11] in dilute sodium hydroxide (60 ml of water + 1.5 ml of 2 *N* sodium hydroxide) was cooled to about 0° in an ice–salt bath. With stirring and continued cooling, 15.5 g of fluorodinitromethane was added, most of which dissolved rapidly. A saturated solution of potassium dihydrogen phosphate was then added dropwise until the mixture had a pH of about 7. After 0.5 hr of stirring at 0° the solution was acidified with dilute sulfuric acid and extracted with four 50-ml portions of methylene chloride. The extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. The remaining oil was held under a vacuum of 1 mm for several hours until it had solidified completely. The product was broken up under and digested thoroughly with 25 ml of chloroform and filtered, and the solid was washed with 5 ml of chloroform; 10.8 g of diol, mp 74–77°, was thus obtained. On chilling the filtrate another 0.6 g, mp 70–83°, was obtained; total crude yield, 57%. This material may be purified by vacuum sublimation (0.2 mm, 70°), followed by recrystallization from chloroform, mp 80–84° (mixture of diastereomers), ϵ in 0.01 *N* aqueous KOH (382 nm) 38,800.

Anal. Calcd for $C_5H_6F_2N_4O_{10}$: C, 18.76; H, 1.89; F, 11.87; N, 17.50; mol wt, 320.13. Found: C, 19.0; H, 2.0; F, 11.8; N, 17.6; mol wt (benzene), 312, 313.

1,6-Difluoro-1,1,6,6-tetranitrohexane-2,5-diol (V).—A mixture of 12 g of 2,5-dimethoxytetrahydrofuran, 80 ml of water, and 2 ml of 2 *N* sulfuric acid was stirred at 55° for 1 hr. The solution was then cooled below 5°, 20 g of fluorodinitromethane was added with stirring, and the mixture was brought to a pH of 7 with saturated sodium bicarbonate solution. Stirring and cooling in an ice bath was continued for 0.5 hr, after which time the reaction mixture was acidified with dilute sulfuric acid and extracted with four 30-ml portions of methylene chloride. The extract was dried, the solvent removed *in vacuo* (1 mm), and the semisolid residue triturated with 30 ml of chloroform. After standing in the refrigerator, 20.2 g of crude diol, mp 70–85°, was collected. After two recrystallizations from chloroform the material (15–17 g, 55–63%) melted at 80–100° (mixture of diastereomers), ϵ in 0.01 *N* aqueous KOH (328 nm) 38,000.

Anal. Calcd for $C_6H_8F_2N_4O_{10}$: C, 21.57; H, 2.41; F, 11.37; N, 16.77; mol wt, 345.15. Found: C, 21.8; H, 2.6; F, 10.7; N, 16.7; mol wt (chloroform), 335, 336.

Repeated fractional recrystallization of the mixture of diastereomers from chloroform gave two sharp melting fractions which were readily distinguishable by their ir spectra (see above): Va, mp 86–87°; and Vb, mp 90–92°, 102–104° (isomorphs).

1,7-Difluoro-1,1,7,7-tetranitroheptane-2,6-diol (VI).—A solution of 40 g of 25% aqueous glutaraldehyde in 100 ml of water was cooled to 0° and 25 g of fluorodinitromethane was added. The mixture was stirred and cooled in an ice bath, and the pH was adjusted to 7 by dropwise addition of a saturated aqueous sodium bicarbonate solution. After stirring at about 0° for 0.5 hr, the solution was acidified with dilute sulfuric acid and extracted four times with a total of 200 ml of methylene chloride. Drying the extract and removing the solvent *in vacuo* gave 28.5 g of crude diol; after one recrystallization from chloroform the yield was 26 g (74%). mp 78–101°, ϵ in 0.01 *N* aqueous KOH (382 nm) 37,600.

Anal. Calcd for $C_7H_{10}F_2N_4O_{10}$: C, 24.15; H, 2.90; F, 10.91; N, 16.09; mol wt, 348.18. Found: C, 24.3; H, 2.9; F, 10.7; N, 15.8; mol wt (chloroform), 355, 357.

The pure diastereomers VIa and VIb were obtained by fractional recrystallization of the above mixture from chloroform. The higher melting isomer VIb, mp 99–101°, 106.5–108° (isomorphs), is the more abundant and less soluble and is isolated readily. Either of the isomorphic forms of VIb may be obtained by appropriately seeding saturated solutions of the material in chloforom. The second diastereomer, VIa, had mp 86–88°.

Registry No.—I, 22692-03-1; II, 25244-34-2; III, 25244-35-3; IV, 25244-36-3; V, 25244-37-5; VI, 25244-38-6; fluorodinitromethane, 7182-87-8.

Acknowledgment.—The author wishes to thank Dr. M. J. Kamlet for stimulating discussions and Dr. L. A. Kaplan for obtaining the nmr spectra.

(10) Clark and Lubs: 29.63 ml of 0.1 *N* NaOH and 50 ml of 0.1 *M* KH_2PO_4 diluted to 100 ml.

(11) T. V. Protopopova and A. P. Skoldinov, *Zh. Obshch. Khim.*, **28**, 240 (1958); *Chem. Abstr.*, **52**, 12754 (1958).

Sensitized Photolysis of *cis,cis*-3,5-Cycloheptadienone. On the Intermediacy of *cis,trans*-3,5-Cycloheptadienone[1]

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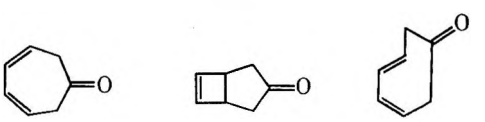
It was shown earlier that direct photolysis of *cis,cis*-3,5-cycloheptadienone (I) leads to decarbonylation and ring opening to a mixture of hexatrienes.[3,4] It is clear that this reaction originates from the excited singlet state (S_1) of I from the observations[4] that (a) triplet quenchers are without effect on this reaction, and (b) triplet sensitization gives a different reaction, isomerization of I to the valence tautomer II. By analogy



I II III

with the course of triplet-sensitized valence isomerization of *cis,cis*-1,3-cyclooctadiene,[5] it was postulated[4]

(1) Part XXV of a series on the photochemistry of unsaturated ketones in solution. Part XXIV: D. I. Schuster and D. H. Sussman, *Tetrahedron Lett.*, No. 19, 1661 (1970).

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) O. L. Chapman and G. W. Borden, *J. Org. Chem.*, **26**, 4185 (1961); O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1220 (1962).

(4) D. I. Schuster, B. R. Sckolnick, and F.-T. H. Lee, *ibid.*, **90**, 1300 (1968).

(5) R. S. H. Liu, *ibid.*, **89**, 112 (1967).

that the conversion of I to II involves, initially, sensitized isomerization of I to the highly strained *cis,trans*-3,5-cycloheptadienone (III), which then undergoes thermally a symmetry-allowed ring closure to II. Because of the strain in III, it would be expected that the thermal ring closure (III → II) should proceed at much lower temperatures than the ring closure of *cis,trans*-1,3-cyclooctadiene.[5,6]

Experiments were attempted in order to obtain evidence as to the intermediacy of III in the sensitized photolysis of I. In earlier work, low-temperature irradiation of *cis*-2-cycloheptenone led to the *trans* isomer, identified from its infrared absorption spectrum and by adduct formation with cyclopentadiene and furan.[7] In the case of I, such a study is complicated by the fact that the proposed[4] *cis–trans* isomerization of I occurs, if at all, only on triplet sensitization, and potential trapping reagents, such as cyclic dienes, would also be expected to act as efficient quenchers of the sensitizer triplets, competing with energy transfer to I. In the event, irradiation of benzophenone in the presence of I and cyclopentadiene (CPD) in ethyl ether at Dry Ice–ethanol temperatures led to partial quenching of the conversion of I → II, but the only new products observed by gas–liquid chromatography (glpc) and column chromatography of the photolysate were CPD dimers.[8] Similar results were obtained when the relative proportions of reactants were varied.

Entirely analogous results were obtained using furan as the potential trapping reagent.[9] The possibility that furan might react with II was eliminated by carrying out the sensitized conversion of I → II in the absence of furan, adding furan and reirradiating. No diminution in the amount of II was observed. Since β-acetonaphthone (E_T = 59 kcal/mol)[11] has a π,π^* configuration in its lowest triplet state, cycloaddition to furan is expected to be unimportant,[10] so that furan should not be consumed in side reactions. Nevertheless, β-acetonaphthone-sensitized irradiation of I at −70° in the presence of furan gave no products attributable to trapping of III, according to glpc and column chromatography.

The failure to trap any reactive intermediate in the sensitized isomerization of I to II implies either that (a) the *cis–trans* dienone III is not an intermediate, or that (b) III isomerizes thermally to II even at low temperatures much more rapidly than it reacts with either cyclopentadiene or furan. The negative results do not allow an unambiguous decision between these alternatives, although it seems to us more likely that alternative (a) is correct, considering the strain anticipated in III on the basis of inspection of molecular models. It seems probable that the triplet of II, formed by energy transfer from the sensitizer, begins to twist in the direction of forming III with a *trans* double bond (as with cycloheptenone,[7] cyclooctenone,[12] and even cyclohexenone[13]). However, crossover to the ground-state potential surface leading to II probably occurs before III is reached. The same sort of explanation may hold for the triplet-sensitized reactions of monocyclic cyclohexenones, particularly photocycloadditions leading to *trans*-fused bicyclo[4.2.0]-octane derivatives.[13,14]

In order to determine the triplet energy of I, studies were made with a series of sensitizers at room temperature and at −70°. In addition to sensitization at room temperature by benzophenone and β-acetonaphthone, the conversion I → II was sensitized by chrysene (E_T = 57 kcal/mol),[15] α-acetonaphthone (E_T = 56),[11] biacetyl (E_T = 55),[11] benzil (E_T = 54),[11] fluorenone (E_T = 53),[11] and 1,2,5,6-dibenzanthracene (E_T = 52),[15] but not by benzoquinone (E_T = 53–55)[16] and pyrene (E_T = 49).[11,15] Quantum yields for the sensitized isomerization of I at 366 nm at room temperature were found to be 0.54 for β-acetonaphthone and 0.01 for fluorenone, whereas intersystem crossing efficiencies for these sensitizers are, respectively, 0.84 and 0.93.[17] These data suggest that the triplet energy of I is probably near 59 kcal/mol.

At −70°, sensitized isomerization of I → II could be effected by benzophenone, α- and β-acetonaphthone, and, surprisingly, dibenzanthracene,[18] but not at all by benzil or fluorenone, even on prolonged irradiation. Benzophenone and β-acetonaphthone were ineffective in sensitizing reaction of I in an ether glass at liquid nitrogen temperatures (−196°), under conditions where extensive reaction occurred at −70°. The temperature effect on fluorenone- and β-acetonaphthone-sensitized photolysis of I was studied over the interval 0 to −70°, and a gradual falloff in quantum yield with decreasing temperature (measured at 10° intervals) was observed. Surprisingly, plots of relative quantum yield *vs.* temperature were linear, while more theoretically defensible plots of log Φ *vs.* $1/T$ gave a much poorer linear correlation. Fair linear correlations were also observed between Φ and the reciprocal viscosity of the solvent, ethyl ether.

The quantum yield for sensitized formation of II from I is given by eq 1, where Φ_{ic} is the quantum yield for intersystem crossing of the sensitizer, k_{et} the rate constant for energy transfer, k_{ds} the rate constant for radiationless decay of sensitizer triplets, k_r that for reaction of triplet I to give II, and k_d the sum of rate constants for all decay processes of triplet I. Very little is

$$\Phi = \Phi_{ic}\left(\frac{k_{et}}{k_{et} + k_{ds}}\right)\left(\frac{k_r}{k_r + k_d}\right) \quad (1)$$

known about the expected temperature dependence of each term in eq 1. It is reasonable to assume that the temperature dependence would be most critical for k_{et}, especially when the energy transfer is endothermic, and perhaps also for the partitioning of triplet I, that is,

(6) W. J. Nebe and G. J. Fonken, *J. Amer. Chem. Soc.*, **91**, 1249 (1969); K. M. Shumate, P. M. Neuman, and G. J. Fonken, *ibid.*, **87**, 3996 (1965).

(7) P. E. Eaton and K. Lin, *ibid.*, **87**, 2051 (1965); E. J. Corey, M. Tada, R. LeMahieu, and L. Libit, *ibid.*, **87**, 2051 (1965).

(8) G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963).

(9) Triplet-sensitized dimerization of furan apparently does not occur, but adduct formation with benzophenone and other triplets is well documented.[10]

(10) D. R. Arnold, *Advan. Photochem.*, **6**, 301 (1968); G. R. Evanega and E. B. Whipple, *Tetrahedron Lett.*, No. 23, 2163 (1967); G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963).

(11) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4537 (1964).

(12) P. E. Eaton and K. Lin, *ibid.*, **86**, 2087 (1964).

(13) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968).

(14) P. J. Wagner and D. J. Buchek, *J. Amer. Chem. Soc.*, **91**, 5090 (1969).

(15) D. P. Craig and J. G. Ross, *J. Chem. Soc.*, 1589 (1954).

(16) P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, **1**, 21 (1968); see p 127.

(17) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

(18) There is the possibility that dibenzanthracene transfers energy from its second triplet state, as is well established for anthracene and some 9,10-disubstituted anthracenes; see R. S. H. Liu and R. E. Kellogg, *J. Amer. Chem. Soc.*, **91**, 250 (1969), and earlier papers cited therein.

for the ratio k_r/k_d. It is tempting to postulate that energy transfer takes place to an upper vibrational level of I so as to allow a vertical Franck–Condon transition to the excited triplet state. Since the diene system of I is twisted,[3,4] flattening of the molecule corresponds to an increase in the ground-state potential energy. The nmr spectrum of I indicates that the α-hydrogens are equivalent at room temperature; *i.e.*, ring flipping is rapid on the nmr time scale at room temperature. The efficiency of energy transfer would be related to the population of the vibrational levels only if decay of sensitizer triplets competes with energy transfer to vibrationally excited ground states of I. Clearly, much more data are necessary to establish whether such an effect can operate in this or other systems. An alternative possibility is that low-energy triplet sensitizers are inducing reaction by a Schenck mechanism[19] involving initial bond formation to I. Such a mechanism has been invoked for sensitized olefin isomerization induced by donors with lowest n,π^* triplet states.[20]

Since the earlier publication,[4] a preliminary value for the quantum yield of the direct photodecarbonylation of I has been measured at 313 nm and found to be 0.31 for disappearance of I. Since intersystem crossing from the excited singlet is clearly unimportant,[4] the inefficiency of the reaction must be attributed either to rapid radiationless decay of the singlet or to reversible formation of an intermediate formed by α cleavage on one side of the double bond.[21,22] Decarbonylation might proceed from such a diradical intermediate, in competition with return to starting material I, or might be the result of a concerted reaction of the excited singlet which competes with α cleavage. Further experiments are necessary to decide between these alternatives. It is certain, however, that all pathways for singlet-state deactivation and reaction are much faster than intersystem crossing to the triplet,[4] although this does not appear to be the case with some unsaturated ketones of comparable symmetry.[23]

Experimental Section

Materials.—*cis,cis*-3,5-Cycloheptadienone was prepared as described previously.[4] Solvents, reagents, and sensitizers were purified by distillation or recrystallization before use.

Photolysis Procedure.—Photolyses of I at room temperature, sensitized and unsensitized, were carried out as described previously.[4] Photolyses at liquid nitrogen (−196°) temperatures were carried out in a Pyrex tube immersed in liquid nitrogen in a large dewar attached at one end to a quartz glass tube. The dewar was placed inside a Rayonet reactor and irradiated with 3650-Å lamps for 4.5 hr. Photolyses at −70° were carried out by immersing a Hanovia immersion cell containing a 450-W high-pressure mercury lamp in a large dewar containing Dry Ice and ethanol. There was an insulating air space around the immersion well provided by a large reaction cell so that water could be circulated within the immersion well without freezing. Samples were in solution in Pyrex tubes surrounding the immersion well outside the insulation but within the dewar. Typical runs involved 40–60 mg of dienone I in 35 ml of ether containing enough sensitizer to absorb >99% of the incident light. In some runs, Corning 7380 filters were placed between the lamp and the sample tube to restrict the incident light to >340 nm. The progress of the reaction was followed by glpc analysis[4] on a 4-ft column of 5% SE-30 silicone on Chromosorb G.

For the controlled-temperature irradiations between 0 and −70°, the degassed solutions of I, sensitizer, and internal standard were sealed in a 3- or 4-mm Pyrex tube, which was irradiated externally with a Hanovia 450-W lamp inside a Pyrex immersion well through a Corning 7380 filter. The temperature within the tube was maintained using the cooling apparatus for the esr spectrometer, in which a stream of nitrogen at a set temperature was passed around the outside of the sample tube. The heat exchanger for the cooling gas was a Dry Ice–acetone bath. Experiments at lower temperatures with a liquid nitrogen bath for cooling the gas were less reproducible. Analysis by glpc was carried out as above.

Quantum yields for disappearance of I were determined as described earlier,[24] using a Bausch and Lomb high-intensity grating monochromator and ferrioxalate actinometry.

Registry No.—I, 25090-28-2; III, 25090-29-3.

Acknowledgments.—We are grateful to the Alfred P. Sloan Foundation and to an Institutional Grant from the National Institutes of Health for support of this research.

(19) G. O. Schenck and R. Steinmetz, *Bull. Soc. Chim. Belg.*, **71**, 781 (1962).

(20) N. C. Yang, J. I. Cohen, and A. Shani, *J. Amer. Chem. Soc.*, **91**, 3265 (1969); J. Saltiel, K. R. Neuberger, and M. Wrighton, *ibid.*, **91**, 3658 (1969).

(21) P. J. Wagner and R. W. Spoerke, *ibid.*, **91**, 4437 (1969).

(22) In the earlier paper, it was explicitly stated that the results did not exclude a two-step nonconcerted decarbonylation mechanism; see especially footnote 34 in ref 4.

(23) P. S. Engel and H. Ziffer, *Tetrahedron Lett.*, **59**, 5181 (1969).

(24) D. I. Schuster and D. J. Patel, *J. Amer. Chem. Soc.*, **90**, 5145 (1968).

Photochemical Rearrangements of α-Benzyloxystyrenes to β-Phenylpropiophenones

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There are a number of examples of photochemical rearrangements of aryl ethers, *e.g.*, the rearrangements of aryl phenyl ethers to arylphenols,[1a,b] that of phenoxycarboxylic acids to hydroxyphenylcarboxylic acids,[2] and that of allyl phenyl ether to allylphenol.[3] They may be initiated by homolytic fission of phenoxy–carbon bonds in electronically excited ether molecules, since phenol is detected in the products. Among them, the photochemical rearrangement of allyl phenyl ether, or Claisen rearrangement, is important since it can be discussed in view of the orbital symmetry.[4]

The rearrangement of α-benzyloxystyrene to β-phenylpropionphenone catalyzed by azobisisobutyronitrile (AIBN) has been known to be intermolecular radical-chain reaction, where $\cdot CH_2Ph$ acts as a chain carrier.[5a] The rearrangement also occurs on heating at *ca.* 200° in the absence of AIBN. In this case, orbital symmetry arguments may suggest that the shift of 1,3-benzyl radical with continuous overlap is not

(1) (a) D. P. Kelly and J. T. Pinhey, *Tetrahedron Lett.*, 5933 (1966); (b) H.-I. Joschek and S. I. Miller, *J. Amer. Chem. Soc.*, **88**, 3269 (1966).

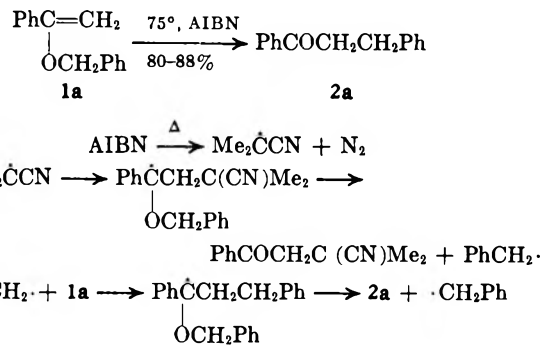
(2) D. P. Kelly and J. T. Pinhey, *Tetrahedron Lett.*, 3427 (1964).

(3) (a) M. S. Kharasch, G. Stampa, and W. Nudenberg, *Science*, **116**, 309 (1952); (b) G. Koga, N. Kikuchi, and N. Koga, *Bull. Chem. Soc. Jap.*, **41**, 745 (1968).

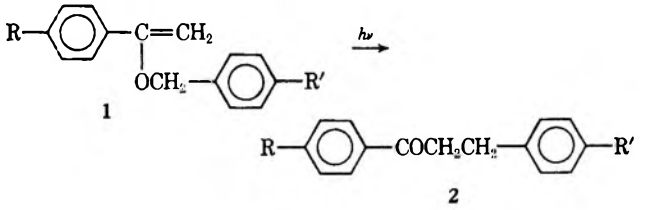
(4) (a) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965); (b) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(5) (a) K. B. Wiberg, R. R. Kintner, and E. L. Motell, *J. Amer. Chem. Soc.*, **85**, 450 (1963). (b) It was observed that **1a** was stable but **1c** was rearranged partially to the corresponding photo ketone (**2c**) in a glpc column.

feasible. This means the intermolecular nature of the thermal rearrangement.



In contrast, if the similar rearrangement occurs photochemically, the orbital symmetry arguments suggest that the 1,3-benzyl shift should be feasible and hence the rearrangement is intramolecular. In fact, the rearrangement of **1a** easily occurs on uv irradiation in *n*-hexane at room temperature, resulting in a high yield (91%) of **2a**.



a, R, R′ = H
b, R = H; R′ = Me
c, R = Me; R′ = Me
d, R = Cl; R′ = H
e, R = MeO; R′ = H

The present paper describes results of our study on the nature of this photorearrangement including the effects of a heavy atom solvent and various substituents to discuss a probable mechanism.

A *n*-hexane solution of 0.32 m*M* of α-benzyloxystyrene (**1a**) was irradiated in a sealed quartz cell. The uv spectra at intervals of 30 min are shown in Figure 1. After 1.5 hr irradiation the spectrum becomes identical with that of authentic β-phenylpropiophenone (**2a**), and the yield was estimated uv spectrophotometrically to be 91%. Passing oxygen through the solution before irradiation gave lower yield (35%) of **2a**, while passing oxygen during irradiation gave no photo ketone but an autoxidation product, benzoic acid.

This rearrangement was further confirmed by the following experiments. For the isolation of the photo ketone, a *n*-hexane solution of **1a** (1 g) was irradiated at 28° for 11 hr, N_2 gas being bubbled into the mixture during irradiation. After irradiation, the reaction mixture was chromatographed on silicic acid column to isolate the photo ketone (0.2 g) which was identified as **2a** by direct comparison of mp 69.5–70.0° (lit.[5a] 70.0–71.0°) and uv and ir spectra with the authentic sample. The lower yield on the preparative scale might be caused by deposit of photoproducts on the wall of the reaction vessel during irradiation.

The quantum yields for the formation of photo ketones are listed in Table I. Accuracy is within ±0.01. The order of reactivity by these *para* substituents in styrene residue is Me > H > MeO > Cl, although the substituent effect is small. The effect of *p*-methyl group in benzyl residue is negligibly small.

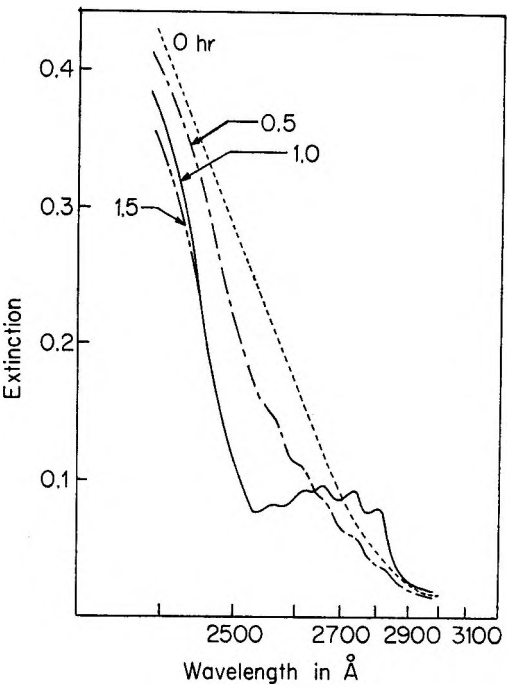


Figure 1.—Absorption spectra for **1a** in *n*-hexane as a function of irradiation time (hr) at 25–28°.

TABLE I
QUANTUM YIELDS, φ, FOR THE FORMATION OF PHOTO KETONES (2) IN *n*-HEXANE AT 20–23°

Compd	R	R′	φ
2a	H	H	0.11
2b	H	Me	0.12
2c	Me	Me	0.15
2d	Cl	H	0.04
2e	MeO	H	0.07

For the estimation of intramolecularity of rearrangement, an equimolar mixture of **1a** (φ = 0.11) and **1c**[5b] (φ = 0.15) was irradiated in *n*-hexane, the product being chromatographed on a silicic acid column to isolate photo ketones. The resulting mixture of photo ketones was then subjected to glpc analysis. Thus 92% intramolecularity was observed for the rearrangement by comparing the areas of peaks. The results of crossed reaction indicate that an intramolecular mechanism is predominating as has been observed in other photochemical rearrangements such as the rearrangements of aryl esters[6] and sulfonamides.[7]

The absorption spectra of **1** are relatively simple and λ_{max} in 2470–2610 Å are shown in Table II. The irradiation with 2400–2700 Å light probably populates the π,π^* states of **1**. As described above, the rearrangement is quenched by oxygen. Hence, it seems likely that a triplet state rather than a singlet state is involved in the rearrangement in spite of the low efficiency of intersystem crossing of most conjugated olefins.[8] An increase of quantum yield for the formation of **2a** to 0.47 in *n*-propyl chloride as a heavy atom solvent confirms the above conclusion. The result

(6) (a) V. I. Stenberg, "Organic Photochemistry," O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 127; (b) D. V. Rao and V. Lambert, *J. Org. Chem.*, **32**, 2896 (1967); (c) M. R. Sandner and D. J. Trecker, *J. Amer. Chem. Soc.*, **89**, 5725 (1967).

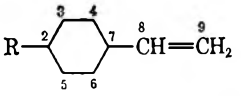
(7) H. Nozaki, S. Okada, Y. Noyori, and S. Kawanishi, *Tetrahedron*, **22**, 2177 (1966).

(8) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA OF 1 AND 2 IN *n*-HEXANE

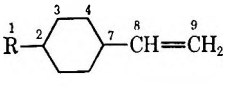
Compd	λ_{max}, Å (log ϵ)	Compd	λ_{max}, Å (log ϵ)
1a	2470 (3.75)	2a	2392 (4.22), 2650 (2.89), 2685 (2.94), 2790 (2.94), 2870 (2.82), 3240 (1.78)
1b	2470 (3.84)	2b	2370 (3.87), 2656 (2.98), 2685 (2.99), 2744 (3.02), 2875 (2.71), 3260 (1.84)
1c	2500 (3.50)	2c	2755 (3.12), 2890 (2.70), 3210 (1.99)
1d	2490 (4.01)	2d	2515 (4.19), 2740 (2.94), 2873 (2.60), 3250 (1.79)
1e	2610 (4.13)	2e	2650 (4.18), 2770 (4.00), 3180 (2.06)

may be explained by assuming an increased yield of intersystem crossing, ϕ_{ST}, by the heavy atom.[9]



Calculations of the electron densities in the lowest excited states originating from π,π^* transitions of *para*-substituted styrenes in place of **1** were performed by means of HMO method using the values of a, l, and λ reported by Hatano, Tamura, and Kambara.[10] The electron densities at 8 and 9 positions are summarized in Table III. As shown in Table III, it seems that

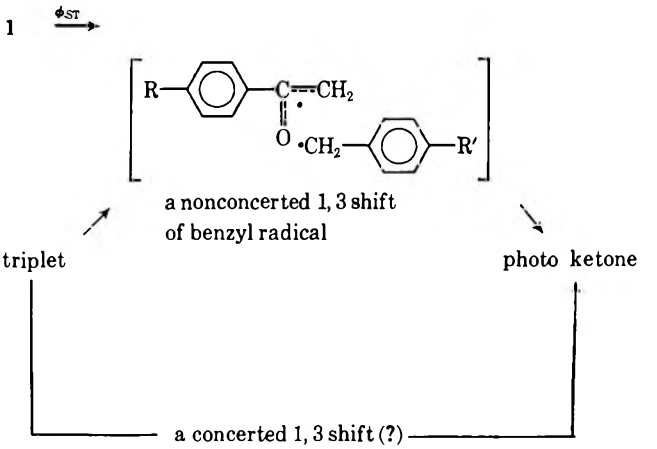
TABLE III
ELECTRON DENSITIES AT 8 AND 9 POSITIONS IN THE LOWEST EXCITED *para*-SUBSTITUTED STYRENES



R	Electron density C_8	Electron density C_9
H	0.3105	0.5095
Me	0.2109	0.5139
Cl	0.2213	0.5346
MeO	0.1077	0.3244

the quantum yield, ϕ, depends on the electron density in the lowest excited state at the 9 position except in **1d**. The lower yield of **2d** may be explained by assuming a shorter lifetime of the triplet state of **1d** by the presence of a halogen atom.[11]

As described above, the orbital symmetry arguments suggest that the 1,3-benzyl shift, that is, a sigmatropic reaction of order [1,3], should be feasible photochemically, and hence the photochemical rearrangement should be intramolecular. However, our results on the crossed reaction indicated the presence of 8% crossover products. This could be explained by a nonconcerted reaction involving competition between cage recombination and diffusion out of the solvent cage. Therefore, the mechanism may be as follows.



Experimental Section

Materials.—α-Benzyloxystyrene (**1a**) was prepared from styrene and benzyl alcohol according to the known procedure,[5a] bp 133–134° (2 mm), $n^{25}D$ 1.5835 (lit.[5a] 1.5850). Authentic β-phenylpropiophenone (**2a**) was prepared by azobisisobutyronitrile (AIBN) catalyzed rearrangement[5a] of **1a** followed by duplicate recrystallizations from *n*-hexane, mp 70.0–70.5° (lit.[5a] 70.0–71.0°). α-*p*-Methylbenzyloxy-*p*-methylstyrene (**1c**), bp 156–159° (1 mm), was similarly prepared from *p*-methylstyrene, bp 66.0–66.5° (22 mm), and *p*-methylbenzyl alcohol, mp 60° (lit.[12] 61°), which was obtained by direct hydrolysis of ω-bromo-*p*-xylene in the presence of an emulsifier. Authentic β-*p*-tolylethyl *p*-tolyl ketone (**2c**) was prepared by the similar catalytic rearrangement of **1c** followed by recrystallization from *n*-hexane, mp 65.0–65.5°.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.10; H, 7.61.

p-Tolyl β-phenylethyl ketone (**2f**) was prepared by Grignard synthesis from *p*-bromotoluene and cinnamaldehyde,[13] mp 68.5–69.0° (lit.[13] 69°).

Other substituted benzyloxystyrenes were similarly prepared from substituted styrenes and benzyl alcohols. They were identified by means of ir and uv spectra and melting points of the corresponding ketones obtained by their AIBN-catalyzed rearrangements: α-*p*-methylbenzyloxystyrene (**1b**), bp 150–154° (1 mm), β-*p*-tolylpropiophenone (**2b**), its oxime, mp 84–85° (lit.[13] 85–86°), α-benzyloxy-*p*-chlorostyrene (**1d**), bp 166–168° (2.5 mm), *p*-chlorophenyl β-phenylethyl ketone (**2d**), mp 77.8–78.3° (lit.[13] 78°), α-benzyloxy-*p*-methoxystyrene (**1e**), bp 148–151° (2.5 mm), *p*-anisyl β-phenylethyl ketone (**2e**), mp 96.0–96.2° (lit.[14] 97°).

n-Hexane (first grade) was passed through a silica gel column followed by distillation, bp 67.5–68.0°. *n*-Propyl chloride was prepared by the reaction of *n*-propyl alcohol with concentrated hydrogen chloride,[15] bp 44–45°.

The ir spectra were measured by a Perkin-Elmer Model 337 grating instrument and uv spectra were recorded by a Shimadzu type SV-50A spectrophotometer. A Yanagimoto Model GCG-220 gas chromatograph was used for glpc.

Irradiation of 1a.—A solution of 0.32 mM **1a** in *n*-hexane was placed in a quartz square cell (path length 1 cm), and it was sealed after bubbling a slow stream of dry N_2 through the mixture. A Halos 30W low-pressure Hg lamp, which emits almost exclusively 2537-Å light, was used as a light source. The cell was placed at the distance of 25 cm from the light source and irradiation was carried out at 32–35°. The uv spectra of the reaction mixture were recorded at intervals of 30 min for 1.5 hr.

Isolation of 2a.—A solution of **1a** (1 g) in *n*-hexane (400 ml) was placed in a reaction vessel equipped with a N_2 gas inlet, a

(9) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 57.
(10) M. Hatano, N. Tamura, and S. Kambara, *Kogyo Kagaku Zasshi*, **70**, 2016 (1967).
(11) D. S. McClure, *J. Chem. Phys.*, **17**, 905 (1949).
(12) D. Davidson and M. Weiss, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1948, p 590.
(13) H. Burton and C. K. Ingold, *J. Chem. Soc.*, 904 (1928).
(14) P. Pfeiffer and P. A. Negreanu, *Ber.*, **50**, 1465 (1917).
(15) J. E. Copenhaver and A. M. Whaley, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1946, p 142.

thermometer, and a condenser. The Halos 30W low-pressure Hg lamp was immersed in the reaction mixture. The solution was irradiated under N_2 at 28° for 11 hr. After irradiation, the reaction mixture was carefully condensed and introduced into a silicic acid column (diam 1 cm, height 20 cm) for chromatography. Elution with *n*-hexane gave **2a** (0.2 g) and elution with a mixed solvent of 50% ethanol and 50% *n*-hexane gave unreacted **1a** (0.5 g).

Crossed Reaction of 1a and 1c.—A solution of **1a** (1.1 g) and **1c** (1.2 g) in *n*-hexane (800 ml) was irradiated similarly at 28–35° for 54 hr. The irradiated solution was carefully condensed and chromatographed on silicic acid column. Elution with *n*-hexane gave a mixture of photo ketones. Analysis of the mixture was done by means of glpc, employing a Yanagimoto Model GCG-220 operated with a 1 × 4 mm column packed with 10% PEG 20M on 40–60 mesh Fire Brick C-22 with a He flow of 60 ml/min at 241°. The similarity of the retention times of the peaks of authentic materials with those of the samples established their identity.

Determination of Quantum Yields for Formation of Photo Ketones.—The quantum yields were determined by means of a liquid phase chemical actinometer using potassium ferrioxalate at 20–23°. A Halos 30W low-pressure Hg lamp without filter was used as a light source, and produced photo ketones were determined by uv spectrophotometry. A general procedure is as follows. A solution of 0.1–0.2 m*M* **1a** in *n*-hexane was placed in a square quartz cell (path length 1 cm), and it was sealed under N_2 atmosphere. A solution of 6 m*M* potassium ferrioxalate in 0.1 *N* H_2SO_4 was placed in an actinometer cell (path length 5 cm). Irradiation was started by opening a shutter and continued for 1 hr. The number of molecules of produced **2a** in a cell was determined spectrophotometrically. The light intensity absorbed by the reactant was determined by the procedure reported by Parker and Hatchard.[16] The quantum yield was calculated from these data.

Registry No.—**1a**, 25109-98-2; **1b**, 25186-49-6; **1c**, 25186-50-9; **1d**, 25186-51-0; **1e**, 25150-08-7; **2a**, 1083-30-3; **2b**, 1669-50-7; **2c**, 20615-46-7; **2d**, 5739-37-7; **2e**, 5739-38-8.

Acknowledgment.—The authors wish to thank Dr. Y. Sawaki for his gifts of *p*-methylstyrene and *p*-chlorostyrene.

(16) (a) C. A. Parker, *Proc. Roy. Soc., Ser. A*, **220**, 104 (1953); (b) C. G. Hatchard and C. A. Parker, *ibid.*, **235**, 518 (1956).

A Facile Synthesis of Methanesulfonate Esters

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Received March 11, 1970

Reactive sulfonate esters are especially useful because of their synthetic versatility and ability to initiate carbonium ion reactions. The usual Tipson procedure[4] is not suited for the synthesis of reactive sulfonate esters owing to facile alkylation of the solvent, pyridine, by the products.[5] For the synthesis of propargyl brosylates and tosylates, this side reaction has been suppressed by the use of excess 2,6-lutidine in methylene chloride solution,[6] and, in the case of benzyl tosylates, by reaction of tosyl chloride with the appropriate lithium[7] or sodium[5] alkoxide. Although very reactive species may be prepared by these procedures, the relatively long reaction times (days) of the former and the strongly basic conditions of the latter seem to limit both procedures to products which are stable to elimination. Another successful procedure for the preparation of reactive tosylates is reaction of the corresponding alkyl iodide with silver tosylate.[8] Both benzyl and branched chain tosylates may be prepared by this method; however, the stereochemistry of the product is uncertain. Recently Coates and Chen have published a synthesis of reactive tosylates which involves oxidation of the corresponding sulfinates with *m*-chloroperbenzoic acid in methylene chloride solution.[9] This method appears to have general applicability, although, from the corresponding alcohol, two synthetic steps are required. The method also seems to be restricted to molecules not containing easily oxidized functionality.

For some time we have synthesized methanesulfonate esters (mesylates) from the corresponding alcohols using a procedure based on the mechanistic studies of Truce.[10] We wish to report the experimental details of this procedure which is extraordinarily simple and rapid and appears to be of diverse applicability. Table I lists some of the mesylates prepared by this procedure. Repetitive integration of the 60-MHz ^1H nmr spectra showed that in each case the product was over 95% esterified. No by-products were observed. Our procedure deviates from the usual Tipson procedure[4] by the use of triethylamine as base and methylene chloride as solvent. In the light of recent evidence[11] it is apparent that the mechanistic course of the reaction has been changed from the usual nucleophilic addition of the alcohol to the sulfonyl group to addition of the alcohol to the *sulfene*[12] derived from mesyl chloride by E2 elimination of hydrogen chloride.[11] The facile esterification of a number of tertiary and neopentyl systems (Table I) indicates that the reagent has a small steric requirement. The nucleophilicity of the alcohol is unimportant as shown by the ready esterification of 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol. Furthermore, conditions are sufficiently mild that even very reactive systems such as 1-methylcyclobutyl[13] and α-phenethyl may be esterified. Indeed, in our experience, all alcohols are esterified by this procedure; the limiting factor seems to be the stability of the product.[14]

(1) Department of Chemistry, Indiana University.

(2) Taken in part from the Ph.D. dissertation of R. K. C., University of Southern California, 1969; Stauffer Chemical Company Fellow, 1966; National Science Foundation Summer Trainee, 1967–1968; Petroleum Research Fund Fellow, 1968. We are grateful for this financial aid and support.

(3) Department of Chemistry, University of Southern California; Alfred P. Sloan Fellow, 1969–1971.

(4) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(5) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3443 (1953).

(6) Private communication of unpublished results from Mr. William Dowd, Department of Chemistry, Indiana University.

(7) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Sheppele, *J. Amer. Chem. Soc.*, **89**, 370 (1967).

(8) H. M. R. Hoffman, *J. Chem. Soc.*, 6748 (1965).

(9) R. M. Coates and J. P. Chen, *Tetrahedron Lett.*, 2705 (1969).

(10) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3231 (1963).

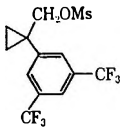
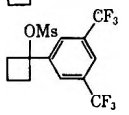
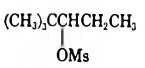
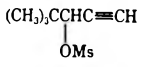
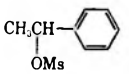
(11) J. F. King and T. W. S. Lee, *ibid.*, **91**, 6524 (1969).

(12) For leading references to sulfenes as reaction intermediates, see G. Opitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 107 (1967).

(13) This mesylate has been prepared previously in methylene chloride solution using pyridine as base: A. Majerski, M. Nikoletic, S. Borcic, and D. E. Sunko, *Tetrahedron*, **23**, 661 (1967).

(14) Those systems which decompose under the reaction conditions give the corresponding olefins. For example, with 2.5 molar equiv of amine, attempted esterification of 2-(3,5-ditrifluoromethylphenyl)-2-propanol gave α-methyl-3,5-ditrifluoromethylstyrene in 73% yield.

TABLE I
SOME MESYLATES PREPARED USING TRIETHYLAMINE AS BASE IN METHYLENE CHLORIDE SOLUTION

Compd[a]	No.	Yield, %[b]	Physical properties[c]
	1	95	Mp 70–71[d,e]
	2		Highly reactive liquid which decomposes slowly at 0°[e]
	3	92	Mp 48.5–49° dec[d,e]
Adamantyl-1-OMs	4	82[g]	Mp 46–48° dec
	5	90	Colorless liquid[f]
	6	92	Colorless liquid[f,h]
	7		Highly reactive liquid which decomposes violently at room temperature
CF_3CH_2OMs	8	87[i]	Colorless liquid, bp 97–99° (35 mm)
$(CF_3)_2CHOMs$	9	85[i]	Colorless liquid, bp 157–158°

[a] All mesylates were characterized by their 60-MHz ^1H nmr spectra. [b] Corresponds to weight of product obtained after removal of solvent and pumping the residue down to 1 mm at 0° for 4 hr. [c] Melting point and boiling point data are uncorrected. [d] See ref 16 for preparation and characterization of the precursor alcohol. [e] Purity was further confirmed by titrimetric rate analysis of solvolysis and infinity titer (see ref 16). [f] Purity was further confirmed by conductometric rate analysis of solvolysis. [g] Yield after recrystallization from hexane. [h] Precursor alcohol and mesylate were prepared by Mr. William Dowd, Department of Chemistry, Indiana University. [i] Yield after fractional distillation.

We have found mesylates to be quite useful as synthetic intermediates. They are about three times *less* reactive toward solvolysis than the corresponding tosylates.[15] With suitably unhindered systems, mesylate is easily displaced by nucleophiles such as halide or hydride.[16] In the latter case, where reduction is performed with excess lithium aluminum hydride in ether, mesylates are especially useful because the mesylate fragment reduces to methyl mercaptan, which is easily removed.

Experimental Section

General Procedure for the Preparation of Mesylates.—To an approximately 0.2 *M* solution of the alcohol in methylene[17] chloride solution containing a 50% molar excess of triethylamine at 0 to −10° was added a 10% excess of methanesulfonyl chloride (mesyl chloride) over a period of 5–10 min.[18] Stirring for an additional 10–15 min completed the reaction. The reaction mixture was transferred to a separatory funnel with the aid of more methylene chloride. The mixture was first extracted with ice water, followed by cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine. Drying of the methylene chloride solution followed by solvent removal gave the product,[19] which was pure enough for most uses including solvolysis.

Registry No.—**1**, 25236-57-1; **2**, 935-20-6; **3**, 25236-59-3; **4**, 25236-60-6; **5**, 25236-61-7; **6**, 25236-62-8; **7**, 25236-63-9; **8**, 25236-64-0; **9**, 25236-65-1.

Acknowledgment.—The latter stages of this research which were carried out at Indiana University were supported in part by Grant AT(11-1)-1008 from the U. S. Atomic Energy Commission (Document No. COO-1008-7).

(15) R. E. Robertson, *Progr. Phys. Org. Chem.*, **4**, 213 (1967).

(16) R. K. Crossland, Ph.D. Dissertation, University of Southern California, Los Angeles, Calif., 1970.

(17) Both cyclohexane and pentane may also be used as solvent. The choice is based solely on the solubility of the starting alcohol.

(18) Mesyl chloride was redistilled; triethylamine was refluxed over phthalic anhydride, distilled, and then redistilled from potassium hydroxide pellets; methylene chloride was taken from a freshly opened bottle of AR grade. Anhydrous reaction conditions were maintained.

(19) The more reactive the product mesylate, the more slowly the mesyl chloride was added and the lower the temperature. For very reactive systems the glassware used in the work-up was prechilled and the temperature of the mesylate was never allowed to exceed 0°. With large-scale preparations (~1 mol) the excess of triethylamine may be reduced to 20%.

Thermal Decomposition of Liquid *t*-Amyl Peroxide

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Decomposition of liquid *t*-butyl peroxide (I) at its boiling point (110°) in absence of any solvent proceeds at a rate approximately 2.8 times faster than expected from its unimolecular decomposition rate (reaction 1) in the gas phase.[2] Isobutylene oxide (II) is formed as a major decomposition product along with *t*-butyl alcohol and acetone (see Table I). The induced decomposition of I and formation of II along with the other products are explained in terms of a free-radical reaction including the chain sequence 3 and 4.[2]

$$\underset{\text{I}}{(CH_3)_3COOC(CH_3)_3} \longrightarrow 2(CH_3)_3CO\cdot \qquad (1)$$

$$(CH_3)_3CO\cdot + \text{I} \longrightarrow CH_3COCH_3 + CH_3\cdot \qquad (2)$$

$$(CH_3)_3CO\cdot \text{ (or } CH_3\cdot) + \text{I} \longrightarrow \underset{\text{(or } CH_4)}{(CH_3)_3COH} + (CH_3)_2\underset{\displaystyle CH_2\cdot}{COOC(CH_3)_3} \qquad (3)$$

$$(CH_3)_2\underset{\displaystyle CH_2\cdot}{COOC(CH_3)_3} \longrightarrow \underset{\displaystyle CH_2}{(CH_3)_2C\!-\!O} + \cdot OC(CH_3)_3 \qquad (4)$$

II

Reaction of *t*-amyl peroxide (III) by a similar route would involve abstraction of a secondary hydrogen as shown in reactions 8 and 10. The greater reactivity of secondary hydrogens relative to primary hydrogens toward abstraction would suggest that the chain sequence 8 and 10 could possibly be a more important route for the decomposition of III than it is for I. The products of the decomposition of III in the liquid phase

(1) Taken in part from the thesis submitted by K. J. J. in partial fulfillment of the requirements for the Ph.D. degree from the University of Kansas, 1969.

(2) J. H. Raley, F. F. Rust, and W. E. Vaughn, *J. Amer. Chem. Soc.*, **70**, 88 (1948); E. R. Bell, F. F. Rust, and W. E. Vaughn, *ibid.*, **72**, 337 (1950).

TABLE I
THERMAL DECOMPOSITION PRODUCTS OF DIALKYL PEROXIDES

Peroxide	Temp, °C	Products	Mole/100 mol of[a] t-alkoxy radical
t-Butyl peroxide[b] (I)	110	t-Butyl alcohol	24.8
		Acetone	32.8
		Isobutylene oxide (II)	34.9
t-Amyl peroxide (III)	115	t-Amyl alcohol	8.5
		Acetone	83.0
		2-Butanone	2.0
		1,1,2-Trimethylethylene oxide (IV)	5.0
		1-Ethyl-1-methylethylene oxide (V)	1.1

[a] Based on moles of peroxide decomposed. [b] Data from ref 2.

at 115° indicate, however, that only a small amount of 1,1,2-trimethylethylene oxide (IV) is formed. The rate of decomposition of III in the liquid state is, however, faster than either in the gas phase or in solvents (Table II) that do not produce radicals that induce the decomposition of dialkyl peroxides.[3]

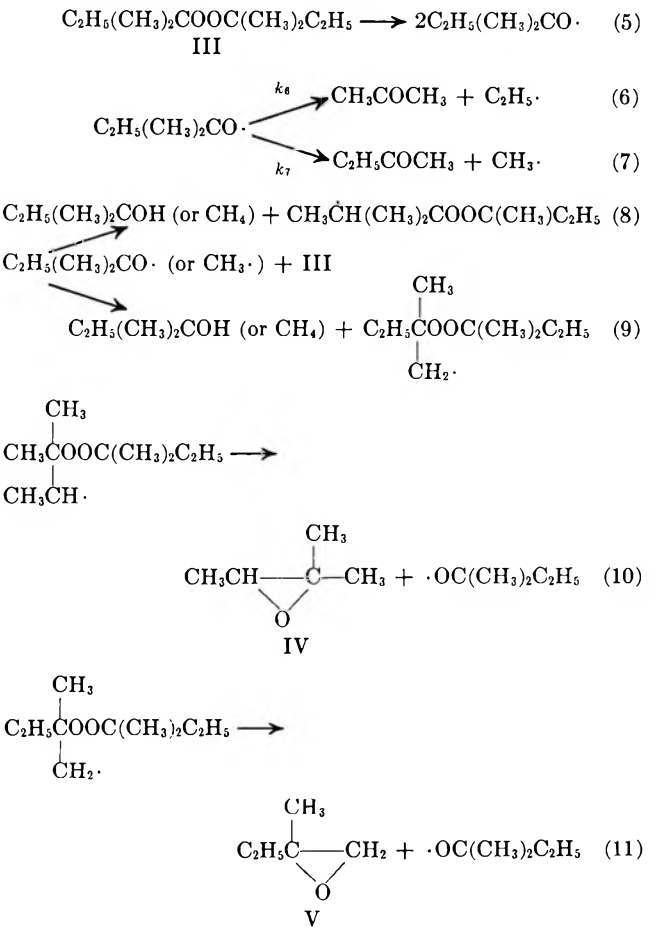
TABLE II
DECOMPOSITION RATE OF t-AMYL PEROXIDE (III)

Solvent[a]	Temp, °C	$k \times 10^4$ sec^{-1}	Half-life, min
Gas phase	132.2	0.72[b]	
Neat	132.2	(1.15)[c]	100.4
Gas phase	125.0	0.27[d]	427.7
Neat	125.0	(0.57)[c]	200.8
trans-Decalin	125.0	0.28	402.4
cis-Decalin	125.0	0.28	408.0
Triethylamine	125.0	0.35	323.0
Cyclohexane	125.0	0.36	313.0
Cyclooctane	125.0	0.29	386.0
Octane	125.0	0.30	381.0

[a] Mole ratio of solvent to peroxide is 5:1. [b] Reference 2. [c] First-order kinetics observed through first half-life of the decomposition. [d] Extrapolated from data in ref 2.

Hydrogen abstraction from t-butyl peroxide to yield the precursor of isobutylene oxide is performed, for the most part, by the t-butoxy radical, a species reactive enough to abstract the primary alkyl hydrogens of I. Some of the hydrogen abstraction from I (~30%) is performed by methyl radicals which are also reactive hydrogen abstractors. Methyl radicals are formed in the fragmentation reaction of the t-butoxy radical (reaction 2), a reaction which competes favorably, but not to the exclusion of, hydrogen abstraction from I by the t-butoxy radical.

The small amount of t-amyl alcohol formed in the reaction of III indicates that fragmentation of the t-amyloxy radical is faster than hydrogen abstraction from the alkyl portion of III by the radical. Furthermore, elimination of an ethyl radical occurs more readily than elimination of a methyl radical ($k_6/k_7 = 20.8$)[4] as evidenced by the amount of acetone formed relative to 2-butanone. The small amounts of 1,1,2-trimethylethylene oxide (IV) and 1-ethyl-1-methylethylene oxide (V) formed in the chain sequence 9 and 11 indicate that hydrogen abstraction from the alkyl portion of the peroxide does not occur readily. Apparently the hydrogen atom abstraction is performed only by the reactive t-amyloxy and methyl radicals, both of which are present in small amounts owing to the rapid fragmentation of alkoxy radicals yielding mainly ethyl radicals. The ratio of attack of the secondary with respect to the primary hydrogens of III, calculated from the relative amounts of IV and V, is 4.5 indicating a reactivity ratio of secondary to primary hydrogens of 13.5. Abstraction of hydrogen atoms apparently is performed by reactive free radicals (or radical) that do not discriminate greatly between primary and secondary hydrogens. Both alkoxy and methyl radicals would be expected to be less selective in hydrogen abstraction reactions than the energetically more stable ethyl radicals which likely couple or disproportionate in these reactions.



Our work does not explain the enhanced rate of decomposition of III in the liquid phase. It does suggest, however, that it is not the result of extensive attack at the alkyl portion of the peroxide as in the t-butyl peroxide reactions. The observation that the decomposition rate increases with increasing pressure in the gas phase[2] may be indicative of a mechanism for the reac-

(3) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964); E. S. Huyser, C. J. Bredeweg, and R. M. VanScoy, *ibid.*, **86**, 4148 (1964).
(4) See J. K. Kochi, *ibid.*, **84**, 1193 (1962).

tion more complex than the assumed unimolecular decomposition of this dialkyl peroxide.

Experimental Section

Materials.—*t*-Amyl peroxide was prepared by the method described by Milas and Surgenor.[5] The crude peroxide was distilled twice [bp 44–45° (10 mm)] through a 40-mm glass bead column and yielded a sample at least 98% pure by gas chromatographic analysis. Authentic samples of 1,1,2-trimethylethylene oxide (IV) and 1-ethyl-1-methylethylene oxide (V) for gas chromatographic analysis were prepared from the appropriate alkenes by reaction with peracetic acid as described by Sorenson and Campbell.[6] The nmr spectrum of 1,1,2-trimethylethylene oxide (bp 74–74°) showed a multiplet at 1.2 ppm and a quartet at 2.7 ppm in a ratio of 10:1. The 1-ethyl-1-methylethylene oxide (bp 80–81°) has an nmr spectra with a triplet at 0.9 ppm, a singlet at 1.2 ppm, a quartet at 1.5 ppm, and a singlet at 2.4 ppm.

Rate Determinations.—Samples approximately 1 ml in size of either the pure peroxide or solution were placed in several 9 mm × 9 in. Pyrex tubes. After sparging with nitrogen and cooling, the tubes were sealed and placed in a constant-temperature oil bath at the temperature indicated in Table II. The tubes were withdrawn at various time intervals; the amount of peroxide remaining was determined by gas chromatographic analysis of the contents of the tubes employing the method described previously for determination of *t*-butyl peroxide.[3]

Thermal Decomposition of Liquid *t*-Amyl Peroxide.—A small amount of peroxide was placed in a glass tube, sealed, and heated for 17 hr at 115°. A portion of the resulting mixture was subjected to gas chromatographic analysis on two different columns (0.25 in. × 13 ft column packed with 17% dodecyl phthalate on Chromosorb W and 1/8 in. × 19 ft column packed with 20% TCEP on Chromosorb W). The products of the reaction were identified by comparison of their retention times on both columns with authentic samples of the materials. The quantities were determined from the peak areas of each components as measured with a Disc Integrator. No attempt was made to analyze the gaseous products of the reaction.

Registry No.—III, 10508-09-5.

(5) N. A. Milas and D. N. Surgenor, *J. Amer. Chem. Soc.*, **68**, 643, (1946).
(6) W. R. Sorenson and T. W. Campbell, "Preparative Methods of Polymer Chemistry," 2nd ed, Interscience, New York, N. Y., 1968, p 370.

A Ten-Membered-Ring Cyclic Disulfide[1]

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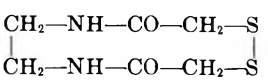
Reaction of ethylenediamine with methyl or butyl dithiodiglycollate in the absence of solvent affords the cyclic disulfide diamide N,N′-ethylenedithiodiglycollamide (perhydro-1,2,5,8-dithiadiazecine-4,9-dione, I) in excellent yield. The same product, rather than the



I

expected low polymer with amine end groups, results in fair yield even from reaction of the ester with a considerable excess (up to 1.6 mol) of the amine. Poorer yields result from reaction in solution in ethanol or dimethylformamide. The disulfide is quite stable at room temperature but undergoes some decomposition upon heating, in solution in dimethylformamide, and at temperatures above 100°.

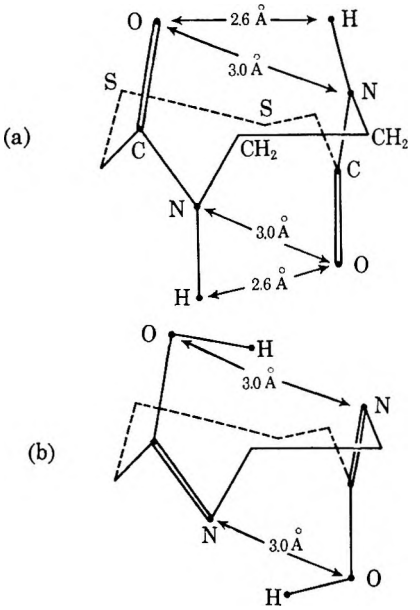


Figure 1.—Skeletal structures for N,N′-ethylenedithiodiglycollamide: (a) amide extreme, (b) isoamide extreme.

The monomer structure, I, is indicated by the mass spectrum and elemental analysis. Chromatographic homogeneity and the expected retardation are observed upon gel filtration (Sephadex G 10 or G 15), by which means the material is readily separated from a putative dimer[2] which results from it upon exposure, in aqueous solution, to X-rays.

Such ready formation of a ten-membered ring is unusual.[3] Several contributing restrictions are apparent, however. Substantial hindrance to free rotation about the disulfide bond[4] and the necessary planarity of the amide group in the presumptive monoamide intermediate ($NH_2CH_2CH_2NHCOCH_2SSCH_2COOR$) restrict the conformations which this may adopt essentially to those available to apodeictically cyclizable six-centered systems such as δ-aminovaleric acid. The cyclic product can adopt a strain-free and uncrowded, though compact, conformation (Figure 1) in which all six centers of each amide unit are coplanar, the preferred (10–15 kcal mol^{-1})[4] dihedral angle of ~90° about the disulfide group is maintained and, indeed, even the diamidoethane moiety has the *gauche* conformation. It is noteworthy that the length of the disulfide bond (2.04 Å) contributes significantly to the lack of both crowding and strain. The internuclear distance between each carbonyl oxygen and the juxtaposed nitrogen of the antipodal amide group is 2.9–3.0 Å, approximately the sum of the respective van der Waals' radii. The probability of duple, strong intramolecular hydrogen bonding seems considerable. The formal

(1) Financial support from the National Institute of General Medical Sciences, Public Health Service, Research Grant GM 16477, is gratefully acknowledged.

(2) T. C. Owen and A. C. Wilbraham, *J. Amer. Chem. Soc.*, **91**, 3365 (1969).

(3) H. Stetter and J. Marx, *Justus Liebigs Ann. Chem.*, **607**, 59 (1957), have prepared a number of simple macrocyclic diamides. The yields of larger rings (12 centers and above) were good but the 10-membered rings, ethyleneadipamide and tetramethylenesuccinamide, were obtained only in yields of 24 and 34%, respectively, even under high-dilution conditions and with carefully purified reactants.

(4) O. Foss, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961.

diamide structure (Figure 1a) requires an O---H–N angle of ~90° and an O---H internuclear distance of 2.6–2.8 Å whereas the diisoamide extreme (Figure 1b) offers the more attractive O–H---N angle of ~152°. The two structures are interconvertible by concerted electromeric shifts and simultaneous intramolecular transfer of both protons. Spectroscopic studies of the C–O and N–C bond orders are in progress.

Experimental Section

Analyses were by Galbraith Laboratories. Mass spectra were by Morgan-Schaeffer Corp.

Equimolar quantities of ethylenediamine and methyl dithiodiglycollate are admixed. Reaction is moderately exothermic and cooling is desirable for large-scale reactions. The mixture becomes viscous and sets to a yellow crystalline solid within 30 min. The solid, allowed to stand overnight or heated briefly on a steam bath and then washed with ethanol, affords the disulfide diamide (I) as pale yellow crystals, mp 205°, in 90–100% yield. Crystallization from hot dimethylformamide (20–40 ml/g), a process attended by some decomposition, removes the yellow color but does not raise the melting point.

Anal. Calcd for $C_6H_{10}N_2O_2S_2$: C, 34.95; H, 4.85; N, 13.59; S, 31.12; Found, C, 34.77; H, 5.16; N, 13.68; S, 30.88.

Spectra follow: ir (Nujol) 3290, 3250, 1640, and 1530 cm^{-1}; mass spectrum (50 eV) *m/e* (rel intensity), 208 (S^{34} molecular ion, 3), 206 (S^{32} molecular ion, 37), 177 (2), 173 (2), 164 (9), 160 (23), 142 (90), 132 (21), 106 (13), 104 (22), 87 (56), 84 (56), and 72 (100), no fragments above mass 208; solubility, very slowly soluble in H_2O (150 mg $l.^{-1}$ at 25°), dilute HCl, MeOH, EtOH, $CHCl_3$, and other common solvents, moderately soluble in hot dimethylformamide (some decomposition), soluble in concentrated HCl (36%) from which it precipitated essentially quantitatively, and chloride free after washing, upon dilution.

Registry No.—I, 25286-76-4.

A Safe and Convenient Synthesis of Dichloroacetylene

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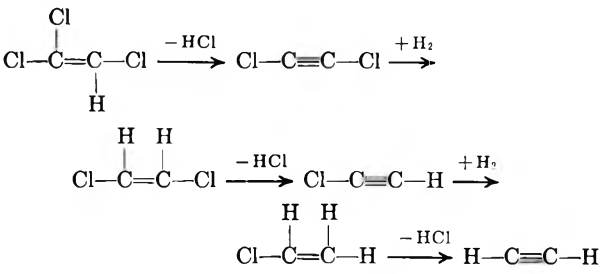
During the course of our investigation of the toxicology of dichloroacetylene (DCA), the necessity of producing substantial quantities of this compound under safer conditions became quite evident. In 1942, Ott[1] reported that in the presence of ether the autoxidation of dichloroacetylene is retarded and the hazard of explosion is greatly reduced. However, Riemschneider and Brendel[2] found the preparation, as reported by Ott, to be extremely dangerous, and there were frequent explosions.

The important advantages of the synthesis presented here is that the preparation is carried out in a liquid medium (ethylene glycol) instead of in a dry combustion tube filled with NaOH; excess ether is present in the system at all times thus reducing the hazards of explosions, and side reactions of DCA with ether are kept minimal. The by-products of the reaction have been identified as being acetylene, monochloroacetylene, dichloroethylene, and acetaldehyde.

The reaction apparently proceeds by a dehydrohalogenation and reduction, which are not unknown in strongly basic solutions. The reactions may be illustrated as follows.



The acetaldehyde present in the crude product may arise from either the ether or ethylene glycol present in the reaction mixture.

From a 1:1 mol solution of trichloroethylene and ether according to the subsequent procedure, we obtained a product containing 55% w/w of DCA in ether.

Identification of the product was made by mass spectrometry, ir spectrometry, and retention time indices on glc using the following conditions: a 12 ft × $^1/_8$ in. stainless steel column packed with 30% diisodecyl phthalate on Chromosorb W 60–80 mesh at an oven temperature of 50°. Helium flow was 50 ml/min and FID detector temperature was 200°. Analysis was made using a Dohrmann microcoulometer connected to a glc system as previously described.

Experimental Section

To a 2-l. three-necked round bottom flask equipped with an efficient mercury-sealed stirrer, thermometer, gas inlet and dropper tube, and a tube to an upright Liebig condenser having a 1-l. receiver flask at its base to collect the reaction products, was added 400 g of technical flake KOH and 350 ml of ethylene glycol. The top of the condenser was connected to a 500-ml trap flask immersed in a Dry Ice bath and the condenser cooled to −10°. All connections were ground glass. A 1:1 mol mixture of trichloroethylene and ether was added dropwise at 3–5 ml/min while nitrogen was passed through the system at 100 ml/min, and the reaction mixture was maintained at 140°.

The contents of the receiver and trap were mixed together and the water layer was decanted. The ether solution was dried over magnesium sulfate for 12 hr. The dried solution was distilled through a 550-mm Widmer column and the fraction between 31–33° was collected. The still pot residue was reusable as starting material; yield, 90% (based on TCE lost).

Registry No.—DCA, 7572-29-4.

Acknowledgment.—The Chemical Dynamics Branch and the Physical Chemical Branch of the Chemistry Division, Naval Research Laboratory, conducted the mass spectrographic and ir analyses and their assistance is gratefully acknowledged.

(1) E. Ott, W. Ottemeyer, and K. Packendorff, *Chem. Ber.*, **63**, 1941 (1930); E. Ott and K. Packendorff, *ibid.*, **64**, 1324 (1931); E. Ott, *ibid.*, **75**, 1517 (1942); E. Ott, G. Dittus, and H. Wissenburger, *ibid.*, **76**, 87 (1943).

(2) P. Riemschneider and K. Brendel, *Justus Liebigs Ann. Chem.*, **640**, 5 (1961).

Chemistry of *gem*-Dihalocyclopropanes. VII.[1] Ring Opening of 7,7-Dichloro-2-oxabicyclo[4.1.0]heptane. The Synthesis of 2H-3,4-Dihydropyran-5-carboxaldehyde

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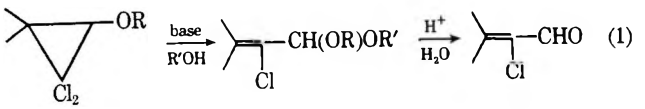
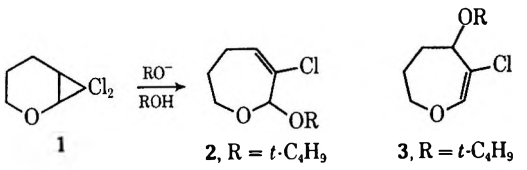
The thermally induced ring opening of dihalocyclopropanes has been studied by several groups, but most extensively by Parham and coworkers.[3] 1,1-Dihalocyclopropyl ethers are particularly prone to undergo ring opening; in the presence of alcohols, acetals are formed which can subsequently be hydrolyzed to aldehydes in high yields (eq 1).[4,5] The main purpose of the



(1)

present note is to report reactions of 7,7-dichloro-2-oxabicyclo[4.1.0]heptane (**1**) under the above conditions.

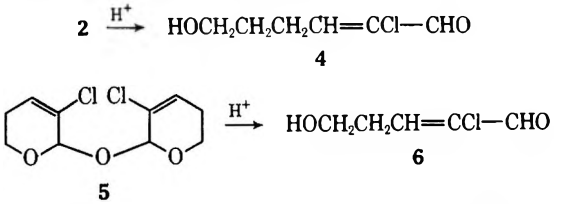
When **1** was heated under reflux with potassium *t*-butoxide in *t*-butyl alcohol a liquid product was obtained in 79% yield; the most reasonable structure would be 3-chloro-2-*t*-butoxy-2,5,6,7-tetrahydrooxepin (**2**), although the isomeric structure **3** could not *a priori*



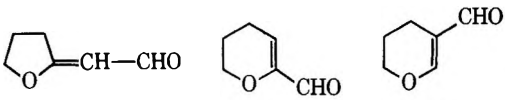
1 **2**, R = *t*-C$_4$H$_9$ **3**, R = *t*-C$_4$H$_9$

be excluded. The ir spectrum could not unequivocally distinguish between the two, but the nmr spectrum was quite conclusive. A singlet at δ 5.06 due to the tertiary proton could only be identified with structure **2** since, in the case of **3**, it would be coupled with the neighboring methylene protons. Moreover, a weakly split triplet ($J < 1$ Hz) at δ 5.99 is only compatible with structure **2**; the weak coupling is probably the result of an unfavorable dihedral angle between the olefinic and the methylene protons.[6]

Compound **2** formed a 2,4-dinitrophenylhydrazone derivative, mp 198° dec, which by elemental analysis and spectroscopic evidence was shown to derive from aldehyde **4**. The latter would indeed be the expected hydrolysis product from **2** having close analogy in the literature; by acid hydrolysis of compound **5**, Reese and coworkers[7] obtained the aldehyde **6**, characterized as the 2,4-dinitrophenylhydrazone.



If, however, the acetal **2** was treated at room temperature with dilute aqueous acid a liquid product, $C_6H_8O_2$, was formed, the 2,4-DNP of which melted at 239° dec. The ir spectrum of the liquid showed strong bands at 1665 and 1625 cm^{-1} and a medium intensity band at 2715 cm^{-1}, characteristic of an α,β-unsaturated aldehyde. This was confirmed by the uv absorption; in *n*-heptane a maximum appeared at 241.5 nm while in methanol it was shifted to 250 nm.[8] Strong bands at 1245 and 1180 cm^{-1} could be the C–O stretching vibrations of a vinyl ether.[9] On the basis of this evidence three structures, **7**, **8**, and **9**, appeared most likely. The



7 **8** **9**

nmr spectrum showed a complex multiplet centered at δ 2.02 and a triplet at δ 4.20 due to the six ring protons, the latter representing the methylene group adjacent to oxygen. This is compatible with all of the above structures. The remaining protons appeared as singlets, the olefinic at δ 7.35 and the formyl at δ 9.18. The lack of coupling between these clearly rules out **7** as a possible structure. It proved more difficult, however, to distinguish between the dihydropyran structures **8** and **9**, isomers of acrolein dimer. One would expect the olefinic proton in **8** to be coupled with the neighboring methylene protons, but because the magnitude is strongly dependent on the dihedral angle,[6] it might only be very weak; in 2H-3,4-dihydropyran, however, the coupling is about 3 Hz. It is not expected that the formyl group of **8** should change the ring conformation significantly from that of dihydropyran and therefore the absence of coupling disfavors structure **8**. Furthermore, the chemical shift of the olefinic resonance also is not compatible with this assignment, which becomes evident from the data of Table I. The deshielding effect of the formyl group on the β proton would be almost compensated by the shielding of the same proton by the ether oxygen; accordingly, the

TABLE I

Compd[a]	Chemical shift of olefinic hydrogen (δ ppm) Hα	Hβ
2H-3,4-Dihydropyran	6.37	4.65
Crotonaldehyde	6.13	6.87
9	7.35	
Cyclohexene	5.57	
cis-2-Butene	5.47	

[a] Measured in CCl_4 as solvent.

(1) Part VI: L. Skattebøl, *Tetrahedron*, **23**, 1107 (1967).

(2) Department of Chemistry, University of Oslo, Blindern, Oslo 3, Norway.

(3) For reviews, see W. E. Parham and E. E. Schweizer, *Org. React.*, **13**, 55 (1963); W. E. Parham, *Rec. Chem. Progr.*, **29**, 3 (1968). See also, S. R. Sandler, *J. Org. Chem.*, **32**, 3876 (1967), and references therein.

(4) L. Skattebøl, *J. Org. Chem.*, **31**, 1554 (1966).

(5) F. Nerdel, J. Buddrus, W. Brodowski, P. Hentschel, D. Klamann, and P. Weyerstahl, *Justus Liebigs Ann. Chem.*, **710**, 36 (1967).

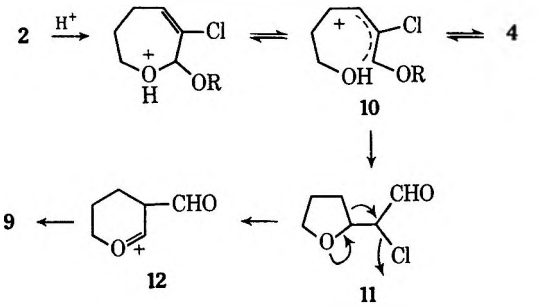
(6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(7) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, **20**, 2091 (1964).

(8) The large bathochromic shift caused by methanol is additional evidence for an α,β-unsaturated carbonyl structure: R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1942); L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

(9) G. D. Meakins, *ibid.*, 4170 (1953).

chemical shift of the olefinic proton in **8** should be shifted only slightly downfield as compared with cyclohexene; on the other hand a large (1.5–2.0 ppm) downfield shift would be expected for structure **9**, in agreement with observation. The following mechanistic scheme provides an explanation for the formation of **9**.



The protonation of **2** will result in the formation of the ring-opened allylic ion **10** which can either give the hydroxy aldehyde **4** or the tetrahydrofuran derivative **11**. The solvolysis of α-chloro aldehydes by an SN1 mechanism would be expected to be quite slow; it is more reasonable to depict the reaction as an anchimerically assisted displacement of chloride ion on the aldehyde itself or on its hydrate. This would lead to the stabilized carbonium ion **12** and the observed product **9**. Cope and Graham[10] and more recently Pasto[11] and coworkers have presented evidence for similar transformations in the solvolysis of α-halo ketones. One can think of other explanations for the formation of **9**, but it seems futile to elaborate further on this without more experimental results.

The reaction sequence represents a convenient route to the aldehyde **9**, particularly since the isolation of the intermediate oxepin derivative is not necessary.

Experimental Section[12]

3-Chloro-2-*t*-butoxy-2,5,6,7-tetrahydrooxepin (2).—To a solution of potassium *t*-butoxide from 8.6 g (0.22 g-atom) of potassium in 220 ml of *t*-butyl alcohol was added all at once 33.4 g (0.2 mol) of 7,7-dichloro-2-oxabicyclo[4.1.0]heptane.[13] The mixture was heated under reflux for 24 hr; excess of *t*-butyl alcohol was distilled on a rotatory evaporator. The residue was added to water and the product extracted with ether. The extract was washed with water (containing some Na_2CO_3) and dried (Na_2CO_3 anhydrous). The ether was evaporated and the residue fractionated giving 32.2 g (79%) of **2**, bp 54–55° (0.5 mm), $n^{24}D$ 1.4670.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37. Found: C, 58.62; H, 8.44.

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate, mp 198° dec. When heated further, the compound solidified and remelted at 222° dec, uv λ_{max} (ethanol) 372 nm (ε 18,800), 247 (10,000), 283 infl (5700).

Anal. Calcd for $C_{12}H_{13}ClN_4O_5$: C, 43.84; H, 3.99; N, 17.05. Found: C, 43.91; H, 4.03; N, 17.03.

2H-3,4-Dihydropyran-5-carboxaldehyde (9).—A mixture of the acetal **2** (51.1 g, 0.25 mol), 20 ml of dioxane, and 100 ml of 2 *N* HCl was shaken mechanically at room temperature overnight (~12 hr). A homogeneous yellow-colored solution was obtained from which the product was isolated by continuous extraction with ether. The dried ($MgSO_4$) extract was evaporated and the liquid residue distilled to give 25.9 g (92%) of the aldehyde **9**: bp 68° (3 mm); $n^{24}D$ 1.5140; ν_{max} (liq) 2715, 1665 (–CHO), 1625 cm^{-1} (C=C); λ_{max} (heptane) 241.5 nm (ε 17,600), (methanol) 250 nm (ε 19,900).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.40.

The **2,4-dinitrophenylhydrazone** was recrystallized from chloroform, mp 239° dec, λ_{max} (ethanol) 391 nm (ε 17,100), 290 (6100), 258 (10,300).

Anal. Calcd for $C_{12}H_{12}N_4O_5$: C, 49.31; H, 4.14; N, 19.17. Found: C, 49.63; H, 4.17; N, 18.85.

Registry No.—**1**, 7556-13-0; **2**, 25090-31-7; **4** (2,4-dinitrophenylhydrazone), 15299-59-9; **9**, 25090-33-9; **9** (2,4-dinitrophenylhydrazone), 25111-11-9.

(10) A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951).

(11) D. J. Pasto and M. P. Serve, *ibid.*, **87**, 1515 (1965); D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967).

(12) Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR 5 instrument. The nmr spectra were measured with a Varian A-60 instrument, using carbon tetrachloride as solvent and tetramethylsilane as internal standard.

(13) W. E. Parham, E. E. Schweizer, and S. A. Mierzwa, *Org. Syn.*, **41**, 76 (1961).

Pyrolysis of Heptafluorobutyric Anhydride

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Received February 2, 1970

Pyrolytic reactions of fluorocarbons containing functional groups have not been studied sufficiently that the mode of decomposition of a relatively simple compound such as heptafluorobutyric anhydride could be predicted. There is good precedent for radical decomposition followed by coupling. The pyrolyses of perfluoroacyl bromides[1] and perfluoroacyl hypobromites[2] give bromoperfluoroalkanes, the pyrolysis of trifluoroacetyl nitrite gives trifluoronitrosomethane,[3,4] and the pyrolysis of pentafluoropropionic anhydride[5a] and heptafluorobutyric anhydride[5b] were reported to give perfluorobutane and perfluorohexane, respectively.

In contrast with these rather straightforward radical formation and coupling reactions, however, is the report that trifluoroacetic anhydride decomposes thermally to give trifluoroacetyl fluoride, carbon dioxide, and carbon monoxide.[6] Mechanistically this was thought to involve first a dissociation to trifluoroacetyl fluoride and a difluoroacetoxy diradical.

$$(CF_3CO)_2O \longrightarrow CF_2COF + \cdot CF_2COO\cdot \longrightarrow \text{polymer on wall} \longrightarrow \text{polymer} + CO_2 + CO$$

At higher temperatures some tetrafluoroethylene was observed, probably from coupling of difluorocarbene arising from the diradical.

Related to this is the thermal decomposition of hexafluoroacetone[7] which, at over 500°, produces trifluoroacetyl fluoride and difluorocarbene. At lower temperatures hexafluoroethane is formed, but mechanistic studies indicated that this reaction involved a first-order rearrangement rather than dissociation and coupling of radicals.

It has now been found that heptafluorobutyric anhydride decomposes by two pathways. The most prominent involves a fluoride transfer leading to hepta-

(1) J. D. Lazerte, W. H. Pearlson, and E. A. Kauk, U. S. Patent 2,704,776 (May 22, 1955).

(2) M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Macmillan, New York, N. Y., 1962, pp 182–185.

(3) J. Banus, *J. Chem. Soc.*, 3755 (1953).

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(5) (a) R. N. Haszeldine and K. Leedham, *ibid.*, 1548 (1953); (b) A. D. Kirshenbaum, A. G. Streng, and M. Hauptschein, *J. Amer. Chem. Soc.*, **76**, 3141 (1953).

(6) J. P. Corbett and E. Whittle, *J. Chem. Soc.*, 3247 (1963).

(7) W. Batey and A. B. Trentwith, *ibid.*, 1388 (1961).

TABLE I: CATALYTIC DECOMPOSITION OF HEPTAFLUOROBUTYRIC ANHYDRIDE

Catalyst	Temp, °C	Contact time, sec	Yield, mol %[a] C_3F_6	C_3F_7COF	C_6F_{14}	$(C_3F_7CO)_2O$	Ratio coupling/elim
Ag on Al_2O_3[b]	150	200	0.8	0.8	0	99.2	0
Ag on Al_2O_3	250	200	16.0	27.6	4.4	76.3	0.20
Ag on Al_2O_3	300	100	80.2	39.8	10.6	29.3	0.18
Ag on Al_2O_3	350	100	171.0	0.0	8.4	5.6	0.10
Al_2O_3	300	100	21.0	16.4	0	81.7	0
Pt on Al_2O_3[c]	230	100	6.8	7.4	0	92.9	0
Pt on Al_2O_3[d]	230	100	84.6	79.9	0	4.0	0

[a] Yields were estimated using some distillation and weighing and some gas chromatography assuming area per cent equal to weight per cent. The products were identified by their physical properties and mass spectra. [b] This catalyst was prepared from silver nitrate and Norton LA-956 alumina. It contained 6.7% of silver. [c] This catalyst was prepared from 3.13 g of hexachloroplatinic acid and 250 g of Norton LA-956 alumina. [d] This platinum catalyst was commercial Houdry, grade 100s, 0.5% platinum-on-alumina catalyst. The surface area was about 100 m^2/g.

fluorobutyryl fluoride and carbon dioxide, and the second, observed only over a metallic silver catalyst, appears to be a radical decomposition followed by coupling to give perfluorohexane.

$$(CF_3CF_2CF_2CO)_2O \rightarrow \begin{cases} CF_3CF{=}CF_2 + CF_3CF_2CF_2COF + CO_2 \\ \quad\downarrow \\ CF_3CF{=}CF_2 + COF_2 \\ CF_3(CF_2)_4CF_3 + CO_2 + CO \end{cases}$$

The first of these two routes is apparently the result primarily of thermal activation of the heptafluorobutyric anhydride although it is catalyzed by alumina, platinum on alumina, as well as occurring in a bomb reactor, and it is the major reaction over metallic silver. Over silver at temperatures of 300° and above, the heptafluorobutyryl fluoride observed at lower temperatures is converted to carbonyl fluoride and hexafluoropropene. The reaction is similar to that observed for trifluoroacetic anhydride[6] and hexafluoroacetone at higher temperatures.[7]

The second pathway of reaction is very similar to the decomposition of silver heptafluorobutyrate[5,10] and of the reaction of heptafluorobutyric anhydride with silver oxide,[5b] which gives in each case perfluorohexane, carbon oxides, and metallic silver. The present study does not start with silver(I) so the mechanism, although probably related, would not be the same.[8] Silver apparently complexes with the anhydride in a way that alumina or platinum does not. A reasonable picture involves the silver complexing with oxygen inducing the loss of a heptafluorobutyryl radical and leaving silver heptafluorobutyrate. The loss of carbon monoxide from a perfluoroacyl radical is known to be fast,[9] and the radical decomposition of the silver salts of perfluoro acids is well documented.[5,10] The earlier work with silver oxide[5b] probably involved a similar reaction, but with formation of only the silver salt.

$$C_3F_7CO \qquad C_3F_7CO \longrightarrow C_3F_7\cdot + CO$$
$$\diagdown O \diagup \longrightarrow +$$
$$C_3F_7CO\cdots Ag \qquad C_3F_7COOAg \longrightarrow C_3F_7\cdot + CO_2 + Ag$$
$$2C_3F_7\cdot \longrightarrow C_6F_{14}$$

(8) A 1,4 shift is needed for a first-order rearrangement. This is less likely than the 1,2 shift proposed for the hexafluoroacetone decomposition, and a free radical pathway seems more likely.

(9) The loss of carbon monoxide from perfluoroacyl radicals is best noted in photochemistry in which fluorinated ketones are used as a source for fluoroalkyl radicals. The absolute rate of decarbonylation has been determined. See, for example, J. C. Amphlett and E. Whittle, *Trans. Faraday Soc.*, **63**, 80 (1967); J. S. E. McIntosh and G. B. Porter, *ibid.*, **64**, 119 (1968).

(10) M. Hudlicky, ref 2, p 271

Surprisingly, decomposition of heptafluorobutyric anhydride did not occur in open tubes of 0.75-in. diameter made of either tantalum or silver at temperatures up to 850° and contact times of 100 sec. It seems that surface contact is very important in this reaction and this may be the reason why it has not been noted before. It is expected that similar results will be found for other perfluoro acid anhydrides.

Experimental Section

Pyrolysis of Heptafluorobutyric Anhydride over a Catalyst.—A 0.75-in. × 5-ft silver-lined tube mounted vertically in a direct-wound furnace was packed with 200 cc of a silver-on-alumina catalyst[11] using supports to hold the catalyst in the high-temperature zone of the tube. Perfluorobutyric anhydride was fed from a buret at a rate to give a contact time of about 100 sec. The products were analyzed by gas chromatography and mass spectroscopy as well as by physical properties.

A series of experiments were made using a silver catalyst, two platinum catalysts, and a sample of the alumina support used for the silver and one of the platinum catalysts. The results are given in Table I.

Pyrolysis of Heptafluorobutyric Anhydride in a Titanium Bomb.—A 500-cc titanium bomb was charged with 57.4 g of heptafluorobutyric anhydride and heated to 350° for 12 hr. At temperature the pressure reached 2500 psig, and after cooling there was still 400 psig pressure in the bomb. The volatile components, 42 g, were condensed in Dry Ice–acetone cooled traps backed by a gas sample bottle, and an additional 4 g of black liquid was poured from the bomb. Distillation separated 13 g (62%) of hexafluoropropene, 17 g (56%) of heptafluorobutyryl fluoride, and 15 g (26%) of heptafluorobutyric anhydride. This accounts for only 86% of the starting material, and there were black carbon-like solids coating the bomb wall. There was, however, no evidence by gas chromatography or mass spectroscopy for any perfluorohexane.

Pyrolysis of Heptafluorobutyric Anhydride in an Open Tube.—A 0.75 in. × 5 ft tantalum tube was mounted in a direct-wound furnace and heated with a nitrogen purge to establish a series of temperature profiles. Heptafluorobutyric anhydride was then fed from a buret to the top of the tube at a rate to give a contact time of 100 sec. At both 350 and 450° there was no evidence of reaction.

The above procedure was repeated using the same size silver-lined stainless steel tube at 450, 550, 700, and 850°, all at 100-sec contact time. Again no reaction was observed, except that at 850° there was a small amount of black solids formed on the reactor wall near the outlet.

The experiment at 700° in the silver-lined tube was repeated with 0.1% by weight of iodine added as a possible radical initiating source. There was again no reaction.

Registry No.—Heptafluorobutyric anhydride, 336-59-4.

(11) The silver-on-alumina catalyst was prepared by impregnating 200 cc of $^3/_{16}$ in. × $^3/_{16}$ in. Norton LA-956 α-alumina with 30 g of silver nitrate in 40 ml of water under vacuum. The salt was converted to metallic silver by reduction using a flow of 5 l./hr of hydrogen as the catalyst was heated up to 700° over a 29-hr period.

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solid: $(C_3H_5)_4Sn + 2n\text{-}C_4H_9Li \rightarrow 2C_3H_5Li \downarrow + (C_3H_5)_2Sn(C_4H_9)_2$

Vinyllithium

ether solution: $(C_2H_3)_4Sn + 4C_6H_5Li \rightarrow 4C_2H_3Li + (C_6H_5)_4Sn \downarrow$

solid: $(C_2H_3)_4Sn + 2n\text{-}C_4H_9Li \rightarrow 2C_2H_3Li \downarrow + (C_2H_3)_2Sn(C_4H_9)_2$

Benzyllithium

ether solution: $(C_6H_5CH_2)_2Hg + 2RLi \rightarrow 2C_6H_5CH_2Li + R_2Hg$

Phenyllithium, halide-free

ether solution: $(C_6H_5)_2Hg + 2Li$ (shot or wire) $\rightarrow 2C_6H_5Li + Hg/Li$

B-Styryllithium

ether solution: $(C_6H_5)_3SnH + HC{\equiv}CC_6H_5 \rightarrow (C_6H_5)_3SnCH{:}CHC_6H_5$

$(C_6H_5)_3SnCH{:}CHC_6H_5 + C_6H_5Li \rightarrow C_6H_5CH{:}CHLi + (C_6H_5)_4Sn \downarrow$

Reagents for the above reactions available from Alfa:

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44109	$n\text{-}C_4H_9Li$	7.30/mole
71146	$(C_2H_3)_4Sn$	18.00/10 grams
37121	$(C_6H_5CH_2)_2Hg$	14.50/5 grams
44113	CH_3Li	13.50/mole
37119	$(C_6H_5)_2Hg$	16.00/25 grams
00189	Li shot	16.50/100 grams
00190	Li wire	10.00/25 grams
87806	$(C_6H_5)_3SnH$	16.20/10 grams

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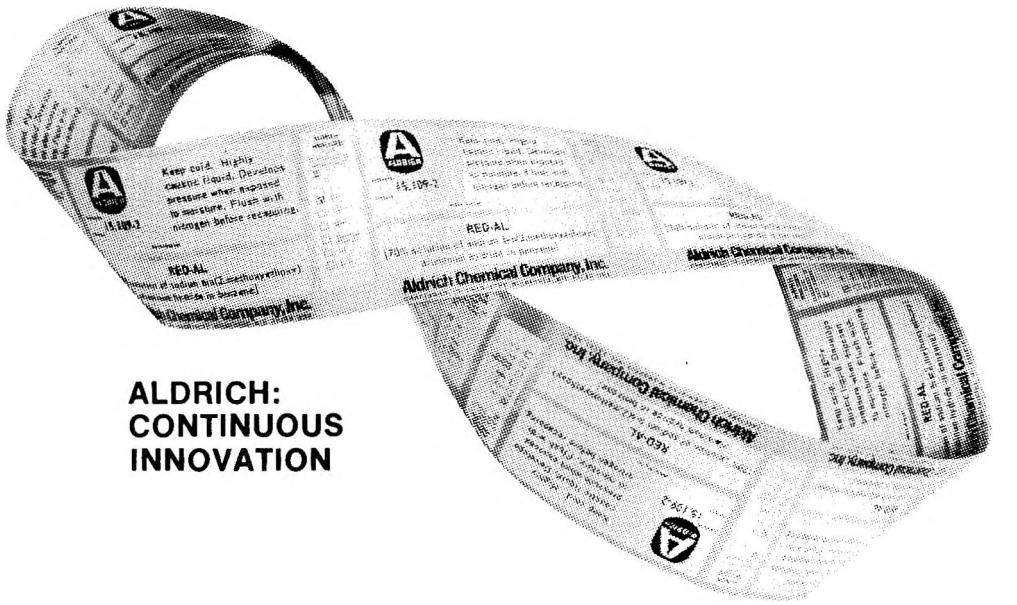

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